NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer [ID811]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Decision problem

- Both the appraisal remit and the marketing authorisation cover 2nd or 3rd line treatment, after any prior chemotherapy. Most evidence is for 2nd-line after *platinum*-based chemotherapy. Is there sufficient evidence for recommendations across the whole remit?
- Docetaxel is the main comparator, but erlotinib and best supportive care were included in the NICE scope. Is docetaxel is the only relevant comparator?

Clinical effectiveness

- Some population groups seen in clinical practice (e.g. ECOG >1, people taking high-dose steroids) were excluded from CheckMate-017. Are the results generalisable to people with NSCLC in England?
- There is uncertainty regarding the effect of nivolumab in people aged >75 (average age at diagnosis: 74). Is there sufficient evidence to support recommendations for people with NSCLC seen in clinical practice in England?
- Both the company and the ERG accept there are limitations in the indirect comparisons with erlotinib and best supportive care. Do the indirect comparisons provide sufficient evidence to inform decision making for these comparators?

Cost effectiveness

- Are the assumptions in the company's economic model appropriate and clinically plausible?
- 3 key areas of concern in the company's economic modelling:
  - ***Survival projections:*** Are the ERG's concerns about the company's extrapolations for progression-free, post-progression and overall survival valid? What are the most appropriate methods for extrapolating these outcomes?
  - ***Drug costs:*** What are the most appropriate assumptions for calculating the acquisition costs, administration costs and duration of treatment?
  - ***Utility values:*** What is the most appropriate approach to estimating utility scores for the pre-progression and post-progression states?

Other considerations

- Are the end-of-life criteria met for this appraisal?

1 Remit and decision problem

1.1 The remit from the Department of Health for this appraisal is: To appraise the clinical and cost effectiveness of nivolumab within its marketing authorisation for previously treated locally advanced or metastatic non-small cell lung cancer.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People with previously treated locally advanced or metastatic (stage IIIB or IV) squamous NSCLC		–	The evidence presented is specifically for people previously treated with platinum combination chemotherapy.
Intervention	Nivolumab		–	–
Comparators	• Docetaxel • Erlotinib (subject to ongoing review of NICE technology appraisal 162) • Best supportive care	• Docetaxel • (Erlotinib – sensitivity analysis only)	Docetaxel is the most relevant comparator. Erlotinib is not established practice (its use is limited and declining), and limited evidence was available. There is limited evidence comparing nivolumab with best supportive care, so this comparator was excluded.	Docetaxel, erlotinib and best supportive care are all relevant comparators. Based on expert advice and market shares, the ERG agreed that docetaxel is the most relevant. The ERG agreed with the company that there are limitations in the evidence available for comparison with erlotinib and best supportive care.
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life		–	–
Other considerations	If the evidence allows, consideration will be given to subgroups based on biological markers.		–	Clinical effectiveness evidence is presented for subgroups including those based on biomarkers; no subgroups are presented in the economic analysis.

2 The technology and the treatment pathway

2.1 Nivolumab (Nivolumab BMS/Opdivo[1], Bristol-Myers Squibb) is a monoclonal antibody that targets a receptor on the surface of lymphocytes known as PD-1 (programmed cell death protein 1). PD-1 binds to 2 ligands PD-L1 and PD-L2. The PD-1 receptor is part of the immune checkpoint pathway, and reduces the immune response by causing the death of T-cells (a type of lymphocyte or white blood cell that destroys tumour cells). Blocking PD-1 activity may restore T-cells and stimulate the patient's own immune system to attack tumour cells. 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 through the Early Access to Medicines Scheme (EAMS) from the UK Medicines and Healthcare products Regulatory Agency (MHRA), for a period of 1 month; the EAMS approval was withdrawn when the marketing authorisation was granted. It is administered by intravenous infusion over 60 minutes, at a dose of 3 mg/kg every 2 weeks. Nivolumab has also been granted a marketing authorisation for the treatment of advanced (unresectable or metastatic) melanoma in adults (NICE technology appraisal in development [ID845]). It is also being appraised by NICE for non-squamous NSCLC (anticipated publication: September 2016 [ID900]).

2.2 Squamous NSCLC is a type of NSCLC arising from the flat, surface-covering cells in the airways, and comprises about 25–30% of lung cancers. Squamous NSCLC is often diagnosed late in life; the median age at diagnosis is 74 years. The treatment pathway for squamous NSCLC is summarised in Figure 1. NICE clinical guideline 121 (CG121)

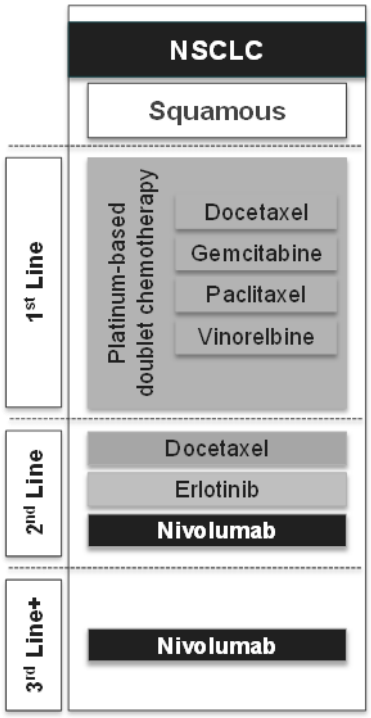
[1] The marketing authorisation for nivolumab for treating non-small-cell lung cancer has been granted under the brand name 'Nivolumab BMS'; nivolumab with the brand name 'Opdivo' has been granted a positive opinion for this indication by the Committee for Medicinal Products for Human Use (CHMP; 24 September 2015).

recommends platinum-based chemotherapy (cisplatin or carboplatin, in combination with gemcitabine, vinorelbine or a taxane) as an option for people with untreated stage III or IV NSCLC and good performance status, followed by docetaxel monotherapy if the cancer progresses. People with squamous tumours that have progressed after chemotherapy may also be treated with erlotinib, which was recommended as an option in NICE technology appraisal 162. However, erlotinib is currently being reviewed by NICE; in the latest published ACD, it is recommended as an option for treating locally advanced or metastatic NSCLC that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive, or in certain circumstances in people with tumours of unknown EGFR-TK mutation status. However, for this appraisal the company stated that erlotinib has limited efficacy for squamous NSCLC, because most squamous tumours do not have mutations in EGFR-TK (which the drug inhibits). People with NSCLC that has progressed after chemotherapy may also receive best supportive care. However. the company does not regard this to be an appropriate comparator for nivolumab and stated that all people with lung cancer have supportive care, regardless of whether they also have active cancer therapy. As shown in figure 1, the company proposed that nivolumab could be considered in either the second- or third-line settings, consistent with the marketing authorisation (for squamous NSCLC after any prior chemotherapy); the majority of the clinical effectiveness evidence (section 4.1) and the company's economic model are for the second-line setting, and specifically after prior therapy with *platinum* combination chemotherapy.

2.3 The ERG noted that people with squamous tumours rarely have EGFR or ALK mutations. Consequently, modern treatments for lung cancer that target EGFR or ALK (such as erlotinib and crizotinib) are often unsuitable for squamous NSCLC; there have been no advances in the treatment of squamous NSCLC since docetaxel was introduced 10 years ago, and

there remain few effective treatment options. The ERG also noted the company's statements that first-line treatment with platinum-based chemotherapy is not suitable for all patients, because of its toxicity, and that the overall survival rate after treatment is low.

Figure 1 Systemic treatments for squamous non-small-cell lung cancer



Source: company submission, figure 5

Table 2 Technology and comparators

	Nivolumab	**Docetaxel**	**Erlotinib**
Marketing authorisation	For treating locally advanced or metastatic squamous non-small-cell lung cancer after prior chemotherapy in adults.	In combination with cisplatin, for treating previously untreated unresectable, locally advanced or metastatic non-small cell lung cancer. For treating locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.	For the first-line treatment of locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations. For treating locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

Dosage and administration	3 mg/kg, intravenously over 60 minutes, every 2 weeks	75 mg/m^2, intravenously over 60 minutes, every 3 weeks	150 mg, orally, once daily
List price[1]	40-mg vial: £439.00	140-mg vial: £900	30 x 150-mg tablets: £1631.53
Estimated cost per month/per year[1,2]	£2634 per dose = £5268 per month, £68,484 per year	£900 per dose = £1200 per month, £15,600 per year	£1631.53 per month, £19,850 per year
[1]Source: company submission and British National Formulary online [accessed October 2015]. [2]For a person weighing 73 kg, with a body surface area of 1.82 m^2.			

3 Comments from consultees

3.1 Consultees noted that relapsed squamous NSCLC is typically treated with docetaxel (usually 4–6 cycles), erlotinib or best supportive care. However, they noted that these treatments have limited effectiveness, and the prognosis is often poor. They also noted that docetaxel in particular is associated with significant adverse effects.

3.2 Patient groups emphasised the importance of improvements in survival, symptoms and quality of life for people with squamous NSCLC. They stated that even small gains in length of life (particularly near the end of life) would be highly valuable for this population and their families. The patient group also highlighted the debilitating and distressing symptoms of lung cancer. Consultees noted the promising results from clinical trials (see section 4); they considered that the trial conditions were consistent with current NHS practice, and that the trials had captured appropriate outcomes.

3.3 Consultees noted that nivolumab is generally well tolerated, although some specific immune-related side effects were noted. Clinical experts noted that additional training may be needed to support clinicians in identifying and managing these side effects, although this is already under way. Consultees stated that no other implementation issues were anticipated.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review identified 1 relevant randomised controlled trial: CheckMate-017. This was an international, open-label, phase III study in adults with squamous NSCLC that had progressed during or after treatment with 1 platinum combination chemotherapy. Patients were randomised to receive either nivolumab (n=135) or docetaxel (n=137), continued until disease progression or unacceptable toxicity. The company stated that patient characteristics were well balanced between treatment groups (Table 3). The primary outcome was overall survival; secondary outcomes included progression-free survival, response rates, time to and duration of response, and quality of life. Results were analysed at a pre-planned interim analysis (December 2014) and a further analysis in [redacted]; after the interim analysis, the trial was stopped because the primary endpoint had been met, and patients in the docetaxel arm were permitted to switch (cross-over) to nivolumab. No further comparative data was available after this point (January 2015), at which the protocol was amended to allow any eligible patients who had been randomised to receive docetaxel to cross over to nivolumab in an extension phase of the study (n=6). Full details of CheckMate-017 can be found in section 4.3 of the company submission.

Table 3 Patient characteristics in CheckMate-017

	Nivolumab (N=135)	**Docetaxel (N=137)**
Age: median (range), years	62 (39–85)	64 (42–84)
Sex: % male	82%	71%
Race: % white	90%	95%
PD-L1 expression level: %		
<1%	46%	48%
<5%	64%	64%
<10%	69%	69%
Not quantifiable at baseline	13%	21%

Smoking status: % current/former smokers	90%	94%
ECOG status: % ECOG 0	20%	27%
Disease stage: % stage IV	78%	82%
ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death 1 ligand Source: company submissions, table 13		

4.2 In addition to the CheckMate-017, the company identified 3 non-randomised studies:

- **CheckMate-063** was an open-label, single-arm, phase II study of nivolumab in people with squamous NSCLC who had previously had treatment with platinum-based chemotherapy and at least 1 other systemic therapy (referred to as 'heavily pre-treated'; n=117).
- **CheckMate-003** was an open-label dose-escalation study of nivolumab in people with advanced or recurrent cancer, including 54 patients with squamous NSCLC. Patients had received between 1 and 5 previous systemic anti-cancer treatments before enrolment. During the study, patients received nivolumab 1, 3 or 10 mg/kg every 2 weeks for up to 96 weeks.
- **CheckMate-153** is an on-going long-term safety and tolerability study, in which people with squamous or non-squamous NSCLC (n=824) have nivolumab until disease progression or for a maximum of 1 year; at this point, patients were randomised to either continue treatment until disease progression or stop at 1 year and restart if their disease progressed.

The company stated that the study populations of CheckMate-063 and -003 were representative of people with heavily pre-treated squamous NSCLC in clinical practice. Full details of CheckMate-063 and -003 can be found in section 4.11 of the company submission; CheckMate-153 is described in the company's response to clarification.

4.3 No studies were identified that directly compared nivolumab with erlotinib. The company presented an indirect comparison to compare these treatments; see section 4.18.

ERG comments

4.4 The ERG stated that the company's literature search was appropriate, and it was not aware of any additional studies that should have been included.

4.5 The ERG considered that CheckMate-017 was well-conducted, captured appropriate outcomes and included the most relevant comparator for nivolumab. It noted that the assessments of disease progression were based on the RECIST criteria, and highlighted that this may not be ideal for an immunological treatment such as nivolumab. The population in CheckMate-017 was generally similar to people for whom nivolumab or docetaxel would be considered in the English NHS. However, the ERG noted that there were some people who would be treated in clinical practice but who were excluded from the trial – specifically, those with an ECOG performance status greater than 1 and people taking high-dose steroids. The ERG highlighted that there were some notable differences in patient characteristics between the 2 treatment arms, but considered that these were unlikely to have biased the results. The ERG noted that there was an unexpectedly high rate of withdrawal from the docetaxel arm in the first week, which led to the possibility of some bias due to drop-outs.

4.6 The ERG noted that treatment cross-over was not permitted in CheckMate-017 (and did not occur before database lock in December 2014), although patients could receive subsequent lines of therapy consistent with the standard of care. It highlighted that the European Public Assessment Report reports an analysis of the trial results in which subsequent treatments were taken into account, and the results are broadly consistent with the overall study results (presented below).

Clinical trial results

CheckMate-017

4.7 The company presented results from the interim analysis (company submission, section 4.7) and the [redacted] analysis (response to clarification, question A1).

4.8 Nivolumab was associated with statistically significant improvements in overall survival, progression-free survival and overall response rates, compared with docetaxel (Table 4 and Figure 2). The company also noted that in people whose disease responded, the duration of response was longer in the nivolumab group than the docetaxel group.

4.9 As permitted in the trial protocol, 28 patients in the nivolumab arm (20.7%) continued treatment beyond progression. Of these, 9 (32.1%) derived a clinical benefit from treatment beyond disease progression, referred to as a 'non-conventional benefit'.

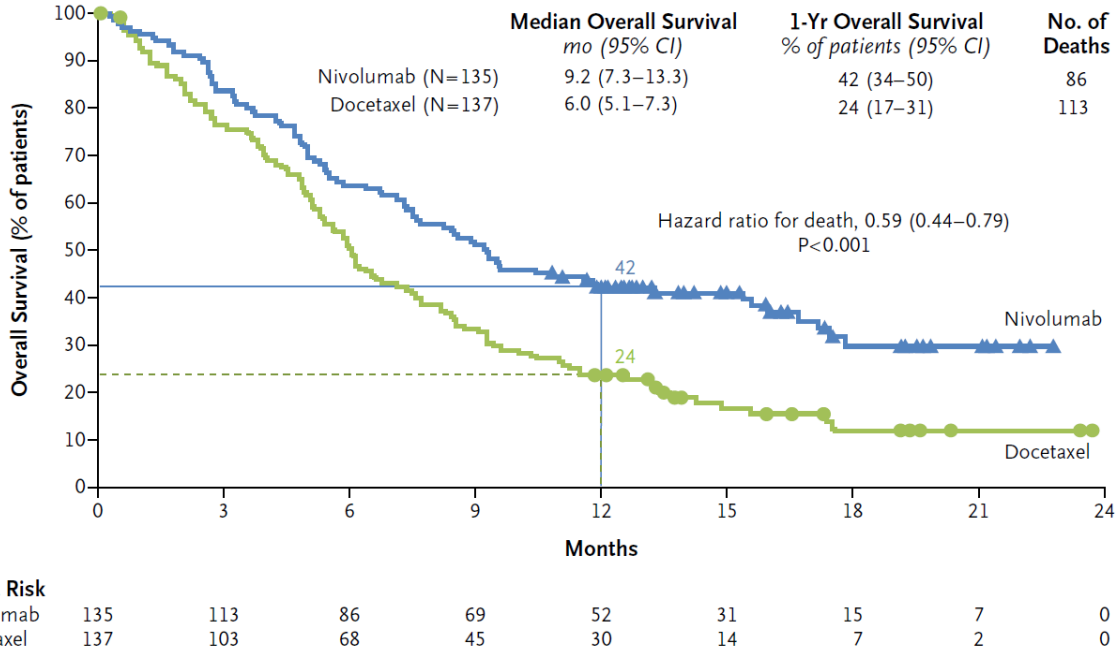
Table 4 Clinical effectiveness outcomes in CheckMate-017 (interim and [redacted] analyses)

	Nivolumab (N = 135)	Docetaxel (N = 137)
Overall survival		
Median (95% CI), months	9.2 (7.33–12.62)	6.0 (5.29–7.39)
Hazard ratio (95% CI)	0.62 (0.48–0.81) p=0.0004	
Overall survival at 12 months: % (95% CI)	42 (34–50)	24 (17–31)
Progression-free survival		
Median (95% CI), months	3.5 (2.14–5.06)	2.8 (2.14–3.52)
Hazard ratio (95% CI)	0.63 (0.48–0.83) p<0.0008	
Progression-free survival at 12 months: % (95% CI)	21 (14–28)	6 (3–12)

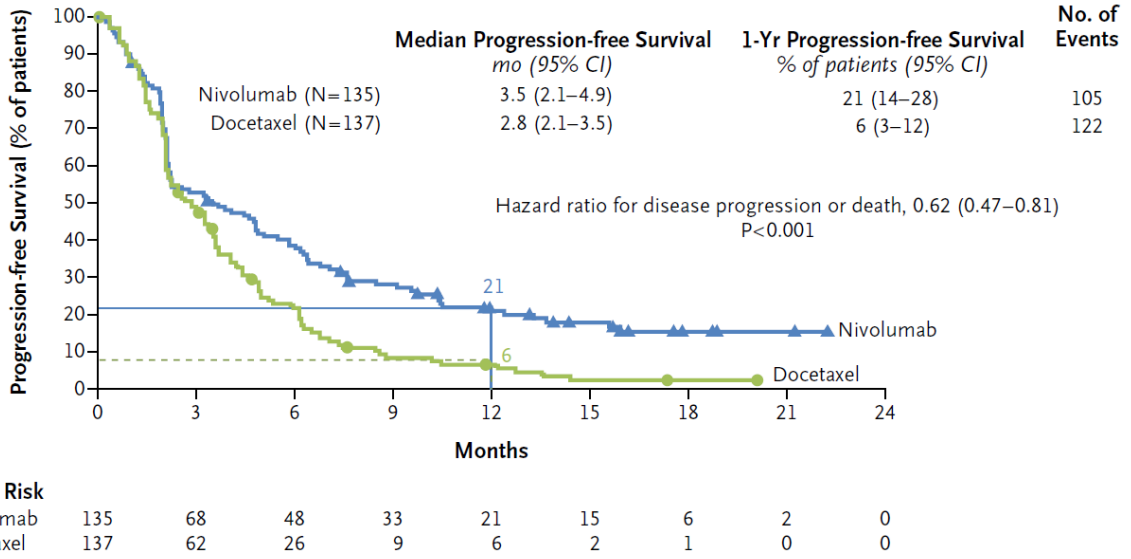
Response rates		
Overall response rate: % (95% CI)	20 (14–28)	9 (5–15)
Time to response: median (range), months	2.2 (1.6–11.8)	2.1(1.8–9.5)
95% CI, 95% confidence interval Source: company response to clarification, question A1, and company submission, table 17		

Figure 2 Overall survival and progression-free survival in CheckMate-017 (interim analysis)

A, overall survival



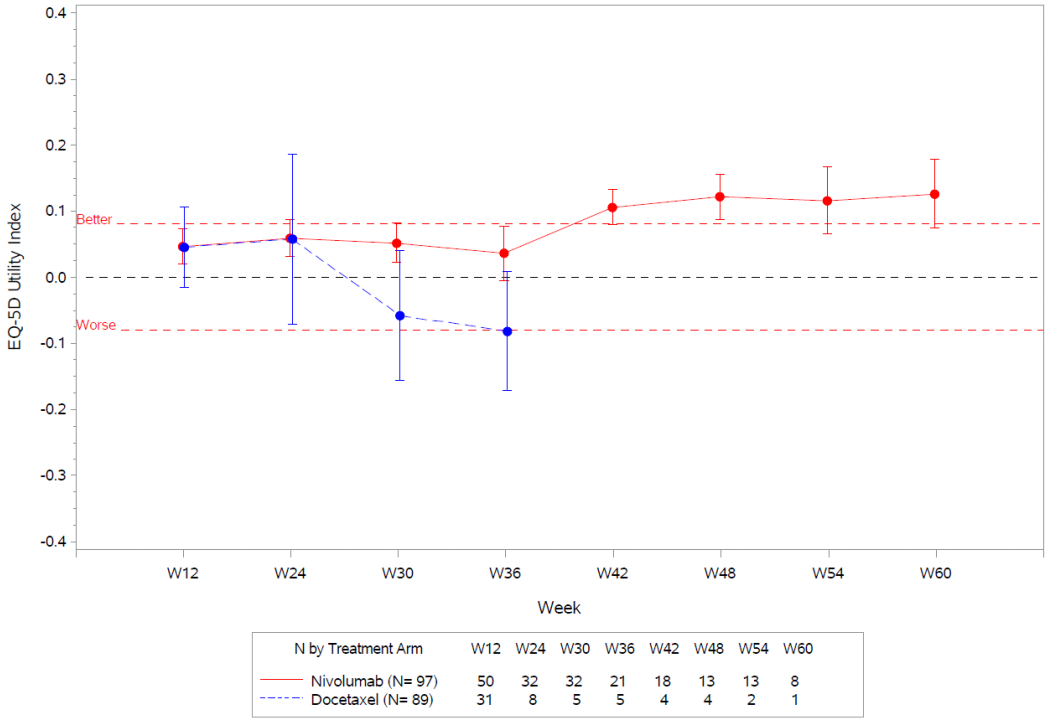
B, progression-free survival



Source: company submission, figures 8 and 9

4.10 The effect of nivolumab on quality of life was assessed using the EuroQol EQ-5D visual analogue scale and utility index and the Lung Cancer Symptom Scale Average Symptom Burden Index (LCSS ASBI). Nivolumab was associated with statistically significant improvements from baseline in all 3 measures of quality of life at most time points after week 12 (Figure 3), whereas there were no significant changes from baseline in people treated with docetaxel. Improvements in EQ-5D utility index and LCSS ASBI with nivolumab also reached clinical significance at weeks 42–54 (that is, the changes were greater than a published estimate for the 'minimum important difference' in EQ-5D in lung cancer; the minimum important difference is the smallest change in a measure that would be perceived by patients to be beneficial). Further details can be found in section 4.7 of the company submission.

Figure 3 EQ-5D utility index in CheckMate-017



Dashed lines show minimum important difference of ±0.08. Source: company submission, figure 24.

4.11 Pre-specified subgroup analyses suggested that the effect of nivolumab on overall survival and progression-free survival was consistent across subgroups based on patient and disease characteristics and the key biological marker (expression of 'programmed cell death ligand 1', PD-L1; [redacted]). Full details can be found in section 4.8 of the company submission and questions A5 and A6 of the response to clarification.

CheckMate-063 and CheckMate-003

4.12 Details of these studies are presented in section 4.11 of the company submission. In CheckMate-063, a total of 14.5% of patients treated with nivolumab had an objective response and 26% had stable disease; the median overall survival was 8.2 months. In the subgroup of patients from CheckMate-003 that matched the current decision problem (that is, with squamous tumours and treated with nivolumab 3 mg/kg ever 2 weeks),

the overall response rate was 22.2%. The company stated that this provided additional evidence for therapeutic benefits and durable responses, in heavily pre-treated patients.

ERG comments

4.13 The ERG noted that the results of CheckMate-017 showed that nivolumab has superior clinical effectiveness compared with docetaxel, across the primary and secondary endpoints. It understood that this trial had been stopped early, and noted that trials that are stopped early may exaggerate the effect of treatment on overall survival. However, the more mature overall survival data ([redacted], provided in the company's response to clarification) were consistent with the interim findings. The ERG also noted that there was only a small difference in median progression-free survival between the 2 treatment arms, but these results were skewed by the fact that the first radiological assessment of tumours took place after 9 weeks; the rates of progression-free survival at 12 months supported the clinical effectiveness of nivolumab. However, because of this skew, the ERG considered that the proportional hazards assumption (that is, the hazard of progression in 1 arm at any time point, is proportional to the hazard at the same time point in the other arm) did not hold for progression-free survival, so the hazard ratio for this outcome was not valid.

4.14 The ERG noted that the evidence on health-related quality of life outcomes was limited by low response rates and considered it likely that continuing responders would be those with the better health status and ECOG performance status. It therefore considered that the results should be interpreted with caution.

4.15 The ERG highlighted some uncertainty about the effect of nivolumab in people aged over 75 (recall that the median age at diagnosis for squamous NSCLC is 74 years). [redacted] there was no statistically

significant overall survival benefit associated with nivolumab in this group (hazard ratio 1.85; 95% confidence interval 0.76–4.51), albeit a small group.

4.16 The ERG noted that the trial protocol permitted people to continue nivolumab treatment after disease progression, because of the possibility of unconventional immune-related response associated with treatments such as nivolumab. It highlighted that the 21% of patients who continued treatment after progression received approximately [redacted] of additional therapy, and a third benefitted from this treatment. The ERG stated that it was unclear how 'non-conventional benefitters' could be identified and treated in clinical practice.

4.17 The ERG considered that the non-randomised trials (CheckMate-003 and -063) were unlikely to be representative of clinical practice in England – notably because they included heavily pre-treated populations but were limited to people with ECOG performance statuses of 0 or 1. Conversely, it noted that the overall survival results in CheckMate-003 were comparable to those in CheckMate-017. It noted that the clinical outcomes were worse in CheckMate-063, and suggested that this may have been because of the high proportion of people who had received several previous lines of therapy.

Indirect comparison

4.18 The company presented indirect comparisons between nivolumab and erlotinib, and between nivolumab and best supportive care. The analysis was performed 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 versus erlotinib; and Br.21: erlotinib versus best supportive care). The company highlighted differences between the trial populations and stated that it was not possible to control for this heterogeneity; it stated that the results should be interpreted with caution. The company also noted that the comparison

with best supportive care was only possible if the population was expanded to include people treated with 1 or more prior therapies (rather than just 1 prior therapy). Full details are provided in section 4.10 and appendix 7 of the company submission, and questions A11 and A12 of the response to clarification.

4.19 The results of the indirect comparison suggested that nivolumab was associated with improved overall survival compared with [redacted] best supportive care ([redacted]). Nivolumab was also associated with a statistically significant improvement in progression-free survival compared with erlotinib ([redacted]).

ERG comments

4.20 The ERG considered that the company's modelling approach for the indirect comparison was appropriate. However, it highlighted the heterogeneity of the studies included in the analysis. It also highlighted that there was insufficient information in the TAILOR and Br.21 studies to confirm whether the proportional hazards assumption was met. The ERG therefore agreed with the company that the results of the indirect comparisons should be interpreted with caution, and considered that the results were unreliable. It stated that the clinical effectiveness of nivolumab compared with erlotinib and best supportive care remains unknown.

Adverse effects of treatment

4.21 The company presented detailed adverse event data from CheckMate-017, -063 and -003 in section 4.12 of its submission, and additional data from CheckMate-153 in its response to clarification. The company reported that in CheckMate-017, nivolumab had a more favourable safety profile than docetaxel and was associated with fewer treatment-related adverse events (Table 5). The most common treatment-

related adverse events in the nivolumab group included fatigue, decreased appetite and asthenia. There were no deaths in the nivolumab arm that were related to the study drug.

4.22 The company identified a group of 'select adverse events', defined as immune-related adverse events that are associated with the mode of action of nivolumab and that require additional monitoring (Table 5). The most common nivolumab-related select adverse events in CheckMate-017 included diarrhoea, pneumonitis, hypothyroidism and rash. The company reported that most select adverse events in the nivolumab group were manageable and resolved using a defined treatment algorithm.

4.23 The company stated that similar rates of adverse events were seen in CheckMate-063, and that the safety data seen in CheckMate-153 were consistent with other clinical trials of nivolumab.

Table 5 Summary of adverse events in CheckMate-017

	Nivolumab, n (%) (N = 131)	**Docetaxel, n (%) (N = 129)**
Patients with 1 or more AE	127 (96.9)	125 (96.9)
Toxicity grade 3–4 AE	[redacted]	[redacted]
Select AEs	[redacted]	[redacted]
SAEs	61 (46.6)	70 (54.3)
AEs leading to discontinuation	14 (10.7)	26 (20.2)
Deaths	82 (62.6)	106 (82.2)
Deaths related to study drug toxicity	0	3 (2)
Treatment-related AEs		
Patients with 1 or more AE	76 (58)	111 (86)
Select AEs	[redacted]	[redacted]
SAEs	9 (7)	31 (24)
AEs leading to discontinuation	4 (3)	13 (10)

AE, adverse event; SAE, serious adverse event; 'select' AEs are a group of immune-related adverse events that are associated with the mode of action of nivolumab and that require additional monitoring. Source: company submission, tables 27 and 28.

ERG comments

4.24 The ERG considered that the adverse event data suggested that nivolumab was better tolerated than docetaxel. It noted that the safety profile in the non-randomised trials was consistent with CheckMate-017, and the overall safety profile is consistent with clinical expectations.

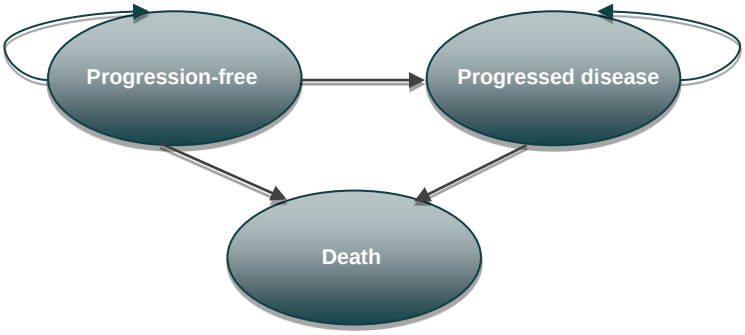
4.25 The ERG also reviewed the safety of nivolumab compared with erlotinib, using evidence from the LUX-Lung 8 trial. It noted that there was little difference in the overall incidence of adverse events between nivolumab and erlotinib, but there were fewer drug-related deaths with nivolumab. It also highlighted that although rash and diarrhoea have been identified as immune-related adverse events associated with nivolumab, both were more common in people treated with erlotinib.

5 Cost-effectiveness evidence

Model structure

5.1 The company presented an economic model with a partitioned survival structure based on 3 states: progression free, progressed disease and death (Figure 4). In the base case, the company compared nivolumab with docetaxel; a comparison with erlotinib was presented in a scenario analysis. The model used a cycle length of 1 week and had a time horizon of 20 years (lifetime). The model perspective was the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.

Figure 4 Model structure



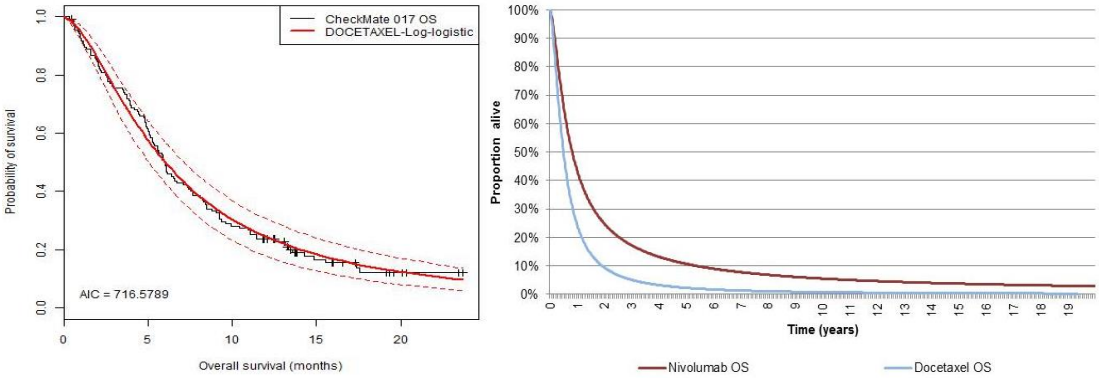
Source: company submission, figure 14

Model details

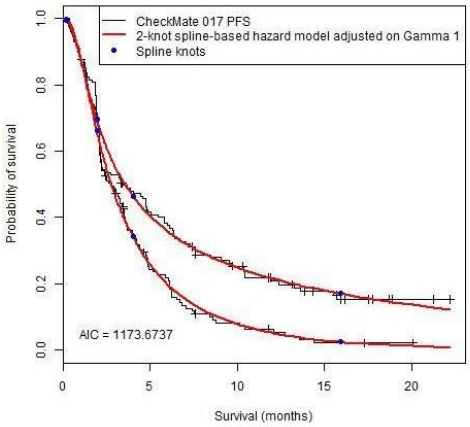
5.2 Patients entered the model in the 'progression-free' state, in which they had treatment with nivolumab or docetaxel until their disease progressed and they moved to the 'progressed disease' state, or they died. The proportion of people in the each health state in each cycle was based on estimates 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, December 2014) 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: overall survival was extrapolated using a log-logistic function, and progression-free survival was extrapolated using a 2-knot spline hazards model (Figure 5). Alternative models were explored in scenario analyses.

Figure 5 Extrapolation of overall survival and progression-free survival: company base case

A: overall survival, log-logistic model



B: progression-free survival, 2-knot spline hazards model



Source: company submission, figures 18, 20 and 22

5.3 Health-related quality of life was incorporated into the model by applying utility scores to each health state. The utility scores were derived from EQ-5D utility index data collected in CheckMate-017 (section 4.10), 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 events, by applying utility decrements for each event 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).

5.4 The model incorporated costs associated with each health state. Costs in the progression-free state included acquisition and administration of the initial treatment (based on the list prices for nivolumab and docetaxel), monitoring, and disease management; the progressed disease state included costs associated with 1 subsequent line of lung cancer therapy (based on treatments used in CheckMate-017) and disease management. The model also included costs for end of life care and management of adverse events (events with a severity grade of 3 or more and an incidence of at least 5% in either arm of CheckMate-017). The costs were informed by estimates in the ongoing appraisal of erlotinib and gefinitib (ID620), the appraisal of nintedanib (TA347), and NHS reference costs.

Company's base-case results and sensitivity analysis

5.5 In the base case, nivolumab was associated with additional costs of £65,355 and 0.76 additional quality-adjusted life years (QALYs), compared with docetaxel, giving an incremental cost effectiveness ratio (ICER) of £85,950 per QALY gained (Table 6).

Table 6 Results of the company's base case analysis

	Total cost	**Total LYG**	**Total QALYs**	**Incr cost**	**Incr LYG**	**Incr QALYs**	**ICER (£/QALY gained)**
Deterministic analysis							
Nivolumab	£86,599	2.26	1.30	£65,355	1.31	0.76	£85,950
Docetaxel	£21,243	0.95	0.54				
Probabilistic analysis							
Nivolumab	£91,677	*NR*	1.35	£68,938	*NR*	0.77	£89,343
Docetaxel	£22,739	*NR*	0.58				
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; NR, not reported; QALY, quality-adjusted life year. Source: company submission, table 72.							

5.6 The company presented both deterministic and probabilistic sensitivity analyses. The 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 the utility values in the progression-free and progressed disease health states. 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 ICER therefore increased to £89,343 per QALY gained (Table 6); the probability that nivolumab was cost effective was less than 10% if the maximum acceptable ICER were £50,000 per QALY gained. The company stated that the uncertainty in the ICER was driven by treatment efficacy, resource use, body weight and utility values.

Scenario analyses

5.7 The company presented a series of scenario analyses to explore the effect of assumptions about survival modelling, treatment discontinuation and vial optimisation. 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 (Table 7).

Table 7 Results of the company's scenario analyses

Scenario	Incr cost	Incr QALYs	ICER (£/QALY gained)
Base case	£65,355	0.76	£85,950
Scenario 1: 2-knot spline distribution for overall survival	£62,347	0.58	£108,096
Scenario 2: independent survival curves for progression-free survival	£67,202	0.76	£87,925
Scenario 3: 1-year stopping rule for nivolumab*	£34,575	0.76	£45,470

Scenario 4: 2-year stopping rule for nivolumab*	£46,325	0.76	£60,923
Scenario 5: vial optimisation	£60,496	0.76	£79,559
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALY, quality-adjusted life year. Source: company submission, tables 72 and 96–108. *Assumes acquisition and administration costs for nivolumab stop after 1 or 2 years, but there is no effect on clinical effectiveness.			

5.8 The company also presented a scenario in which the cost effectiveness of nivolumab was compared with erlotinib. This analysis was based on the assumptions in the company's base case, the company's indirect comparison, and the list price for erlotinib (that is, not including the erlotinib PAS discount). Nivolumab was associated with an ICER of £85,862 compared with erlotinib (Table 8).

Table 8 Cost effectiveness of nivolumab compared with erlotinib

	Total cost	**Total LYG**	**Total QALYs**	**Incr cost**	**Incr LYG**	**Incr QALYs**	**ICER (£/QALY gained)**
Nivolumab	£86,599	2.26	1.30	£69,698	1.45	0.81	£85,862
Erlotinib	£16,901	0.81	0.49				
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALY, quality-adjusted life year. Source: company submission, appendix 20, table 41.							

ERG comments and exploratory analyses

5.9 The ERG commented that the company's model was structured consistently with previous economic models for appraisals of cancer drugs, and was implemented to a good standard. It noted that the base case compared nivolumab with docetaxel only; a comparison with erlotinib was presented as an exploratory analysis only, and no comparison with best supportive care was presented. Based on the structure of the company's model and the limitations in the available evidence, the ERG

considered that it would not be possible to reliably compare nivolumab with erlotinib or best supportive care.

5.10 The ERG identified 3 key areas of concern in the company's economic modelling: survival projections, drug costs, and utility values.

Survival projections

5.11 The ERG noted that the results of the economic model were highly sensitive to the methods used to project overall survival and progression-free survival; it highlighted that the clinical effectiveness evidence provided up to 2 years of follow-up, which was projected to a 20-year time horizon. The ERG therefore reviewed in detail the projections of overall survival, progression-free survival and post-progression survival.

5.12 The ERG highlighted that the log-logistic model for overall survival predicted that the rate of mortality would fall rapidly as time progressed (ERG report, figure 6). This implied that initial treatment with nivolumab would lead to a life-long reduction in the risk of death from any cause; the ERG considered that this was unrealistic. The ERG proposed an alternative approach, in which the trial data were used for the first 40 weeks of the model, followed by an exponential survival model from week 40 onwards (Figure 6). This model predicted a gain in overall survival with nivolumab, compared with docetaxel, of 7.17 months; this compared with an overall survival gain of 15.7 months predicted by the company's model (Table 9).

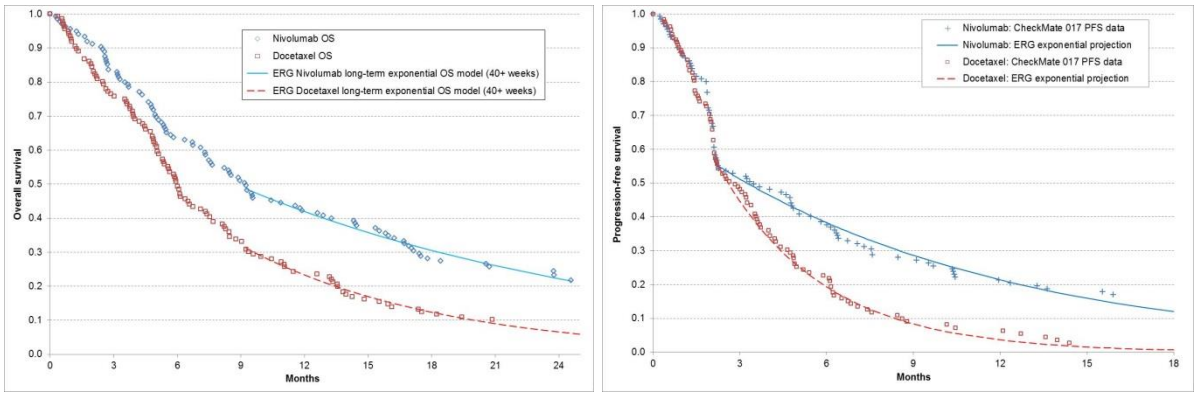
5.13 The ERG stated that the proportional hazards assumption for progression-free survival was not met, so the company's use of hazard ratios in the modelling of pre-progression survival was not valid (see section 4.13). The ERG fitted separate exponential curves to the nivolumab and docetaxel treatment arms (after 2.2 months, before which the curves were the same; Figure 6); this approach implied a mean progression-free survival gain with nivolumab of 3.63 months (compared with 6.5 months in the company's model; Table 9).

5.14 The ERG noted that more than half of the survival gain associated with nivolumab in the company's model (59%, 9.2 months) was accrued after disease progression; given that most people discontinued treatment on progression, this implies a substantial survival gain after nivolumab treatment was stopped. The ERG queried whether this would be plausible, and suggested that it may be an artefact of the survival projections. The ERG noted that there was no apparent difference in post-progression survival between nivolumab and docetaxel in CheckMate-017 (ERG report, figure 7), although some difference would arise if fewer people died before progression. The ERG's exploratory analyses suggested the post-progression survival gain associated with nivolumab may be 1.15 months or 3.54 months.

5.15 Overall, 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.

Figure 6 ERG's survival projections

A, Overall survival B, Progression-free survival



Source: ERG report, figures 9 and 10

Table 9 Company and ERG estimates for progression-free, post-progression and overall survival

	Nivolumab	Docetaxel	Survival gain
Company			
Progression-free survival	10.7	4.3	+6.5
Post-progression survival	16.4	7.2	+9.2
Overall survival	27.2	11.5	+15.7
ERG			
Progression-free survival	7.57	3.93	+3.63
Post-progression survival	8.50	4.96	+3.54
Overall survival	16.06	8.89	+7.17
Source: ERG report, tables 36 and 37.			

Drug costs

5.16 The ERG highlighted concerns about the company's modelling of drug acquisition costs, the duration of treatment and the administration costs:

- ***Acquisition costs:*** The ERG highlighted that the company used single estimates for average body weight and body surface area, based on the CheckMate-017 trial and the Systemic Anti-Cancer Therapy (SACT) database to calculate drug doses. It proposed that it would be more accurate to use weight and surface area distributions (to reflect variation in the population), for both men and women, based on a more representative cohort of UK patients. The ERG also highlighted that the company used the list prices for all drugs, but in practice generic drugs (including docetaxel and third-line chemotherapies) are purchased below the list price. It suggested that using the average NHS cost for generic drugs, obtained from the Commercial Medicines Unit's Electronic Market Information Tool (eMIT), would be more appropriate.
- ***Duration of treatment:*** The company assumed that initial therapy continued until disease progression. However, the ERG noted that in UK practice, treatment with docetaxel is usually limited to a maximum of 4 doses. Moreover, the ERG highlighted that this approach did not

capture people who stopped treatment before progression (for example, because of adverse events). The ERG proposed that using the time to discontinuation data from CheckMate-017, with a limit of 4 cycles of docetaxel, may be more appropriate.

- ***Administration costs:*** The ERG noted that the company assumed a different administration cost for docetaxel and nivolumab, but that this was not necessary. It also noted that the company averaged the administration costs across all cycles, rather than applying the cost at the start of the cycle in which the drug was given.

Utility values

5.17 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 that these data were based on low response rates and, hence, a potentially self-selected and biased population. The ERG stated that the pre-progression utility value was similar to a published estimate for a UK population of the same age; given that people in this model were having second-line treatment for advanced lung cancer, this was considered unrealistic. The ERG identified alternative utility values in a study by Nafees et al (2008) in which UK societal based utility values were elicited for disease states associated with metastatic NSCLC that has progressed following first line treatment. The values were 0.65 in the progression-free state and 0.43 in the progressed disease state.

5.18 The ERG considered that the disutilities associated with adverse events were unreliable. It identified limitations in the evidence on which the disutility scores were based, and highlighted that the company effectively assumed 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; although the size of the underestimate was not known, it was not expected to be large.

Exploratory analyses

5.19 The ERG conducted a series of exploratory analyses to address each of the issues described above. In addition, it requested from the company survival data with an alternative censoring rule (people who withdrew or were lost to follow-up were censored at the time of data cut-off); these data were used in all of the ERG's analyses. Individually, the ERG's amends each had different effect on the ICER (that is, some amends increased the ICER while others decreased it, and by varying amounts). Combined, the ERG's amends increased the ICER by £47,039 per QALY gained, compared with the company's base case (Table 10).

Table 10 ERG's exploratory analyses

Model scenario		**Total cost**	**Total QALYs**	**Incr cost**	**Incr QALYs**	**ICER (£/QALY gained)**	**Change vs base case**
A. Company's base case	**Nivolumab**	**£86,599**	**1.299**	**£65,355**	**0.76**	**£85,950**	**-**
	Docetaxel	**£21,243**	**0.539**				
R1) ERG PFS estimates	Nivolumab	£71,172	1.265	£50,434	0.732	£68,912	-£17,038
	Docetaxel	£20,738	0.533				
R2) ERG OS estimates	Nivolumab	£79,923	0.894	£60,366	0.457	£131,979	£46,029
	Docetaxel	£19,572	0.437				
R3) Revised costs of 2nd line drugs	Nivolumab	£85,597	1.299	£69,854	0.76	£91,867	£5,917
	Docetaxel	£15,742	0.539				
R4) Revised costs of 3rd line drugs	Nivolumab	£86,089	1.299	£65,539	0.76	£86,192	£241
	Docetaxel	£20,550	0.539				
R5) Common administration cost	Nivolumab	£84,332	1.299	£63,089	0.76	£82,970	-£2,981
	Docetaxel	£21,243	0.539				
R6) Docetaxel limited to 4 cycles	Nivolumab	£86,599	1.299	£68,559	0.76	£90,164	£4,213
	Docetaxel	£18,040	0.539				
R7) Drugs given at the start of cycles	Nivolumab	£87,311	1.299	£65,891	0.76	£86,654	£704
	Docetaxel	£21,420	0.539				
R8) Duration based on time to discontinuation	Nivolumab	£69,196	1.299	£49,837	0.76	£65,542	-£20,409
	Docetaxel	£19,359	0.539				
R9) Alternative utility scores	Nivolumab	£86,599	1.031	£65,355	0.617	£105,915	£19,964
	Docetaxel	£21,243	0.414				
B. ERG revised analysis: A+R1–R6, R8, R9	**Nivolumab**	**£60,292**	**0.689**	**£47,512**	**0.357**	**£132,989**	**£47,039**
	Docetaxel	**£12,780**	**0.332**				

ICER, incremental cost-effectiveness ratio; Incr, incremental; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year. Source: ERG report, table 39

Innovation

5.20 The company considered that nivolumab is innovative and represents a 'step-change' in the management of locally advanced or metastatic squamous NSCLC:

- There are limited treatment options for NSCLC, particularly for squamous tumours which typically do not have EGFR-TK or ALK mutations. The current standard treatments for previously treated squamous NSCLC (docetaxel and erlotinib) have limited efficacy.
- Nivolumab is the first immunotherapy, and the first PD-1 inhibitor, to be licensed for this condition.
- It was designated a 'Promising Innovative Medicine' by the MHRA, and was approved through the Early Access to Medicines Scheme (EAMS).
- It provides a significant survival benefit, equating to a reduction in mortality of approximately 40% compared with docetaxel.

5.21 The patient group also considered nivolumab to be innovative, noting the mechanism of action and stating that it represents a major milestone in the treatment of squamous NSCLC.

6 End-of-life considerations

Table 11 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The company stated that people with advanced or metastatic NSCLC have a short life expectancy of less than 24 months (company submission, table 34). In CheckMate-017, the median survival in patients treated with docetaxel was 6.0 months (company submission, table 15).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared	In CheckMate-017, nivolumab was associated with an increase in median overall survival of 3.2 months compared with docetaxel (9.2 months vs 6.0 months; $p<0.001$; company submission, table 15).

with current NHS treatment	For the modelled mean estimate of the increase in overall survival for nivolumab compared with docetaxel, the company estimated this to be 15.7 months whilst the ERG estimated this to be 7.17 months.
The treatment is licensed or otherwise indicated for small patient populations	The company estimated that the number of people in England with squamous NSCLC for whom nivolumab may be considered is 853. (19,138 people diagnosed with locally advanced or metastatic NSCLC, of whom 35.6% have squamous NSCLC; 25% of these people will have first-line chemotherapy, and first-line therapy will fail in 50% of cases; company submission, table 112.)

6.1 The ERG agreed with the company that nivolumab is indicated for people with a short life expectancy, that it provides an extension to life of at least 3 months, and that the population is small. The ERG estimated that the mean overall survival gain associated with nivolumab compared with docetaxel is more than 6 months. It noted that the company's population estimate of 853 patients in England was reasonable, but refers to the second-line population only (that is, not to nivolumab as a third-line treatment; although the company proposed that nivolumab may be used either second or third line, consistent with its marketing authorisation, the pivotal randomised trial evidence was restricted to the second line setting).

7 Equality issues

7.1 No equality issues were identified during the scoping process for this topic. The company stated in its submission that no equality issues were foreseen, and no equality issues were raised by consultees in their submissions.

8 Authors

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Technical Lead

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with input from the Lead Team (Iain Miller, Peter Selby and Judith Wardle).

Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003840/WC500190651.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab within its marketing authorisation for previously treated locally advanced or metastatic non-small cell lung cancer.

Background

Lung cancer falls into two main histological categories: around 85–90% are non-small-cell lung cancers (NSCLC) and the remainder are small-cell lung cancers[1,2]. NSCLC can be further classified into 3 histological sub-types of large-cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma; about 25–30% of lung cancers are squamous cell carcinomas[1]. Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV). In 2013, approximately 26,800 people were diagnosed with NSCLC in England, of whom 3551 (13.2%) had stage IIIA, 2527 (9.4%) had stage IIIB and 12,229 (45.6%) had stage IV disease[2].

Lung cancer caused 28,000 deaths in England in 2012[3]. The median survival with lung cancer (all stages) is approximately 6 months; 35% of people with lung cancer, and 14% of people with stage IV disease, survive for more than 1 year[2,3].

For the majority of people with NSCLC, the aims of therapy are to prolong survival and improve quality of life. NICE clinical guideline 121 (CG121) recommends platinum-based chemotherapy as an option for people with untreated stage III or IV NSCLC and good performance status. CG121 recommends that for people with locally advanced or metastatic NSCLC whose disease has progressed after chemotherapy, docetaxel monotherapy should be considered. Supportive care may be considered for some people for whom. Treatment choices may be influenced by the presence of biological markers (such as mutations in EGFR-TK), histology (squamous or non-squamous) and previous treatment experience; in clinical practice, squamous tumours that have progressed after chemotherapy are usually treated with docetaxel, erlotinib (NICE technology appraisal 162) or supportive care.

The technology

Nivolumab (Nivolumab-BMS, 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 is administered by IV infusion.

Nivolumab does not currently have a marketing authorisation in the UK for previously treated locally advanced or metastatic non-small cell lung cancer. It has received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) for "the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults".

Intervention(s)	Nivolumab
Population(s)	People with previously treated locally advanced or metastatic (stage III or IV) squamous non-small cell lung cancer
Comparators	• Docetaxel • Erlotinib (subject to ongoing review of NICE technology appraisal 162) • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	If the evidence allows, consideration will be given to

	subgroups based on biological markers. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 162, Nov 2008, 'Erlotinib for the treatment of non-small-cell lung cancer'. Review in progress. Technology Appraisal in preparation, 'Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175)' [ID620]. Expected date of publication TBC. Related Guidelines: Clinical Guideline No. 121, Apr 2011, 'The diagnosis and treatment of lung cancer'. Review date June 2015 Related Quality Standards: Quality Standard No. 17, Mar 2012, 'Quality standard for lung cancer'. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Related NICE Pathways: NICE Pathway: Lung cancer. Pathway created: Mar 2012. http://pathways.nice.org.uk/pathways/lung-cancer
Related National Policy	Department of Health, Improving Outcomes: A Strategy for Cancer, third annual report, Dec 2013 https://www.gov.uk/government/publications/the-national-cancer-strategy-3rd-annual-report--2 NHS England, Manual for prescribed specialised services, service 105: specialist cancer services (adults), Jan 2014. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2013-2014, Nov 2013.

	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf Department of Health, Cancer commissioning guidance, Dec 2009. http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_110115

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1. American Cancer Society (2015) Learn about cancer: What is non-small-cell lung cancer? Accessed June 2015.
2. Health and Social Care Information Centre (2014) National Lung Cancer Audit: 2013 patient cohort. Accessed June 2015.
3. Cancer Research UK (2014) Lung cancer statistics. Accessed June 2015.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer [ID811]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Bristol-Myers Squibb (nivolumab) Patient/carer groups • Afiya Trust • Black Health Agency • British Lung Foundation • Cancer Black Care • Cancer Equality • Equalities National Council • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Roy Castle Lung Cancer Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus • UK Lung Cancer Coalition Professional groups • Association of Cancer Physicians • Association of Respiratory Nurse Specialists • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Thoracic Oncology Group • British Thoracic Society • Cancer Research UK • National Lung Cancer Forum for Nurses • Primary Care Respiratory Society UK	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Accord Healthcare (docetaxel) • Actavis UK (docetaxel) • Dr Reddy's Laboratories (docetaxel) • Hospira UK (docetaxel) • Medac UK (docetaxel) • Roche Products (erlotinib) • Sanofi (docetaxel) • Teva UK (docetaxel) Relevant research groups • Cochrane Lung Cancer Group • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Halton CCG • NHS Lewisham CCG • Welsh Government	• National Institute for Health Research <u>Evidence Review Group</u> • Liverpool Reviews and Implementation Group (LRIG) • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that manufactures the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that manufactures the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that manufacture comparator technologies; Healthcare Improvement Scotland ; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1] Non manufacturer consultees are invited to submit statements relevant to the group they are representing.

[1] Non -company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer [ID811]

Company evidence submission

Submitted by Bristol-Myers Squibb Pharmaceuticals Ltd

August 2015

File name	Version	Contains confidential information	Date
Nivolumab BMS_SQ_NSCLC submission_FINAL (v6.0a)_17 August 20_withoutPAS_clean	6.0	Yes	17 August 2015

Contents

Tables

Figures

Abbreviations

Term	Definition
AE	Adverse Event
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
ASBI	Average Symptom Burden Index
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian Information Criterion
BMS	Bristol-Myers Squibb
BNF	British National Formulary
BOR	Best Objective Response
BSA	Body Surface Area
BSC	Best Supportive Care
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-Effectiveness Analysis
CENTRAL	Cochrane® Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMSTO	Chicago Multidisciplinary Symposium in Thoracic Oncology
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CSR	Clinical Study Report
CT	Computerised Tomography
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
CU	Cost-Utility
DMC	Data Monitoring Committee
DOR	Duration of Response
DOT	Duration on Treatment
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EPAR	European Public Assessment Report

Term	Definition
EQ-5D	EuroQol-5D
EQ-VAS	EuroQol-Visual Analogue Scale
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	European Union
GP	General Practitioner
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
irAEs	Immune-related Adverse Events
IRC	Independent Radiology Review Committee
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
ITC	Indirect Treatment Comparison
ITT	Intention-To-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
LCA	London Cancer Alliance
LCSS	Lung Cancer Symptom Scale
LRiG	Liverpool Reviews and Implementation Group
LUCADA	National Lung Cancer Audit Data Set
LY	Life Year
LYG	Life Year Gained
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHRA	Medicines and Healthcare products Regulatory Agency
MID	Minimally Important Difference
MRI	Magnetic Resonance Imaging
MTA	Multiple Technology Appraisal
N/A	Not Applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate

Term	Definition
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PF	Progression-Free
PFS	Progression-Free Survival
PICOTS	Population, Intervention, Comparator, Outcome, Time and Setting
PIM	Promising Innovative Medicine
PR	Partial Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PS	Performance Status
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Years
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumors
RWD	Real World Data
SAE	Serious Adverse Event
SD	Stable Disease
SEER	Surveillance, Epidemiology, and End Results Program
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TKI	Tyrosine Kinase Inhibitor
TTR	Time to Response
Tx	Treatment
UK	United Kingdom
WCLC	World Conference on Lung Cancer

1 Executive summary

Lung cancer is the second most common cancer in the United Kingdom (UK) and has the highest mortality of any cancer. There were 30,148 deaths from lung cancer in England and Wales in 2011. Most lung cancers in England are diagnosed at an advanced stage when the cancer has spread; these patients are usually older (median age of diagnosis is 74 years) and a large proportion of patients experience increasingly severe morbidity as their disease progresses (Section 3.1). Lung cancer can be categorised as small cell lung cancer or, non-small cell lung cancer (NSCLC). In 2013, there were approximately 27,300 patients with a confirmed diagnosis of NSCLC (Health and Social Care Information Centre 2014b), of these 19,138 patients were diagnosed with Stage IIIb or IV NSCLC. The median survival for Stage III and Stage IV non-small cell lung cancer (NSCLC), in England was 293 days and 100 days respectively in 2013.

Patients with squamous cell NSCLC have a worse prognosis and fewer therapeutic options than other histologies. In England, patients diagnosed with unresectable squamous NSCLC are currently treated with a platinum-based doublet chemotherapy; however, beyond first-line, there are a limited range of treatments available. In England, approximately 25% of patients diagnosed with squamous Stage IIIb/IV NSCLC, are treated with a first-line therapy (approximately 1,706 patients) and 50% of these will fail this line of therapy (approximately 853 patients). Patients eligible for systemic therapy beyond first-line may receive docetaxel, which has modest efficacy and unfavourable safety profile and is not suitable for all patients. Patients may also receive erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that has limited efficacy in patients with squamous NSCLC; however, prescribing data demonstrate that the use of erlotinib is limited and declining in patients who have been previously treated for squamous NSCLC.

Little therapeutic progress has been made since approval of docetaxel over 10 years ago, and no product has demonstrated better survival than docetaxel. There is, therefore, a clear and substantial unmet need for a treatment that improves survival, and has greater tolerability compared with currently available treatments for patients with locally advanced or metastatic squamous NSCLC. Nivolumab meets this need.

Nivolumab is the first licensed immuno-oncology treatment for locally advanced or metastatic squamous NSCLC that acts as a programmed death-1 (PD-1) inhibitor. The clinical evidence for nivolumab is derived from the phase III randomised controlled trial CheckMate 017. This study was stopped early, as the assessment conducted by the independent Data Monitoring Committee (DMC) concluded that the study had met its endpoint, demonstrating significantly superior overall survival (OS) in patients treated with nivolumab compared with patients treated with docetaxel. The results from this trial showed that the median OS rate was 9.2 months for nivolumab compared with 6.0 months for docetaxel, an increase of over 3 months survival benefit. Furthermore, there was a 41% reduction in the risk of death with nivolumab. The number of patients eligible for nivolumab therapy in England is estimated to be 853.

We believe, therefore, that Nivolumab meets NICE's end of life criteria.

The Medicines and Healthcare products Regulatory Agency (MHRA) awarded nivolumab a Promising Innovative Medicine (PIM) designation in the treatment of locally advanced or metastatic NSCLC and it is the first lung cancer drug to be approved through their Early Access to Medicines Scheme (EAMS).

1.1 Statement of decision problem

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously treated locally advanced or metastatic (stage IIIB or IV) squamous NSCLC	As per scope	-
Intervention	Nivolumab	As per scope	-
Comparator(s)	• Docetaxel • Erlotinib (subject to ongoing NICE review of TA 162) • BSC	Base case economic analysis is nivolumab versus docetaxel; a sensitivity analysis of nivolumab versus erlotinib is provided. An economic analysis of nivolumab versus BSC was not possible due to a paucity of data.	Docetaxel is the most relevant comparator for nivolumab in UK clinical practice. Erlotinib is not expected to be standard clinical practice. Clinical evidence for erlotinib was identified via a systematic review, but due to a paucity of data only a limited number of ITC analyses were possible; it is therefore included as a sensitivity analysis in the economic evaluation section. In addition to the lack of comparative data for BSC, BSC is a part of the care package offered to all squamous NSCLC patients, regardless of eligibility for systemic anti-cancer therapies and line of treatment. Furthermore, the economic case of docetaxel versus BSC has been established by (Holmes 2004).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope	-
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	As per scope	-
Subgroups to be considered	No subgroups were identified	As per scope	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	If the evidence allows, consideration will be given to subgroups based on biological markers. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per scope	-

Abbreviations: BSC = Best Supportive Care; ITC = Indirect Treatment Comparison; NICE = National Institute for Health and Care Excellence; NSCLC = Non-Small Cell Lung Cancer; UK = United Kingdom

1.2 Description of the technology being appraised

Nivolumab, an immuno-oncology treatment, is a PD-1 inhibitor and the "first-in-class" in the UK. It is a fully human immunoglobulin G4 (IgG4) monoclonal antibody, and is indicated for the treatment of locally advanced or metastatic squamous NSCLC in pre-treated adults. It is the first lung cancer drug to be approved through the EAMS and the Medicines and Healthcare products Regulatory Agency (MHRA) has designated nivolumab as a PIM in the treatment of locally advanced or metastatic NSCLC.

The main comparator for nivolumab is docetaxel, within its licenced indication. Docetaxel is the standard of care for pre-treated patients with locally advanced or metastatic squamous NSCLC. However, it is associated with modest efficacy and poor tolerability. Erlotinib is also a second-line option in England and Wales as an alternative to docetaxel monotherapy. However, in the UK, there is limited use of erlotinib in clinical practice and its use continues to decline. Although best supportive care (BSC) has been included as a comparator in this submission, it should be recognised that in UK clinical practice, BSC (which comprises a range of supportive measures) is given to all patients with squamous NSCLC regardless of whether they receive systemic therapy.

Table 2: Technology being appraised

UK approved name and brand name	Nivolumab BMS
Marketing authorisation/CE mark status	Nivolumab BMS gained market authorisation on July 20, 2015
Indications and any restriction(s) as described in the summary of product characteristics	Nivolumab BMS is indicated for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults
Method of administration and dosage	IV infusion 3 mg/kg over 60 minutes every 2 weeks

Abbreviations: CE = Cost-Effective; IV = Intravenous; NSCLC = Non-Small Cell Lung Cancer

For patients with locally advanced or metastatic squamous NSCLC previously treated with chemotherapy, there are few effective therapeutic options available. Furthermore, docetaxel, the current standard of care in this patient population is poorly tolerated and has moderate efficacy with limited effect on overall survival (OS). There is a high unmet need in this patient population for whom no new treatments have been developed in the last 10 years.

1.3 Summary of the clinical effectiveness analysis

- The key clinical evidence for nivolumab is derived from the pivotal Phase III, randomised, open-label CheckMate 017 trial evaluating the efficacy, safety and tolerability of nivolumab versus docetaxel in pre-treated advanced or metastatic squamous NSCLC patients.
- CheckMate 017 was stopped early, as the assessment conducted by the independent Data Monitoring Committee (DMC) concluded that the study had met its endpoint demonstrating superior OS in patients treated with nivolumab compared with patients treated with docetaxel.
- Further evidence is derived from two single-arm studies, CheckMate 063 and CheckMate 003, in third- and later-line and heavily pre-treated cohorts, respectively.

- The data from CheckMate 017 show that nivolumab provides an unprecedented survival benefit (41% reduction in death compared to standard of care; Hazard Ratio [HR] = 0.59, p <0.001) with a 1-year survival rate of 42% (95% CI: 34, 50) for nivolumab compared to 24% (95% CI: 17, 31) for docetaxel.
- In Checkmate 017, overall survival benefit was observed regardless of PD-L1 expression
- Furthermore, in Checkmate 017, nivolumab was associated with a significantly improved adverse event (AE) profile. Grade 3-4 treatment-related AEs were 7% in nivolumab compared with 55% in docetaxel, and treatment-related discontinuation rates were 3.1% for nivolumab compared with 10.1% for docetaxel.
- These clinical data present a compelling case that nivolumab represents a 'step-change' in the treatment of squamous NSCLC.
- No subgroups were considered within the economic analysis.

Nivolumab in the treatment of patients with locally advanced or metastatic squamous NSCLC previously treated with chemotherapy fulfils the end of life criteria:

- Patients with advanced or metastatic squamous NSCLC have a short life expectancy of less than 24 months.
- Median OS data from the CheckMate 017 trial is 9.2 months vs. 6.0 months for docetaxel demonstrating that nivolumab extends life by greater than 3 months compared to docetaxel.
- The patient population eligible for nivolumab treatment in this indication is expected to be small (estimated 853 patients in England).

1.4 Summary of the cost-effectiveness analysis

A *de novo* cost-utility (CU) analysis was undertaken to assess the cost-effectiveness of nivolumab in pre-treated patients with locally advanced or metastatic squamous NSCLC. The analysis was based on a standard three-health-state cohort model which used a partitioned survival approach to determine the proportion of patients in each of the three health states (i.e. progression-free, progressed and death). The model structure and health states have been routinely used in previous health technology assessments (HTAs) in oncology.

The base case comparator was docetaxel, which is the current standard of care for advanced NSCLC in a second-line setting. The economic analysis was based primarily on evidence from the CheckMate 017 trial, where docetaxel was the comparator treatment. A sensitivity analysis was also performed comparing nivolumab to erlotinib using an indirect treatment comparison (ITC).

Resource use, costs and utilities were estimated based on information from the CheckMate 017 trial, previous technology appraisals, published sources and clinical experts. As recommended by the National Institute for Health and Care Excellence (NICE), an annual discount rate of 3.5% has been used for both costs and outcomes, measured in quality-adjusted life years (QALYs) and life years gained (LYG). The model perspective is that of the UK National Health Service (NHS) and personal social services (PSS). The base case time horizon of 20 years was applied to ensure the full extent of relevant costs and benefits were captured.

The choice of survival extrapolation was based on NICE Decision Support Unit (DSU) guidance for both OS and progression-free survival (PFS). In the base case analysis, OS was modelled using the log-logistic function as it provided the optimal balance between statistical fit within the trial period where patient-level data existed and long-term clinical plausibility based on real world data (RWD) reported in from the National Lung Cancer Audit (NLCA) and Surveillance, Epidemiology, and End Results (SEER) program registries. The results from the base case analysis are summarised in Table 3, where the log-logistic distribution and the spline 2-knots approach were used to extrapolate OS and PFS, respectively.

Table 3: Results of the base case analysis

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	86,599	2.26	1.30	65,355	1.31	0.76	85,950
Docetaxel	21,243	0.95	0.54				

Abbreviations: LYG = Life Years Gained; QALY = Quality-Adjusted Life Year

There is uncertainty of the length of the long term duration of therapy. Sensitivity analyses of treatment stopping rules at 1 year and 2 years that limited the duration on treatment (DOT) were also undertaken, which resulted in ICERs of £45,470 and £60,923, respectively. This suggests that as DOT is reduced, the ICER is within the cost-effective range.

Deterministic sensitivity analysis revealed that the model was most sensitive to the HR for OS, average body weight, discount rate and utility in the progressive disease state. These factors should be considered in the context of NICE's End of Life criteria and the innovative nature of the technology in an area of high unmet need.

Nivolumab is the first new drug for patients with previously treated, locally advanced or metastatic squamous NSCLC to become available in over 10 years and is the first PD-1 inhibitor to demonstrate a clinically significant survival benefit in locally advanced or metastatic squamous NSCLC. Nivolumab provides an unprecedented survival benefit (41% reduction in mortality compared with standard of care) in patients where no new treatments have been available, representing a step-change in the management of advanced squamous NSCLC.

2 The technology

2.1 Description of the technology

Brand name: Nivolumab BMS

UK approved name: nivolumab

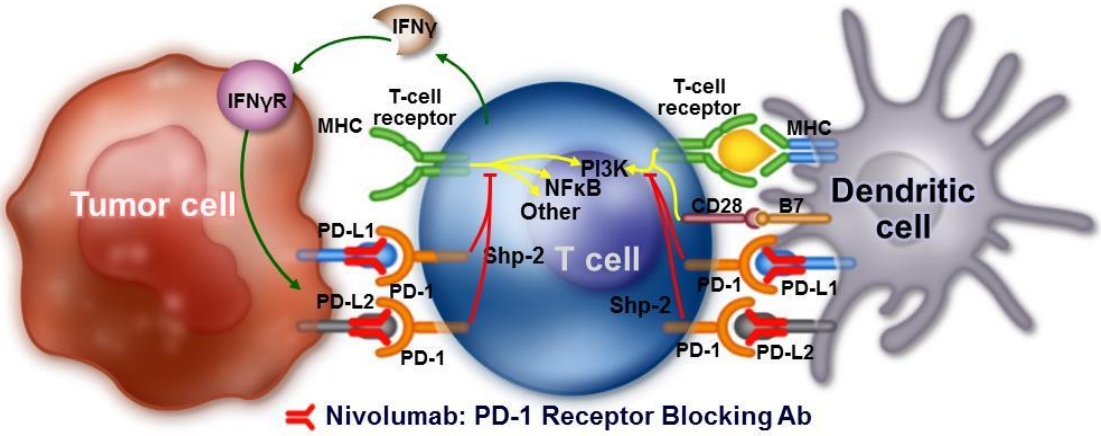
Therapeutic class: Antineoplastic agents, monoclonal antibodies

Brief overview of the mechanism of action:

Conventional anti-cancer therapies generally act through cytotoxicity. They destroy cancer cells “preferentially” due to their fast growing and rapidly dividing nature; however, these treatments are toxic to all rapidly dividing and fast growing cell types. Consequently, non-cancerous cells, such as hair follicles and gut mucosa, are often destroyed alongside cancer cells, resulting in undesirable side effects (such as hair loss and diarrhoea). For non-small cell lung cancer (NSCLC) in particular, there are limited effective and well tolerated treatment options beyond the first-line.

The typical immune response to foreign antigens or cells is the activation of T-cells that can destroy them. Activation of T-cells is regulated through a complex balance of positive and negative signals through receptors on the T-cell surface (Figure 1). Healthy cells can avoid destruction by stimulating inhibitory receptors to suppress the T-cell response. Cancer cells exploit this pathway, by stimulating inhibitory receptors themselves, to avoid destruction and facilitate tumour development (Mellman 2011). Blocking antibodies designed to bind to these inhibitor receptors allows the activation of T-cells to continue, thereby preventing tumour-driven T-cell suppression, as depicted in Figure 1.

Figure 1: Regulation of the T-cell immune response

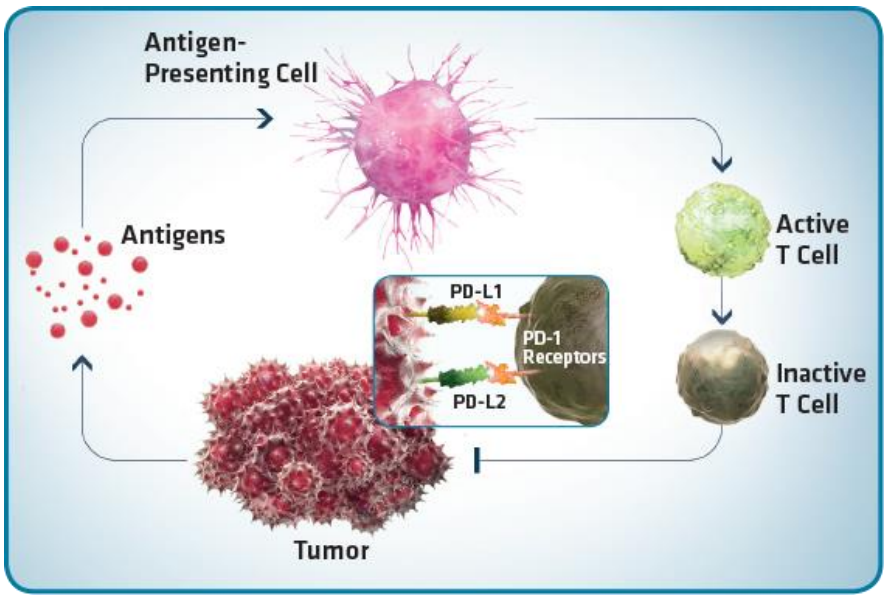


Abbreviation: Ab = Antibody; CD28 = Cluster of Differentiation 28; IFNγ = Interferon gamma; IFNγR = Interferon gamma Receptor; MHC = Major Histocompatibility Complex; NFκB = Nuclear Transcription Factor-κB; PD-1 = Programmed Death 1; PD-L1 = Programmed Death-Ligand 1; PD-L2 = Programmed Death-Ligand 2; PI3K = Phosphoinositide 3-Kinase; Shp-2 = Src homology 2 domain-containing protein tyrosine phosphatase 2

The programmed death-1 (PD-1) receptor is a negative regulator of T-cell activity and is expressed at high levels on activated T-cells. Engagement of PD-1 with its ligands

(programmed death-ligand 1 [PD-L1] and programmed death-ligand 2 [PD-L2]) results in the inhibition of T-cell activation and results in T-cell death. PD-L1 and PD-L2 are expressed on antigen-presenting cells (such as dendritic cells) and may also be expressed by tumours or other cells in the tumour microenvironment (Figure 2) (Brahmer 2010; Chen 2012; Wang 2014). PD-1 has also been shown to control the inhibition of T-cell response in human malignancies (NICE 2014b; Brahmer 2010; Freeman 2000).

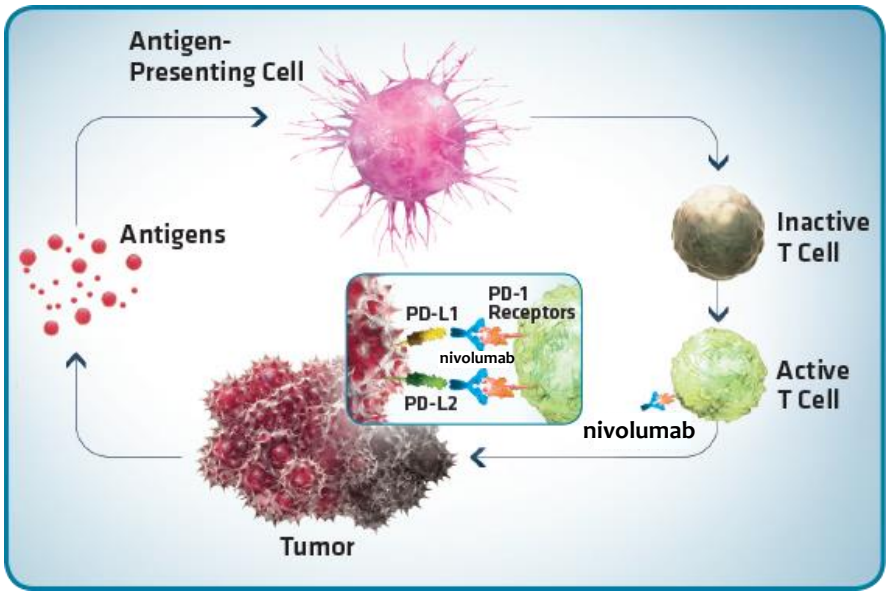
Figure 2: Tumour immune evasion



Abbreviation: PD-L1 = Programmed Death-Ligand 1

Nivolumab (Nivolumab BMS) is the first licensed immuno-oncology treatment for NSCLC and is a human, monoclonal immunoglobulin G4 antibody (IgG4 HuMAb) that acts as a PD-1 inhibitor; blocking the interaction of PD-1 with PD-L1 and PD-L2 (Figure 3) (Wang 2014; Chen 2012). Nivolumab is the first highly-specific PD-1 inhibitor approved for locally advanced or metastatic squamous NSCLC and restores T-cell activity by either preventing inactivation or by reactivating T-cells to mount a direct T-cell attack against tumour cells, i.e. nivolumab stimulates the patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" antigen), resulting in destruction of the tumour (Figure 3).

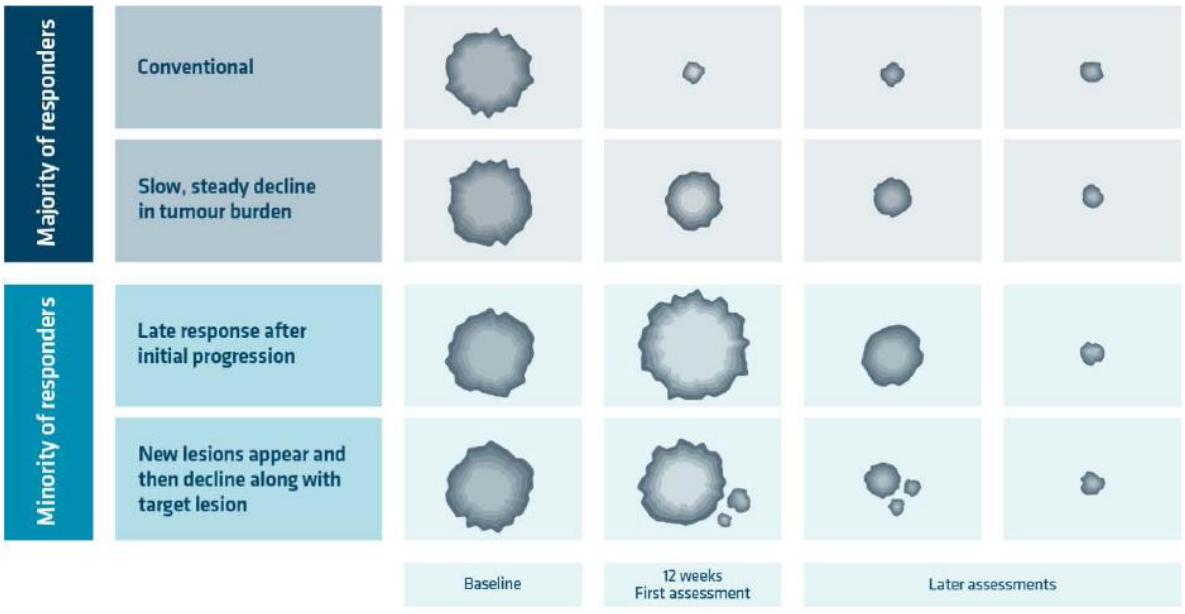
Figure 3: Nivolumab stimulation of immune-mediated destruction



Abbreviation: PD-1 = Programmed Death- 1; PD-L1 = Programmed Death-Ligand 1

Contrary to conventional anti-cancer therapies, where response to treatment is observed as an immediate shrinkage of the tumour, immune-mediated tumour destruction results in varying patterns of response. In some cases, immuno-oncology therapies can have initial effect of making the tumour appear bigger, which is thought to be due to the proliferation of activated T-cells infiltrating the tumour to destroy it. This is commonly referred to as an 'unconventional immune-related response' and can result in 'pseudo-progression' where patients who ultimately achieve a positive clinical outcome may appear to have tumours that appear to have enlarged when assessed in the early stages of treatment. Typical patterns of response observed with immuno-oncology therapies are presented in Figure 4.

Figure 4: Typical patterns of response observed with immuno-oncology



2.2 Marketing authorisation and health technology assessment

Nivolumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 21 May 2015. Marketing authorisation for nivolumab (Nivolumab BMS) was granted on 20 July 2015.

Nivolumab (brand name: Nivolumab BMS) is indicated for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults (Bristol-Myers Squibb 2015c). The Summary of Product Characteristics (SmPC) is included in the Appendix 1. It should be noted that it is anticipated that the brand name will be changed from Nivolumab BMS to Opdivo® in Q3/Q4 2015 by a Type II reconciliation application to the European Medicines agency (EMA).

The European Public Assessment Report (EPAR) is provided in the Appendix 1.

During the assessment of the Marketing Authorisation Application (MAA) for Nivolumab BMS (nivolumab) in the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults, the following issues were discussed by the Committee for Medicinal Products for Human Use (CHMP) in the European Public Assessment Report (EPAR):

Clinical Aspects

From a clinical perspective, the efficacy and safety of nivolumab for the treatment of locally advanced or metastatic squamous NSCLC were investigated in one pivotal trial, an open-label, comparative phase III trial (CA209017), and two supportive studies, a single-arm phase II trial (CA209063) and a dose-escalating phase I trial (MDX1106-03 or CA209003). Based on the results from these clinical trials, the CHMP considered the benefit-risk balance of Nivolumab BMS in the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults favourable.

Conditions of the Marketing Authorisation

As part of the conditions with regard to the safe and effective use of Nivolumab BMS, the CHMP requested the Marketing Authorisation Holder (MAH) to complete some post-authorisation measures including the submission of updated results from the pivotal trial as well as to further explore the value of PD-L1 and other biomarkers to predict the efficacy of nivolumab.

In addition, and as proposed in the nivolumab Risk Management Plan (RMP), additional risk minimisation measures have to be undertaken. These measures entail that, at the time Nivolumab BMS is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Nivolumab BMS will have access to or will be provided with the following educational materials:

- The physician educational material, which contains the SmPC and Adverse Reaction Management Guide (it has information on immune-related adverse events and on how to minimise the safety concern through appropriate monitoring and management)
- A Patient Alert Card, which contains information on other immune-related adverse reactions, signs and symptoms and when to seek help from a healthcare provider along with prescriber details.

These materials are aimed at increasing awareness about the potential immune-related adverse events associated with Nivolumab BMS use, how to manage them and at enhancing the awareness of patients or their caregivers on the signs and symptoms relevant to the early detection of those adverse events.

Nivolumab BMS (nivolumab) for locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults has already been launched and is available in the UK. Nivolumab

has already received a European Marketing Authorisation and is launched in the UK for advanced (unresectable or metastatic) melanoma as a monotherapy in adults.

At the time of submission, marketing authorisation regulatory approval was received in US, Israel and Macau for nivolumab for the treatment of metastatic squamous NSCLC with progression on or after platinum-based chemotherapy. Nivolumab also has approval for the treatment of an advanced melanoma indication in US, Israel, Japan, Korea and Macau.

Nivolumab BMS, will be submitted to the Scottish Medicines Consortium (SMC) and the National Centre for Pharmacoeconomics (anticipated dates of submission October 2015 and September 2015, respectively) for the same indication as this submission.

2.3 Administration and costs of the technology

Table 4: Costs of the technology being appraised

	Description	Cost	Source
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate)		SmPC
Acquisition cost (excluding VAT)*	-	£439.00 per 40mg vial (BMS List Price)	BMS
Method of administration	Intravenous infusion	£269.94	NHS reference cost 2013-2014
Doses	3mg/kg over 60 minutes	£2,634.00 (per dose*)	SmPC
Dosing frequency	Every 2 weeks	-	SmPC
Average length of a course of treatment	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.	-	SmPC
Average cost of a course of treatment	Cost of the technology	£34,769	Treatment cost assumes a mean dose number of 13.2 from CheckMate 017
Anticipated average interval between courses of treatments	Not applicable		
Anticipated number of repeat courses of treatments	Not applicable		
Dose adjustments	Dose escalation or reduction is not recommended		SmPC
Anticipated care setting	Likely hospital or clinic setting		

Abbreviations: VAT = Value Added Tax; SmPC = Summary of Product Characteristics

*Based on an 73kg patient

2.4 Changes in service provision and management

Treatment with nivolumab must be initiated and supervised by physicians experienced in the treatment of cancer.

Hospital oncology units already have the staffing and infrastructure needed for the administration of cancer treatments. It is anticipated that the administration of nivolumab would utilise this existing NHS infrastructure.

The main additional resource use to the NHS is associated with the administration regimen of nivolumab. The 2-weekly dosing requirement represents a more frequent administration

regimen than current therapies (Section 3). This is accounted for in the economic modelling presented in Section 5.

Managing Adverse Events

Nivolumab is generally well tolerated by patients with NSCLC and has a significantly improved AE profile compared to docetaxel. However, AEs observed with immunotherapies such as nivolumab may differ from those observed with non-immunotherapies. Early identification of AEs and intervention are an important part of the safe use of nivolumab. The SmPC states that patients receiving nivolumab should be monitored continuously (at least up to 5 months after the last dose) as an AE with nivolumab may occur at any time during or after discontinuation of nivolumab therapy. This monitoring is expected to occur as part of routine clinical practice.

The immune-based mechanism of action of nivolumab means many of its drug-related AEs are immune-related in nature (irAEs); this profile is in line with other immunotherapies. All irAEs, including severe irAEs, are well characterised and are medically manageable, according to established guidelines, with topical and/or systemic immunosuppressants. They are usually reversible following initiation of appropriate medical therapy, or withdrawal of nivolumab.

A full description of all AEs, along with their severity, is given in Section 4. A full list of AEs and guidelines for discontinuation or withholding of doses in response to irAEs is provided in the SmPC given in Appendix 1.

As detailed in the SmPC for nivolumab, adequate evaluation of the AE should be performed to confirm aetiology or exclude other causes for suspected irAEs. Based on the severity of the irAE, nivolumab should be withheld and corticosteroids administered. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use. Nivolumab must be permanently discontinued for any severe irAE that recurs and for any life-threatening irAE, as specified in the SmPC.

Nivolumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

2.5 Innovation

- Nivolumab is the first immuno-oncology treatment for locally advanced or metastatic squamous NSCLC in the UK receive marketing authorisation
- Nivolumab provides an unprecedented survival benefit (41% reduction in mortality compared with standard of care) in squamous NSCLC patients. There have been no new treatments in the last decade
- The MHRA has designated nivolumab as a PIM in the treatment of locally advanced or metastatic squamous NSCLC
- It is the first lung cancer drug to be approved through the EAMS. A total of 47 patients were accepted onto the EAMS programme
- Nivolumab represents a ‘step-change’ in the treatment of NSCLC in an area of high unmet need

There are currently limited treatment options available for patients diagnosed with squamous NSCLC previously treated with chemotherapy and no new agents have been licensed for previously treated locally advanced or metastatic squamous NSCLC for over 10 years. The unmet need is particularly significant for patients with squamous NSCLC, who typically do not have EGFR or anaplastic lymphoma kinase (ALK) mutations, and hence cannot benefit from available targeted agents.

In the second-line setting, the current UK standard of care is docetaxel chemotherapy, even though this has only modest efficacy and a poor toxicity profile. Erlotinib (an EGFR TKI) offers an alternative treatment option in the second-line setting (given in this context for wild-type patients), but this is under re-review by NICE (ID620). In the third-line setting there are currently no therapies approved by NICE.

Nivolumab is the first immuno-oncology treatment for locally advanced or metastatic squamous NSCLC. It is the first PD-1 inhibitor to show an OS benefit in squamous NSCLC and offers a 'step-change' in the treatment of NSCLC in terms of mechanism of action, degree of clinical benefit, and in addressing a significant unmet medical need. In addition, the MHRA awarded nivolumab a Promising Innovative Medicine (PIM) designation in the treatment of locally advanced or metastatic NSCLC, and it is the first lung cancer drug to be approved through the Early Access to Medicines Scheme (EAMS).

Unlike other PD-1 inhibitors, PD-L1 expression level was not a pre-requisite for inclusion in the nivolumab clinical trial programme in squamous NSCLC. Indeed, the clinical data show nivolumab to be efficacious in patients with both positive and negative PD-L1 expression levels (Section 4.8), meaning it is an effective and well tolerated treatment option for all patients with squamous NSCLC, regardless of PD-L1 expression level.

In summary:

- The ability of tumour cells to evade the immune response is now considered a key hallmark of cancer (Hanahan 2011)
- Nivolumab is the first approved therapy to effectively manipulate the immune system to improve outcomes/survival in locally advanced or metastatic squamous NSCLC, as demonstrated in Phase III studies
- For patients previously treated with chemotherapy, there are few effective therapeutic options available; Docetaxel, the current standard of care in this patient population is poorly tolerated and has poor efficacy
- Nivolumab is the first PD-1 inhibitor licensed in locally advanced or metastatic squamous NSCLC
- No other PD-1 inhibitors are currently available in squamous NSCLC
- Nivolumab is the first new drug for patients with previously treated, locally advanced or metastatic squamous NSCLC to become available in over 10 years
- Nivolumab is the first PD-1 inhibitor to demonstrate a clinically significant survival benefit in locally advanced or metastatic squamous NSCLC
- Nivolumab provides an unprecedented survival benefit (41% reduction in mortality compared with standard of care) in patients where no new treatments have been available, representing a step-change in the management of advanced squamous NSCLC

3 Health condition and position of the technology in the treatment pathway

3.1 Disease background

Lung cancer is the second most common cancer in the UK and has the highest mortality of any cancer. In 2011, lung cancer was the underlying cause for 30,148 deaths in England and Wales, making lung cancer the second and fifth most common cause of death overall for males and females, respectively (Office for National Statistics 2013; Office for National Statistics 2012). Although lung cancer typically affects older patients (median age of diagnosis in England and Wales is 74 years), in 2013 more than one-third of patients diagnosed with lung cancer were aged between 50 and 70 years (Health and Social Care Information Centre 2014b). Approximately 54.4% of patients with lung cancer in 2013 were male (Health and Social Care Information Centre 2014b).

There are two broad groups of lung cancer that differ based on histology: NSCLC and small-cell lung cancer (SCLC). Approximately 84% of lung cancer cases in England and Wales fall within the NSCLC category: in 2013, there were 27,300 patients with NSCLC in England (Health and Social Care Information Centre 2014b). NSCLC can be further divided into squamous NSCLC and non-squamous NSCLC, based on the cell type responsible for the tumour. The majority of patients with NSCLC have a histology that is non-squamous in origin; approximately 36% of patients within England and Wales had squamous NSCLC in 2013 (Health and Social Care Information Centre 2014b; Powell 2013). In addition, two key genetic mutations have been identified for non-squamous NSCLC: EGFR and ALK (United States National Library of Medicine 2015b; United States National Library of Medicine 2015a). These mutations are predominantly present in non-squamous NSCLC as patients with squamous NSCLC rarely have EGFR or ALK mutations (Lindeman 2013; Ameratunga 2014; Heist 2012; Fiala 2013a; Fiala 2013b; Cancer Genome Atlas Research Network 2012).

Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease and unresectable locally advanced disease; stages IIIA and IIIB) or to other parts of the body (metastatic disease; stage IV). Tumours that are staged IIIA and IIIB are termed ‘locally advanced’, whereas tumours that are stage IV are termed metastatic. While stage IIIA tumours may be resectable, stage IIIB tumours are usually not resected; hence, stage IIIB and IV tumours are often considered together and described as ‘advanced NSCLC’.

In 2013, there were 19,138 patients with stage IIIB or IV lung cancer in England, representing approximately 70% of all the 27,300 NSCLC cases (Health and Social Care Information Centre 2014b). The median survival for all lung cancer in England and Wales was 232 days, while the median survival for all stage III patients with NSCLC was 293 days (Health and Social Care Information Centre 2014b). In contrast, the median survival for stage IV patients with NSCLC was only 100 days (Health and Social Care Information Centre 2014b). On average, patients with lung cancer lose 15.2 years of life, as reported in the SEER Cancer Statistics Review (Howlader 2015).

In addition to the high mortality associated with NSCLC, a large proportion of patients experience increasingly severe morbidity as they progress from localised to metastatic disease (Schrump 2011). Approximately 90% of patients with advanced NSCLC experience two or more disease-related symptoms, such as cough, dyspnoea, pain, anorexia, or fatigue (Hirsh 2014). These symptoms, in turn, can cause psychological distress and may have a negative impact on a patient’s health-related quality of life (HRQoL). High degrees of

psychological distress influence the emotional well-being in both patients and their families. In one survey, 68% of patients preferred a therapy that would improve disease-related symptoms without prolonging their life as opposed to treatment(s) that slightly prolonged their survival without improving symptoms (Cella 2003). A separate study of 107 caregivers for patients with lung cancer demonstrated that caregivers experience significantly higher odds of depression, insomnia, headache and gastrointestinal symptoms (all $p<0.02$) as well as worse HRQoL. Caregivers of patients with lung cancer also reported higher rates of work impairment (Jassem 2015).

In England, patients with locally advanced, unresectable (stage IIIB) or metastatic (stage IV) squamous NSCLC are typically treated with platinum-based doublet chemotherapy in the first-line, unless they are otherwise unfit for chemotherapy (Section 3.2). Treatment options beyond first-line are very limited for patients with squamous NSCLC; patients eligible for systemic therapy may receive docetaxel, which has significant toxicities and is not suitable for all patients. Patients may also receive erlotinib, an EGFR TKI that has limited efficacy in patients with squamous NSCLC as this patient population is predominantly without an EGFR mutation. It should be noted that prescribing data demonstrate that the use of erlotinib is limited and declining in patients who have been previously treated for squamous NSCLC in UK clinical practice. Furthermore, erlotinib, is currently part of a multiple technology appraisal (MTA) by NICE and the draft appraisal committee document currently states that it is not recommended, which is likely to further limit the use of erlotinib in patients with squamous NSCLC who have been previously treated.

Traditional therapies (surgery, radiation, chemotherapy, and targeted therapies) have offered benefits to some patients; however, long-term survival, with a good HRQoL, remains elusive for most patients with advanced lung cancer. While there have been therapeutic advances to address this unmet need in some patients with specific mutations, the main systemic treatment for the majority of patients with advanced lung cancer remains cytotoxic chemotherapy, in both treatment-naïve and pre-treated patients.

Whilst BSC has been included as a comparator for this decision problem, in UK clinical practice, all patients with lung cancer are provided with BSC at all points in the treatment pathway, regardless of whether they receive systemic therapy. In addition, there is a paucity of data available for use of BSC alone in locally advanced or metastatic pre-treated squamous NSCLC pre-treated patients.

While there has been some innovation in treating NSCLC, this has only helped a small proportion of patients. In the non-squamous setting, improvements have been seen with the use of targeted agents directed at patients with EGFR+ and ALK+ gene mutations, but many of these agents are only effective in a small subset of patients and have had limited to no efficacy in patients with squamous NSCLC (Heist 2012; Fiala 2013b; Fiala 2013a; Cancer Genome Atlas Research Network 2012).

Therefore, there is a significant unmet need for a treatment that produces symptomatic improvement, improves survival, and has improved tolerability compared with currently available treatments for patients with locally advanced or metastatic squamous NSCLC, and nivolumab meets this need.

3.2 Clinical pathway of care

For the majority of people with NSCLC with squamous histology, the aims of therapy are to prolong survival and improve HRQoL. Treatment of patients with squamous NSCLC depends on a patient's PS and personal choice.

BSC, such as analgesics, antiemetics, and palliative interventions, are a part of the care package offered to all patients with squamous NSCLC, regardless of eligibility for systemic anti-cancer therapies and line of treatment.

An overview of treatments used in clinical practice in England, according to NICE guidance, is provided in Figure 5.

First-line treatment (locally advanced or metastatic squamous NSCLC)

NICE clinical guideline 121 (CG121) recommends platinum-based doublet chemotherapy (cisplatin or carboplatin in combination with gemcitabine, vinorelbine, or a taxane) as a first-line treatment option for people with previously untreated stage III or IV NSCLC and good PS (NICE 2011).

Second-line treatment (locally advanced or metastatic squamous NSCLC)

For patients with locally advanced or metastatic NSCLC whose disease has progressed after non-targeted chemotherapy, NICE recommends systemic monotherapy (docetaxel or erlotinib) as options in certain circumstances (NICE 2011; NICE 2012b).

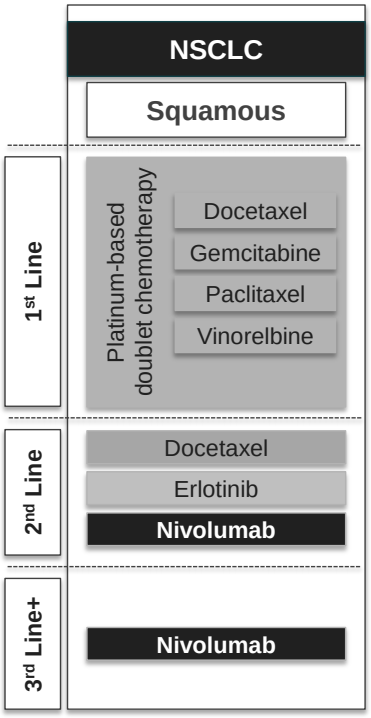
Third-line treatment (locally advanced or metastatic squamous NSCLC)

For all patients with NSCLC, there are no third-line therapies recommended by NICE.

Introduction of nivolumab as a treatment option in locally advanced or metastatic squamous NSCLC

Nivolumab will offer another treatment option for patients with locally advanced or metastatic squamous NSCLC after failure of prior chemotherapy, as indicated in Figure 5.

Figure 5: Overview of systemic treatments in the UK for locally advanced or metastatic squamous NSCLC with the introduction of nivolumab (adapted from NICE guidance CG121 and TA258)



Source: (NICE 2011; NICE 2012a)

Abbreviations: NSCLC = Non-Small Cell Lung Cancer; UK = United Kingdom; Note: All patients may also receive BSC in any line, regardless of therapy

3.3 Life expectancy, prevalence and incidence of the disease

Population estimates

It is estimated that 27,300 patients will be diagnosed with NSCLC, of whom approximately 19,138 are expected to be diagnosed with locally advanced or metastatic NSCLC (Health and Social Care Information Centre 2014b). Approximately 36% of these patients will present with advanced or metastatic squamous NSCLC and it is estimated that 25% of these patients will receive first-line therapy (1,706 patients) (Powell 2013; NICE 2010b). Half of the patients receiving first-line therapy are assumed to fail (Sculier 2009), and will thus be eligible for second-line treatment with nivolumab.

Taking these considerations into account, alongside the expected market share of nivolumab, we estimate the likely number of patients in England and Wales with squamous NSCLC who could receive second-line treatment with nivolumab could be around 853 in 2015.

For more details regarding the calculation of the population eligible to receive nivolumab, please refer to Section 6.

Life expectancy

Patients with advanced or metastatic squamous NSCLC have limited life expectancy. While data for English-only patients with squamous NSCLC are not available, in 2013, the median survival for all stage III patients with NSCLC in England and Wales was 293 days and the median survival for stage IV patients with NSCLC was only 100 days (Health and Social Care Information Centre 2014b). Data from the UK suggest the 1-year relative survival rate (by stage at diagnosis) is 71%, 48%, 35%, and 14% for stage I, II, III, and IV disease, respectively (Cancer Research UK 2015c).

3.4 Clinical guidance and guidelines

NICE guidance and clinical guidelines

Current clinical practice in England and Wales is driven by NICE guidance. The key guidelines and technology appraisals in NSCLC are as follows:

Related guidelines and pathways:

Lung Cancer: The diagnosis and treatment of lung cancer (Clinical Guideline CG121). April 2011. http://www.nice.org.uk/guidance/cg121 (NICE 2011)

Quality Standard No. 17, Mar 2012, 'Quality standard for lung cancer'. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp (NICE 2012c)

NICE Pathway: Lung cancer. Pathway created: Mar 2012. http://pathways.nice.org.uk/pathways/lung-cancer (NICE 2015b)

London Cancer Alliance. LCA Lung Cancer Clinical Guidelines. December 2013. http://www.londoncanceralliance.nhs.uk/media/62369/Lung%20Cancer%20Clinical%20Guidelines%20041213%20FINAL%20REV.pdf (London Cancer Alliance 2013)

Related NICE technology appraisals:

TA310: Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer. April 2014. http://www.nice.org.uk/guidance/ta310 (NICE 2014a)

TA162: Erlotinib for the treatment of non-small-cell lung cancer. November 2008. http://www.nice.org.uk/guidance/ta162 (NICE 2012b)

TA192: Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. July 2010. http://www.nice.org.uk/guidance/ta192 (NICE 2010a)

TA124: Pemetrexed for the treatment of non-small-cell lung cancer. August 2007. http://www.nice.org.uk/guidance/ta124 (NICE 2007)

In development: Lung cancer (non-small cell, second line) – erlotinib and gefitinib (revision of TA162 and TA175) (ID620). Expected date of issue to be confirmed. https://www.nice.org.uk/guidance/gid-tag347/documents/erlotinib-and-gefitinib-for-treating-nonsmallcell-lung-cancer-that-has-progressed-following-prior-chemotherapy-review-of-ta162-and-ta175-appraisal-consultation-document (NICE 2015a)

In development: Nintedanib for treating previously treated metastatic non-small cell lung cancer (ID438). Expected July 2015. https://www.nice.org.uk/guidance/indevelopment/gid-tag449 (NICE 2015c)

3.5 Issues relating to current clinical practice

In the UK, patients with squamous NSCLC are often diagnosed late in the progression of their disease; the median age of diagnosis in the UK is 74 years (Health and Social Care Information Centre 2014b). Due to their age and/or comorbities, most patients in the UK are unlikely to receive systemic treatment. Furthermore, first-line therapy in this patient population is a platinum-based combination therapy, which is associated with high toxicity and may not be suitable for many patients. Consequently, the mortality rate in these patients is high and the OS rate is low following first-line therapy, with a short duration of survival. Long-term survival, with a concomitant good HRQoL, is not currently deemed achievable with current treatments in this patient population.

In second-line patients, docetaxel has been the standard of care with no new treatments in this patient population for the last decade in the UK. Erlotinib has been recommended for use in the second-line setting for squamous NSCLC patients, but this recommendation is currently under review by NICE. There is currently no recommended treatment for patients who fail second-line therapy; therefore, third-line treatment varies for patients with locally advanced or metastatic squamous NSCLC in UK clinical practice.

BSC is used in the case where patients are not eligible or do not wish to undergo systemic therapy. There is an underlying BSC treatment pathway that is provided to all patients.

3.6 Assessment of equality issues

No equality issues are foreseen.

4 Clinical effectiveness

- The key clinical evidence for nivolumab is derived from the pivotal Phase III, randomised, open-label CheckMate 017 trial evaluating the efficacy, safety and tolerability of nivolumab versus docetaxel in advanced or metastatic pre-treated squamous NSCLC patients
- CheckMate 017 was stopped early, as the assessment conducted by the independent DMC concluded that the study had met its endpoint demonstrating superior OS in patients treated with nivolumab compared with patients treated with docetaxel
- CheckMate 017 met its primary objective, demonstrating a significant improvement in OS with nivolumab versus docetaxel in previously treated patients with advanced squamous NSCLC:
    - 41% reduction in risk of death with nivolumab (HR 0.59, p<0.001)
    - 1-year OS: 42% (95% CI: 34, 50) vs. 24% (95% CI: 17, 31);
    - Median OS: 9.2 months (95% CI: 7.3, 13.3) vs. 6.0 months (95% CI: 5.1, 7.3).
- The study demonstrated consistent, statistically significant superiority of nivolumab over docetaxel across the secondary endpoints of overall response rate (ORR) and PFS:
    - ORR: 20% (95% CI: 14, 28) vs. 9% (95% CI: 5, 15) (p=0.008);
    - 1 year PFS: 21% (95% CI: 14, 28) vs. 6% (95% CI: 3, 12);
    - Median PFS: 3.5 months (95% CI: 2.1, 4.9) vs. 2.8 months (95% CI: 2.1, 3.5) (HR 0.62, p<0.001).
- Similar survival outcomes were observed regardless of tumour PD-L1 expression level
    - No detriment was observed in PD-L1 low expressors.
- Further evidence is derived from two single-arm studies, CheckMate 063 and CheckMate 003
    - CheckMate 063 - a single arm Phase II study in third-line+ patients with squamous NSCLC
    - CheckMate 003 - a dose escalation expansion cohort Phase Ib study in a heavily pre-treated patient population with advanced NSCLC, melanoma, kidney, colorectal or castration-resistant prostate cancer. Patients with NSCLC were stratified for squamous versus non-squamous cell histology
    - Results from these two non-randomised, uncontrolled studies demonstrated OS benefit and PFS consistent to that observed in the pivotal study
- The current standard of care in the UK for second-line squamous NSCLC is docetaxel, and this was used as the comparator in the trial. It is associated with modest efficacy and poor tolerability, and there is hence a significant unmet medical need in this group of patients

- The comparison of nivolumab with erlotinib and BSC is via an indirect treatment comparison (ITC) in the absence of direct head-to-head trial data (Appendix 6)
    - In pre-treated patients receiving second-line therapy, it was estimated that OS was better with nivolumab compared to erlotinib, with a [redacted] probability that patients will have a better survival with nivolumab than erlotinib; however, this difference failed to reach the statistical significance by a very small margin
    - In patients receiving second- or further-line of therapy, nivolumab was associated with statistically significantly higher overall survival compared with placebo (p=0.006)
    - It was estimated that the PFS was significantly better with nivolumab compared to erlotinib (p<0.001) in the second-line setting. No additional study was identified in patients receiving second- or further-line therapy

4.1 Identification and selection of relevant studies

Search strategy

A full systematic review has previously been conducted by Liverpool Reviews and Implementation Group (LRiG) as part of the MTA to NICE for erlotinib and gefitinib (review of TA162 and TA175; currently ID620) (NICE 2015a). This review assessed the efficacy, safety and tolerability of erlotinib and gefitinib in a NSCLC patient population that had progressed on previous chemotherapy. As the decision problem for this previous evaluation was similar to the decision problem for nivolumab in terms of population, interventions, comparators, and outcomes, a decision was made to update and expand this review to include more recent studies, additional comparators, and additional data sources, such as conference proceedings. A comparison of the two reviews, including deviations from the LRiG review, is given in Appendix 2.

The clinical systematic review included a broad NSCLC population, namely, both squamous and non-squamous NSCLC in line with the LRiG reviews. The selection of studies relevant to the NICE decision problem (i.e. squamous only) is discussed below. Searches of the electronic databases and relevant conference proceedings were made to 13 March 2015 (Table 5). Due to the timing of the conference, ASCO 2015 was searched and included in the systematic review. The full search strategy is given in Appendix 2.

Table 5: Summary of data sources for the systematic review

Search strategy component	Sources	Date limits
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies (NICE 2015e; CADTH 2014; IQWIG 2008; NICE 2015d)	MEDLINE® MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL)	Original review: For Erlotinib and Gefitinib: 1st January 2013 to 13th March 2015 For all other interventions not included in the MTA of Erlotinib and Gefitinib: database inception to 13th March 2015

Abbreviations: Embase® = Excerpta Medica Database; HTA = Health Technology Assessment; MEDLINE® = Medical Literature Analysis and Retrieval System Online; MTA = Multiple Technology Appraisal

In addition to the database searches, conferences were searched for the last 3 years (2012, 2013, 2014) (Table 6). Due to the timing of the conference, ASCO 2015 was also searched.

Table 6: Conferences searched for the systematic review and the service provider used

Conference	Dates	Website
American Society of Clinical Oncology (ASCO)	2012	http://meetinglibrary.asco.org/subcategories/2012%20ASCO%20Annual%20Meeting
	2013	http://meetinglibrary.asco.org/subcategories/2013%20ASCO%20Annual%20Meeting
	2014	http://meetinglibrary.asco.org/subcategories/2014%20ASCO%20Annual%20Meeting
	2015	http://meetinglibrary.asco.org/subcategories/2015%20ASCO%20Annual%20Meeting
European Society for Medical Oncology (ESMO)	2012	http://www.esmo.org/Conferences/Past-Conferences/ESMO-2012-Congress
	2013	http://www.esmo.org/Conferences/Past-Conferences/European-Cancer-Congress-2013
	2014	http://www.esmo.org/Conferences/Past-Conferences/ESMO-2014-Congress
World Conference on Lung Cancer (WCLC)	2011	http://journals.lww.com/jto/toc/2011/06001
	2013	http://www.2013worldlungcancer.org/

Abstracts of citations identified through the searches were reviewed for inclusion based on title and abstract alone. Full-text copies of studies that potentially met the inclusion criteria were obtained. Full-text papers were screened and included or excluded accordingly. Data from the studies were extracted by two analysts and any discrepancies were reconciled by a third independent analyst. A critical appraisal of the study, using the assessment criteria recommended in the NICE manufacturer's template, was also conducted in a similar manner.

Study selection

The search strategy for the clinical systematic literature review for this submission included a broad NSCLC patient population (both squamous and non-squamous NSCLC). This was to ensure consistency between the original review (conducted by LRiG) and this update. The

NICE decision problem for this submission, as stated in Section1.1, is a patient population defined as adult patients with locally advanced or metastatic squamous NSCLC after prior treatment with chemotherapy. In order to align with the NICE decision problem and the marketing authorisation for nivolumab, all included studies were screened to only include studies that recruited patients with squamous NSCLC or studies with a mixed population with a subgroup analysis of patients with squamous NSCLC.

Eligibility criteria used in the clinical systematic review are listed in Table 7, including the additional step to restrict to patients with squamous NSCLC.

Table 7: Eligibility criteria used in clinical search strategy

	Criteria	Rationale
Inclusion criteria	Population • Age: Adults (≥18 years) • Gender: Any • Race: Any • Disease: Locally advanced or metastatic NSCLC • Line of therapy: all patients with at least one prior therapy	The patient population has been restricted to match that stated in the decision problem for nivolumab in the treatment of NSCLC
	Intervention • Nivolumab	Intervention defined by the NICE decision problem for treatment of patients with squamous and non-squamous NSCLC
	Comparators* Second- or further-line of therapy using: • Afatinib • **Docetaxel** • **Erlotinib** • Nintedanib in combination with docetaxel • Gefitinib • Crizotinib • Ceritinib • Pemetrexed • Platinum therapy (in combination with gemcitabine, vinorelbine, pemetrexed, or taxane) • Placebo • **BSC***	All comparators defined by the NICE decision problem for treatment with nivolumab for patients with squamous and non-squamous NSCLC were included in the search All comparators were included in the systematic review to potentially enable both direct and indirect comparisons between the interventions of interest It should be noted that for the squamous population the relevant comparators were: • Docetaxel • Erlotinib • BSC
	Study design • RCTs with any blinding status	RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of interventions. To enhance the quantity of evidence, studies with double blind, single blind, and open label design were included
	Language • Only studies with the full-text published in English language were included	The restriction would not limit results substantially due to data availability in English language
	Publication timeframe for literature searches • Erlotinib and gefitinib: 1st January 2013 to 13th March 2015 • Other included interventions: database inception to 13th March, 2015	• Erlotinib and gefitinib studies before 2013 were retrieved from MTA (Liverpool reviews and Implementation Group 2013) • Studies that are presented at conferences are usually

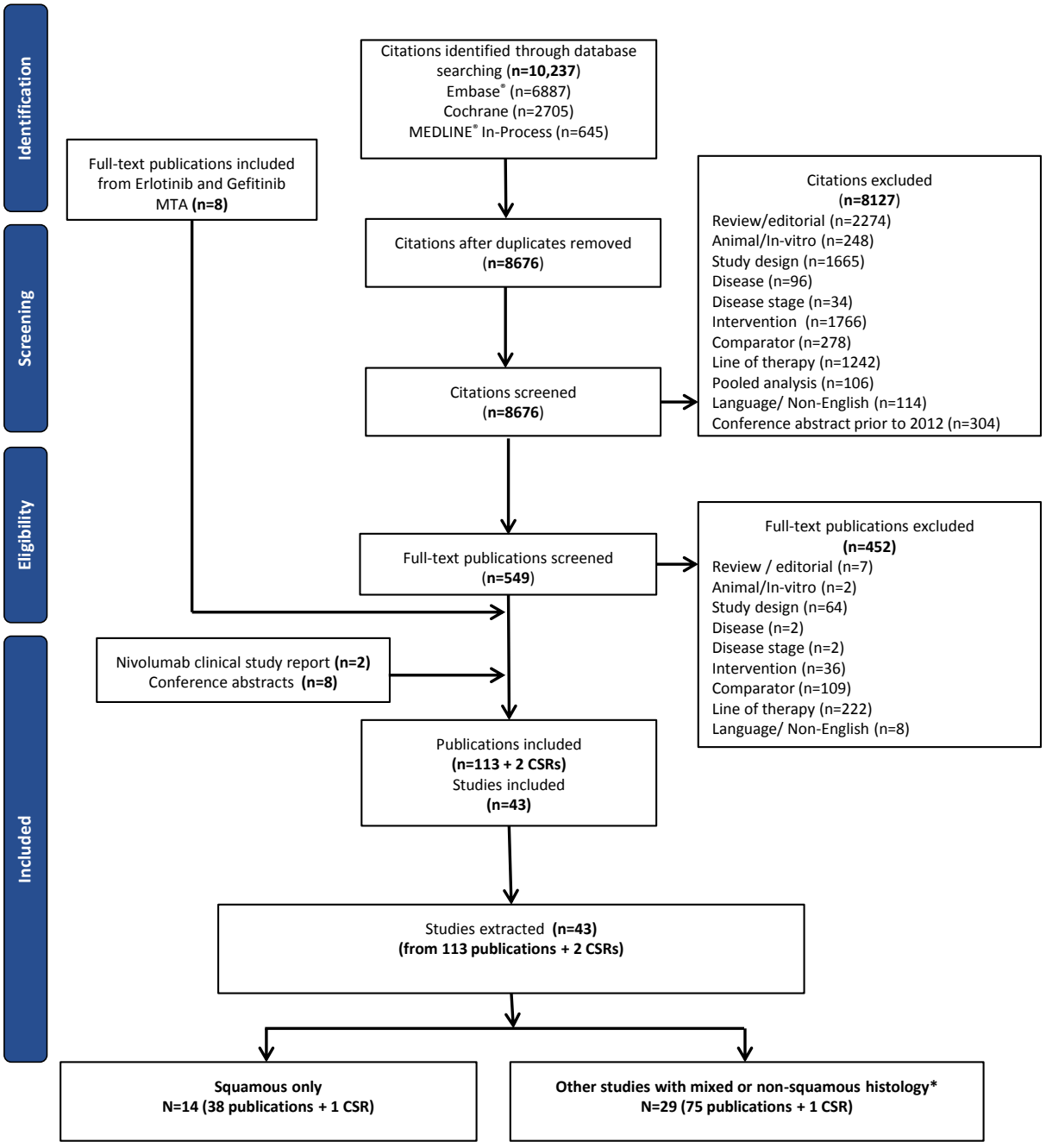
	Criteria	Rationale
	Publication timeframe for conference searching • ASCO: 2012, 2013, 2014 and 2015 • ESMO: 2012, 2013 and 2014 • WCLC: 2011 and 2013	published in journals within 3 years
Exclusion criteria	Excluded population • Patients without a locally advanced or metastatic NSCLC • Children or adolescents (<18 years of age) • Mixed patient population studies where subgroup data for adult patients are not reported • Treatment-naive patients who have not received any prior therapy • Patients receiving first-line therapy • Studies enrolling patients receiving first- or further-line therapy with no sub-group data for patients receiving further-line therapy	• This study population was not relevant to the decision problem
	Excluded interventions/comparators • Studies not assessing any of the included interventions • Studies assessing combination of included and non-included intervention • Studies where interventions are administered for the treatment of AEs • Studies investigating the role of radiotherapy, chemo-radiotherapy, or surgery • Studies assessing interventions used to control the symptoms of the disease such as erythropoietin to treat anaemia, antibiotics to treat infections, and various types of pain medication • Studies assessing adjuvant or neoadjuvant therapy • Studies comparing different doses of the same intervention (i.e. dose-ranging studies), two formulations of the same intervention, and intervention with two different routes of administration	• These interventions are not relevant to the decision problem
	Excluded comparators • Studies assessing comparators other than the included comparators • Studies assessing combination of included and non-included comparators • In line with the MTA, we have not included studies that compare included comparators (e.g. erlotinib) with the combination of included comparator +	• These comparators are not relevant to the decision problem • Studies assessing included intervention with the combination of included + non-included intervention will not contribute to the analysis due to lack of a common

	Criteria	Rationale
	non-included comparator (e.g. erlotinib + bevacizumab)	comparator
	Study design • Non-randomised controlled trials • Prospective/retrospective cohort studies • Single-arm studies • Case studies and case reports • Case-control studies • Cross-sectional studies • Review, letters to the editors, and editorials	• The design of such studies was not relevant to the decision problem
Further selection of studies to squamous NSCLC	Study population was further restricted to include patients with squamous NSCLC only	Patient population restricted to squamous only histology in line with the NICE decision problem and the marketing authorisation for nivolumab

Abbreviations: BSC = Best Supportive Care; LRiG = Liverpool Reviews And Implementation Group; MTA = Multiple Technology Appraisal; NICE = National Institute for Health and Care Excellence; NSCLC = Non-Small Cell Lung Cancer; RCT = Randomised Controlled Trial; Note: * BSC includes no treatment, observation alone, or any other criteria defined by author(s). Additionally, it comprises a number of treatments, which may include (though are not restricted to) non-chemotherapy drugs, palliative care, and even radiotherapy for a small number of patients. *NOTE: due to the broad inclusion criteria of NSCLC (regardless of histology), comparators relevant to both squamous and non-squamous patients were included.

A PRISMA flow diagram showing the number of studies included and excluded at each stage of the systematic review is presented in Figure 6.

Figure 6: PRISMA flow diagram of the systematic review process



Abbreviations: CSR = Clinical Study Report; EMBASE = Excerpta Medica Database; MEDLINE® = Medical Literature Analysis and Retrieval System Online; MTA = Multiple Technology Assessment. *no subgroup data reported for squamous only patients

As shown in the PRISMA flow diagram, 43 studies (reported in 113 publications and 2 clinical study reports [CSR]) met the broader inclusion/exclusion criteria of the systematic review which included patients with both squamous and non-squamous histology. Of these, 14 studies provided data explicitly for pre-treated patients with squamous NSCLC. Only one of these studies provided data for nivolumab in patients with squamous NSCLC (CheckMate 017), and thirteen studies provided data for the comparators (docetaxel, erlotinib and BSC) in pre-treated squamous NSCLC patients. A further 29 studies included either non-squamous patients, or patients with mixed histology but with no sub-group data for the squamous population, and were therefore not considered relevant to the decision problem.

A full list of studies relevant to the decision problem is given in Table 8. A full list of studies included in the systematic review but not relevant to the decision problem is given in the Appendix 7.11. The list of studies that were included in the systematic review and were relevant to the decision problem but were excluded from the network meta-analysis including the reason for exclusion is given in Appendix 7.10. A full list of excluded studies is given in Appendix 2.1.

In UK clinical practice, the most relevant comparator to this patient population is docetaxel and therefore this is the therapy that is mostly likely to be displaced. The use of erlotinib in the patient population is low and its use in clinical practice in England has been steadily declining. Whilst BSC has been included as a relevant comparator by NICE, it is understood that some degree of supportive therapy is currently used in all patients. Whilst the exact therapies forming BSC vary (radiation therapy, analgesics, antiemetics and palliative interventions), almost all patients will receive some type of BSC regardless of therapy. BSC is therefore part of the care package offered to all squamous NSCLC patients. There is a paucity of data relating to the use of BSC alone in locally advanced or metastatic squamous NSCLC pre-treated patients..

Evidence for a comparison of nivolumab with docetaxel can be derived from the CheckMate 017 clinical trial; comparison of nivolumab with erlotinib or BSC requires an ITC. Whilst the systematic review described within this section includes both erlotinib and BSC as comparators there is a distinct paucity of data for these treatments. This limitation is described in further detail later in this section.

Table 8: Summary of methodology of RCTs reporting data for pre-treated squamous NSCLC population

Trial ID (Acronym)	Primary reference	Intervention/ comparators	Patient population
Br.21	(Shepherd 2005)	Erlotinib BSC	• Stage IIIB or IV NSCLC • One or two prior chemotherapy
CheckMate 017 (CA209017)	(Brahmer 2015a)	Nivolumab Docetaxel	• Stage IIIB or IV NSCLC • Recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease
EMPHASIS	(Peters 2015)	Erlotinib Docetaxel	• Advanced squamous NSCLC patients • Progression after standard platinum-based chemotherapy doublet
HORG	(Karampeazis 2013)	Pemetrexed Erlotinib	• Stage IIIB or IV NSCLC • Progression after one or two chemotherapy lines
JMID	(Sun 2013)	Pemetrexed Docetaxel	• Stage IIIB or IV NSCLC
LUME-LUNG 1	(Reck 2014)	Docetaxel plus Nintedanib Docetaxel	• Stage IIIB or IV recurrent NSCLC • Relapse of failure of one previous first-line chemotherapy
	(Juan 2014)	Docetaxel + Erlotinib Erlotinib	• Stage IIIB or IV NSCLC • PD with previous chemotherapy
	(Kim 2015)	Pemetrexed Gefitinib	• Stage IIIB or IV NSCLC • Progression after 1st or 2nd line chemotherapy
	(Li 2012)	Pemetrexed Docetaxel	• Stage IIIB or IV NSCLC • Only one prior chemotherapy regimen for advanced disease

Trial ID (Acronym)	Primary reference	Intervention/ comparators	Patient population
LUX-Lung 8	(Soria 2015)	Erlotinib Afatinib	• Stage IIIB/IV squamous cell NSCLC • Failure of platinum-based chemotherapy
NVALT-7	(Smit 2009)	Pemetrexed Carboplatin + pemetrexed	• NSCLC • Progression after cytotoxic therapy, which included a platinum compound, with the last cycle administered ≥3 months before entry
NVALT-10	(Aerts 2013)	Erlotinib Erlotinib + Docetaxel/Pemetrexed	• Locally advanced or metastatic NSCLC • Progressed on first-line platinum-based chemotherapy
TAILOR	(Garassino 2013)	Docetaxel Erlotinib	• Locally advanced or metastatic NSCLC • Recurrence or progression after platinum-based chemotherapy
TITAN	(Ciuleanu 2012)	Erlotinib) Docetaxel/Pemetrexed	• Advanced NSCLC • Progression after standard platinum-based chemotherapy doublet

Abbreviations: CNS = Central Nervous System; CT = Computerised Tomography; ECOG = European Cooperative Oncology Group; EGFR = Epidermal Growth Factor Receptor; KPS = Karnofsky Performance Status; MRI = Magnetic Resonance Imaging; PS = Performance Status; NSCLC = Non-Small Cell Lung Cancer; PD = Progressive Disease; RECIST= Response Evaluation Criteria in Solid Tumors; TKI = Tyrosine-Kinase Inhibitor

4.2 List of relevant randomised controlled trials

Only one randomised controlled trial (RCT) was identified in the clinical systematic review that evaluated nivolumab in a squamous NSCLC patient population; this was the CheckMate 017 study of nivolumab compared with docetaxel in patients with locally advanced or metastatic squamous NSCLC after one prior therapy. This is the only study relevant to the decision problem described in Section1.1. The data presented in Sections 4.2 to 4.8 are from the CheckMate 017 study (Table 9), and are from both published and unpublished sources.

On 10 January 2015, the independent Data Monitoring Committee (DMC) recommended early termination of the CheckMate 017 study on the basis of a pre-specified interim analysis, which showed that OS among patients receiving nivolumab was superior to that among those receiving docetaxel. Planned enrolment was complete before the study was stopped.

We report the results of the interim analysis in Sections 4.2 to 4.8, which are based on a 15 December 2014 database lock. It is worth noting that another database lock took place on [redacted]; however, the data were not available at the time of writing this submission.

Table 9: List of relevant RCTs to the Decision Problem

Trial no. (acronym)	**CheckMate 017 (CA209017)**
Phase	Phase III
Population	Adult patients with squamous cell NSCLC whose disease has progressed during or after one prior platinum doublet-based chemotherapy regimen.
Intervention	Nivolumab 3mg/kg Q2W until disease progression
Comparator	Docetaxel 75mg/m² Q3W until disease progression
References	**Primary reference:** (Brahmer 2015a; Brahmer 2015b) **Secondary reference:** (Bristol-Myers Squibb 2015a)

Abbreviations: mg = Milligrams; m^2 = Metres Squared; NSCLC = Non-Small Cell Lung Cancer; Q2W = Every 2 Weeks; Q3W = Every 3 Weeks; RCTs = Randomised Controlled Trials

CheckMate 017 was the pivotal Phase III, global, randomised, open-label trial of nivolumab monotherapy versus docetaxel in patients with advanced or metastatic squamous NSCLC whose disease had progressed during or after one prior platinum doublet-based chemotherapy regimen. Docetaxel represents the current standard of care therapy upon progression from first-line therapy for patients with locally advanced or metastatic squamous NSCLC in the UK, and as such, is listed as a key comparator in the NICE Decision Problem (Section 1.1). The CheckMate 017 study provides a direct comparison of nivolumab with docetaxel.

4.3 Summary of methodology of the relevant randomised controlled trials

As stated in the Decision Problem (Section 1.1), the main comparator for nivolumab in this patient population is docetaxel. CheckMate 017 provides clinical data for a direct comparison of nivolumab with docetaxel. A methodological overview of CheckMate 017 can be found in Table 10.

CheckMate 017

The pivotal CheckMate 017 trial was a global Phase III, randomised, open-label trial of nivolumab versus docetaxel in adult (≥18 years) patients with advanced or metastatic squamous cell NSCLC after failure of prior platinum doublet-based chemotherapy.

An open-label study design was selected because the management of similar adverse events (AEs) will differ between treatment arms, given the different mechanisms of action of docetaxel and nivolumab. Different dose modification rules (no dose reductions for nivolumab versus allowance for dose reductions for docetaxel) and different drug-drug interaction profiles would have added complexity to any blinding strategy. Participants were randomised by an interactive voice response system (IVRS) to receive either nivolumab 3mg/kg Q2W (N=135) or docetaxel 75mg/m^2 Q3W (N=137) until disease progression, discontinuation due to toxicity, withdrawal of consent.

The primary endpoint of the CheckMate 017 trial was OS, defined as the time between the date of randomisation and the date of death. OS is a universally accepted and well-established efficacy measure of cancer therapies; it is considered the gold standard primary endpoint (Pazdur 2008) as it is less ambiguous than other endpoints and less likely to be subject to investigator bias (Cheson 2007). OS is also an outcome defined in the decision problem (Section 1.1).

PFS was one of the secondary outcomes in this trial and was defined as the time from randomisation to the date of the first documented tumour progression as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, or death due to any cause. PFS is also a well-established measure of efficacy in cancer trials (Lebwohl 2009). Secondary endpoints also included confirmed investigator assessed ORR (defined as complete response [CR] or partial response [PR], divided by the number of patients). Other secondary endpoints included: duration of response (DOR), time to response (TTR), investigator-assessed PFS, HRQoL, safety, and tolerability.

The parameters used to assess the efficacy and safety profile of nivolumab in CheckMate 017 are consistent with other studies exploring the use of other anti-cancer agents in this patient population.

On 15 December 2014, the clinical database was locked for the planned interim OS analysis, based on 199 reported deaths. The interim analysis of OS was planned after at least 196 deaths (85% of total deaths required for final analysis) had been observed. The independent DMC reviewed the interim OS data on 10 January 2015, and declared that the trial had reached its primary endpoint, demonstrating superior OS in patients receiving nivolumab as compared to docetaxel (Brahmer 2015a; Bristol-Myers Squibb 2015a). The results presented here for the CheckMate 017 trial are based on the database lock date of December 15, 2014.

Table 10: Comparative summary of methodology of the relevant RCT

	CheckMate 017 (CA209-017)
Location	95 sites in 21 countries worldwide (four sites in UK) Argentina, Australia, Austria, Canada, Chile, Czech Republic, France, Germany, Hungary, Ireland, Italy, Mexico, Netherlands, Norway, Peru, Poland, Romania, Russian Federation, Spain, United Kingdom, and United States
Trial design (including method of randomisation)	Global, Phase III, randomised, open-label trial Patients were randomised via IVRS in a ratio of 1:1. Randomisation was stratified according to prior treatment with paclitaxel-based doublet versus other doublet, and region (US/Canada vs. Europe vs. Rest of World).
Trial drugs	Nivolumab at 3mg/kg by IV infusion Q2W (N=135) Docetaxel at 75mg/m^2 by IV infusion Q3W (N=137)
Overview of patient population	Adult (≥18 years) patients with advanced or metastatic squamous cell NSCLC after failure of prior platinum doublet-based chemotherapy

Detailed eligibility criteria for participants (inclusion criteria)	The trial enrolled men and women aged ≥18 years who signed informed consent, and met the following key target disease and other criteria: Patients with histologically- or cytologically-documented squamous cell NSCLC who present with Stage IIIB/ Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease) Patients must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease a) Maintenance therapy following platinum doublet-based chemotherapy was not considered as a separate regimen of therapy b) Patients who received platinum-containing adjuvant, neo-adjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy were eligible c) Patients with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, were eligible Patients must have had measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumour Assessment performed within 28 days of randomisation. Target lesions may have been located in a previously irradiated field if there was documented (radiographic) disease progression in that site ECOG PS of ≤1 A formalin-fixed, paraffin-embedded tumour tissue block or unstained slides of tumour sample (archival or recent) must have been available for biomarker evaluation. Specimens must have been received by the central laboratory prior to randomisation. Biopsy should have been excisional, incisional or core needle. Fine needle aspiration was insufficient

Detailed eligibility criteria for participants (exclusion criteria)	• Patients with untreated CNS metastases. Patients were eligible if CNS metastases had been treated and patients had neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrolment. In addition, patients must have been either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) • Patients with carcinomatous meningitis • Patients with active, known or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enrol • Patients with a condition requiring systemic treatment with either corticosteroids (>10mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomisation. Corticosteroids with minimal systemic absorption (inhaled or topical steroids), and adrenal replacement steroid doses >10 mg daily prednisone equivalent, were permitted in the absence of active autoimmune disease • Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) • Prior treatment on the first-line ipilimumab trial CA184104 • Prior treatment with docetaxel • Patients with interstitial lung disease that was symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity • All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have been resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug Treatment with any investigational agent within 14 days of first administration of study treatment
Permitted concomitant medication	Patients were permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses >10mg daily prednisone were permitted in the absence of active autoimmune disease. A brief (less than 3-week) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen) was permitted. Physiologic replacement doses of systemic corticosteroids were permitted even if >10mg prednisone equivalent dose was administered. Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) was allowed if initiated prior to first dose of study therapy (prior radiotherapy must have been completed at least 2 weeks prior to randomisation). Palliative radiotherapy was allowed, but not recommended while receiving nivolumab. If palliative radiotherapy was required, then nivolumab was to be withheld for at least 1 week before, during, and 1 week after radiation. Only non-target bone lesions that did not include lung tissue in the planned radiation field or CNS lesions were to have received palliative radiotherapy while on study treatment.

Primary outcomes (including scoring methods and timings of assessments)	OS (defined as the time between the date of randomisation and the date of death. For patients without documentation of death, OS was censored on the last date the patient was known to be alive). It should be noted that the primary endpoint was changed 25 April 2014 from a co-primary endpoint including both OS and ORR to a single primary endpoint of OS. This amendment was based on data from the CheckMate 003 study.
Secondary outcomes (including scoring methods and timings of assessments)	• Investigator-assessed ORR (defined as the number of patients whose best confirmed objective response is either a confirmed CR or confirmed PR, as determined by the investigator, divided by the number of randomised patients)* • DOR (defined as the time between the date of first confirmed response to the date of the first documented tumour progression (per RECIST 1.1), or death due to any cause, whichever occurs first)** • TTR (defined as the time from randomisation to the date of the first confirmed response. TTR will be evaluated for responders only) • Investigator-assessed PFS (defined as the time from randomisation to the date of the first documented tumour progression as determined by the investigator using RECIST 1.1 criteria, or death due to any cause)*** • HRQoL as measured by: o Disease-related Symptom Improvement Rate by Week 12 as measured by LCSS (defined as the proportion of randomised patients who had 10 points or more decrease from baseline in ASBI score at any time between randomisation and week 12)# o Overall health status using the EQ-5D Index and Visual Analogue Scale[##] • Safety and tolerability (exploratory outcome) Radiographic assessments of tumour response were performed at Week 9 (+/- 5 days) and every 6 weeks (+/- 5 days) thereafter until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond progression) or other protocol defined reasons
Duration of follow-up	From start of randomisation to final analysis was approximately 38 months (14 months of accrual + 24 months of follow-up). Last patient last visit occurred on 17 November 2014, providing a minimum follow-up of 10.6 months.

Pre-planned subgroups	• OS, ORR, or PFS based on pre-trial PD-L1 expression level
	  ○ Tumour tissue for analysis was prospectively collected and PD-L1 protein expression was evaluated retrospectively in pre-treatment (archival or recent) tumour-biopsy specimens with the use of a validated automated immunohistochemical assay (Dako North America) that used a rabbit monoclonal antihuman PD-L1 antibody (clone 28–8, Epitomics). Samples were categorised as positive when staining of the tumour-cell membrane (at any intensity) was observed at pre-specified expression levels of 1%, 5%, or 10% of cells in a section that included at least 100 tumour cells that could be evaluated.
	• Survival (OS and PFS) by:
	  ○ Age
	  ○ Gender
	  ○ Race
	  ○ Region
	  ○ Baseline ECOG PS
	  ○ Prior paclitaxel vs. other prior treatment
	  ○ Type of prior pre-treatment regimen (cisplatin vs. carboplatin)
	  ○ Time from diagnosis to randomisation
	  ○ Time from completion of most recent regimen to randomisation
	  ○ Presence or absence of CNS metastases
	  ○ Smoking status

Source: (Brahmer 2015a; Bristol-Myers Squibb 2015a)

Abbreviations: ASBI = Average Symptom Burden Index; BOR = Best Objective Response; CNS = Central Nervous System; CR = Complete Response; CT = Computerised Tomography; CTLA-4 = Cytotoxic T-Lymphocyte-Associated Protein 4; DOR = Duration of Response; ECOG = Eastern Cooperative Oncology Group; EQ-5D = EuroQoL-5 Dimensions; FFPE = Formalin Fixed, Paraffin-Embedded; HRQoL= Health-Related Quality Of Life; IV = Intravenous/Intravenously; IVRS = Interactive Voice Response System; kg = Kilograms; LCSS = Lung Cancer Symptom Scale; m^2 = Metres Squared; mg = Milligrams ; MRI = Magnetic Resonance Imaging; NCI CTCAE = The National Cancer Institute Common Terminology Criteria For Adverse Events; NSCLC = Non-Small Cell Lung Cancer; ORR = Objective Response Rate; OS = Overall Survival; PD-L1/PD-L2 = Programmed Cell Death Ligand 1/ Programmed Cell Death Ligand 2; PFS = Progression-Free Survival; PR = Partial Response; PS = Performance Status; Q2W = Every 2 Weeks; Q3W = Every 3 Weeks; RANK-L = Receptor Activator of Nuclear Factor Kappa-B Ligand; RECIST 1.1 = Response Evaluation Criteria In Solid Tumours Version 1.1; TTR = Time To Response; UK: United Kingdom; US: United States

Note: *BOR is defined as the best response designation, recorded between the date of randomisation and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy (excluding on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions), whichever occurs first. For patients without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For patients who continue nivolumab treatment beyond progression, the BOR will be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

**Patients who neither progress nor die will be censored on the date of their last evaluable tumour assessment. Patients who started any subsequent anti-cancer therapy (Excluding on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumour assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. DOR will be evaluated for responders (i.e. patients with confirmed CR or PR) only.

***Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) is not considered progression for purposes of determining PFS. Patients who die without a reported prior progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last evaluable tumour assessment. Patients who did not have any on trial tumour assessments and did not die will be censored on the date they were randomised. Patients who started any subsequent anti-cancer therapy (including on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumour assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

#The patient portion of the LCSS scale consisted of six symptom-specific questions that address cough, dyspnoea, fatigue, pain, haemoptysis, and anorexia, plus three summary items on symptom distress, interference with activity level, and global HRQoL

##EQ-5D essentially has 2 components- the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system is comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The EQ VAS records the patient's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

CheckMate 017

Table 11 gives a summary of the statistical analyses in the CheckMate 017 trial.

The primary objective of CheckMate 017 was to determine whether nivolumab compared with docetaxel improves survival in patients with squamous cell NSCLC after failure of prior platinum-based doublet chemotherapy. As such, both survival outcomes of OS (primary outcome) and PFS (secondary outcome) were compared between the two treatment groups of patients with squamous NSCLC after failure of prior platinum-based doublet chemotherapy. The two treatment groups were compared for the survival outcomes of OS and PFS using a two-sided, log-rank test, stratified by prior use of paclitaxel versus other prior treatment, and region.

The final analysis of OS was planned to take place after 231 deaths were observed among 272 randomised patients. However, one interim analysis of OS was planned after at least 196 deaths (85% of total deaths required for final analysis) had been observed.

On 15th December 2014, the clinical database was locked for the planned interim OS analysis, based on 199 reported deaths. The independent DMC reviewed the interim OS data on 10th January 2015, and declared that the trial reached its primary endpoint, demonstrating superior OS in patients receiving nivolumab as compared with docetaxel (Bristol-Myers Squibb 2015a). The results presented here for the CheckMate 017 trial are based on the database lock date of 15th December 2014.

Table 11: Summary of the statistical analyses of the CheckMate 017 trial

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals	Missing data
CheckMate 017 (CA209-017)	To determine whether nivolumab compared with docetaxel improves survival in patients with squamous cell NSCLC after failure of prior platinum-based doublet chemotherapy	Survival outcomes (OS and PFS) were compared between the two treatment groups using a two-sided, log-rank test stratified by prior use of paclitaxel vs. other prior treatment, and region. The HR and the corresponding CI (100(1-α) % for OS and 95% CI for PFS) was estimated in a stratified Cox proportional hazards model using randomised group as a single covariate. The survival curves for each treatment group were estimated using the KM product-limit method. Two-sided, 95% CI for median survival was constructed based on a log-log transformed CI for the survivor function S(t). Survival rates at various time points were estimated using KM estimates on the PFS curve. Associated two-sided 95% CIs were calculated using the Greenwood's formula for variance derivation and on log-log transformation applied on the survivor function S(t).	The sample size was calculated in order to compare OS between patients randomised to receive nivolumab versus docetaxel. The final analysis of OS was planned to take place after 231 deaths were observed among 272 randomised patients. One interim analysis of OS was planned after at least 196 deaths (85% of total deaths required for final analysis) had been observed. OS distribution was assumed exponential for the docetaxel group, while for the nivolumab group, a long-term survival and delayed onset of benefit were assumed, as observed in patients treated with immuno-oncology drug ipilimumab in recent phase 3 studies (Bristol-Myers Squibb 2015a)	This trial was conducted in accordance with GCP by qualified investigators using a single protocol to promote consistency across sites. OS was censored on the last date the patient was known to be alive. For ORR, patients without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For PFS, patients who die without a reported prior progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last evaluable tumour assessment. Patients who did not have any on trial tumour assessments and did not die will be censored on the date they were randomised.	Missing assessments and inevaluable designation When no imaging/measurement is done at all at a particular time point, the patient is NE at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. PD-L1 expression level missing: Patients without an available tumour biopsy specimen for PD-L1 evaluation will be considered as PD-L1 expression level missing. PFS accounting for missing tumour assessment prior to PFS event (progression or death): This analysis will be performed only if at least 20% of events have missing prior tumour assessment. See (Brahmer 2015a) for more detail.

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals	Missing data
CheckMate 017 (CA209-017)	To determine whether nivolumab compared with docetaxel improves survival in patients with squamous cell NSCLC after failure of prior platinum-based doublet chemotherapy	Investigator-assessed BOR was summarised by response category for each treatment group. ORR was computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. An estimate of the difference in ORRs and corresponding 95% CI was calculated using CMH methodology and adjusted by the same stratification factors as in primary analysis of OS. A by-patient listing of BOR and tumour measurements was provided. The stratified odds ratios (Mantel-Haenszel estimator) between the treatments was provided along with the 95% CI. The difference was tested via the CMH test using a two-sided, 5% α level.	The average overall HR at interim and final OS analysis was estimated to be 0.74 and 0.66 respectively. Power at interim and final OS analysis was 55% and 90% respectively. The stopping boundaries at interim and final analyses were derived based on the number of deaths using O'Brien and Fleming α spending function.	Patients who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumour assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. A CSP was used in this trial to uniformly collect additional information on the following AEs of clinical interest: endocrine, GI, hepatic, pulmonary, renal, and skin.	<u>Conventions:</u> For missing and partial AE onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in BMS Non- Study Medication Domain Requirements Specification

Source: (Brahmer 2015a; Bristol-Myers Squibb 2015a)

Abbreviations: AE = Adverse Event; BOR = Best Objective Response; BMS = Bristol Myers Squibb; CI = Confidence Interval; CMH = Cochran Mantel-Haenszel; CSP = Clinical Safety Program; GCP = Good Clinical Practice; GI = Gastrointestinal; HR = Hazard Ratio; KM = Kaplan-Meier; NE = Non Evaluable; NSCLC = Non-Small Cell Lung Cancer; ORR = Objective Response Rate; OS = Overall Survival; PD = Progressed Disease; PD-L1 = Programmed Death-Ligand 1; PFS = Progression-Free Survival

4.5 Participant flow in the relevant randomised controlled trials

CheckMate 017

The flow of participants through the CheckMate 017 study is presented in Figure 7. A total of 272 patients were randomised to either nivolumab (N=135) or docetaxel (N=137) (the intention-to-treat [ITT] population used for the efficacy analysis). Of these patients, 12 did not receive study medication (four in the nivolumab treatment arm and eight in the docetaxel treatment arm); therefore, the safety analysis (N=260) excludes these patients.

Subsequent therapy was received by some patients and was defined as therapy started on or after first dosing date or date of randomisation if a patient was never treated with the study drug (Brahmer 2015b).

Subsequent radiotherapy was received by 27% of patients in the nivolumab arm, compared with 18% in the docetaxel arm (Brahmer 2015a). Patients could receive more than one subsequent therapy; 36% of patients in the nivolumab arm and 30% of patients in the docetaxel arm received subsequent systemic therapy (Brahmer 2015a).

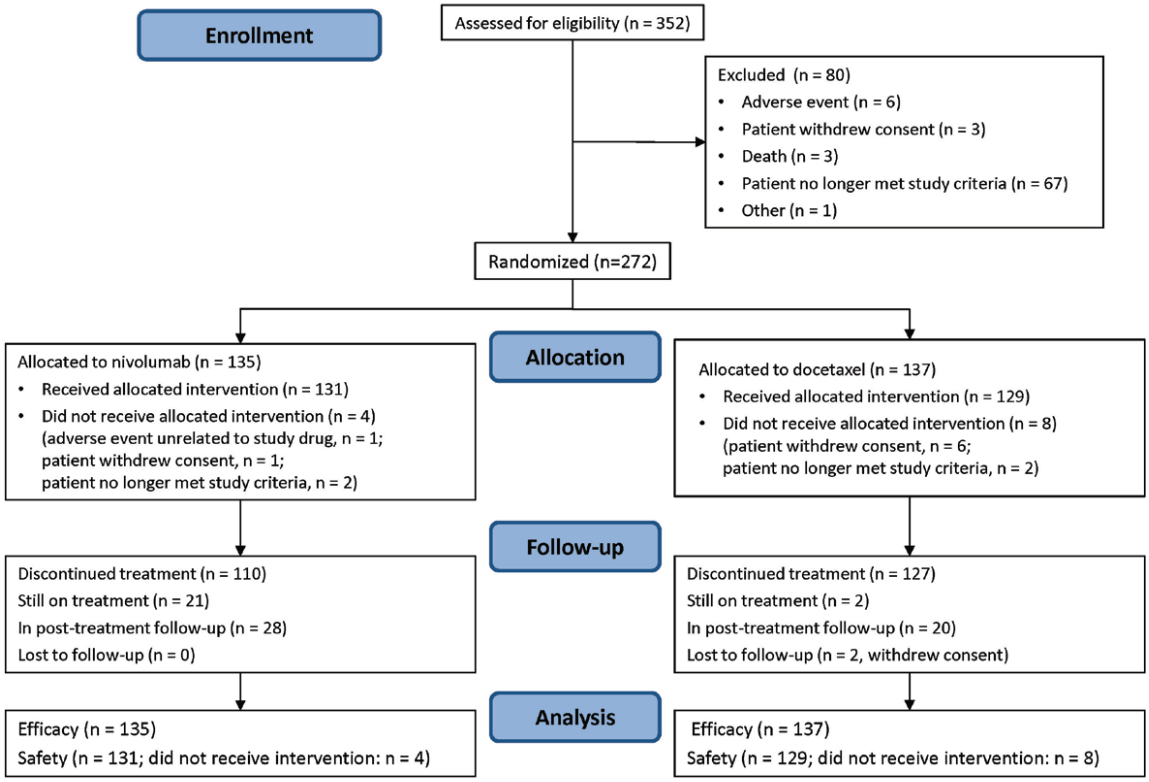
Of the patients that received subsequent chemotherapy in the nivolumab arm: 29% received subsequent taxane chemotherapy, and 24% of patients receiving taxane therapy were treated with docetaxel (Brahmer 2015a). In comparison, 24% of patients in the docetaxel arm received chemotherapy and only 5% of patients in this treatment arm were subsequently treated with a taxane chemotherapy. Very few patients in the nivolumab or docetaxel treatment arms received subsequent EGFR-inhibitors (4% and 6%, respectively), subsequent immunotherapy (1% and 2%, respectively), or subsequent non-immunotherapy experimental agents (2% and 4%, respectively) (Brahmer 2015a). At the January 10, 2015 data assessment, no patients had crossed over during treatment from docetaxel to nivolumab or from nivolumab to docetaxel.

One death unrelated to study drug was observed in the nivolumab arm.

Discontinuation due to AEs unrelated to trial drug was observed in six patients in the nivolumab arm (5%) and 13 patients in the docetaxel arm (10%). Two patients (2%) in the nivolumab treatment group and four patients (3%) in the docetaxel arm requested to discontinue study treatment. Discontinuation due to patient withdrawing consent occurred in three patients (2%) receiving nivolumab and five patients (4%) receiving docetaxel (Brahmer 2015a) (Table 12).

A Consolidated Standards of Reporting Trials (CONSORT) flow chart for the CheckMate 017 trial is presented in Figure 7.

Figure 7: CONSORT flow chart of participants in CheckMate 017



Source: (Brahmer 2015b)

Table 12: Patient disposition in the CheckMate 017 trial

	Nivolumab N=131	**Docetaxel N=129**
Patients continuing in treatment period, n (%)	21 (16)	2 (1.6)
Reason for not continuing in the treatment period, n (%)		
Disease Progression	88 (67)	80 (62)
Study Drug Toxicity	5 (4)	13 (10)
Death*	1 (1)*	0
Adverse event unrelated to study drug	6 (5)	13 (10)
Patient request to discontinue study treatment	2 (2)	4 (3)
Patient withdrew consent	3 (2)	5 (4)

Source: (Brahmer 2015b)

* Unrelated to treatment.

Patient characteristics and demographics at baseline were well balanced and comparable across both treatment groups (Table 13).

For all randomised patients in the CheckMate 017 trial the median age was 63 years, the majority of patients were white (93%) and male (76%) (Brahmer 2015a). Most patients had Stage IV disease at baseline (80%) (Brahmer 2015a). There were a greater number of

patients with Eastern Cooperative Oncology Group (ECOG) PS1 in the nivolumab group versus the docetaxel group (79% vs. 73%, respectively) (Brahmer 2015a).

The [redacted] the most common site of disease reported outside the primary site of disease ([redacted] of nivolumab patients vs. [redacted] of docetaxel patients) (Bristol-Myers Squibb 2015a). [redacted] did not have [redacted] metastases reported at baseline (Bristol-Myers Squibb 2015a). All patients who had locally advanced disease were previously treated with multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation), as this was one of the key inclusion criteria for study entry (Brahmer 2015a; Bristol-Myers Squibb 2015a).

All randomised patients had tumour samples collected at baseline. Patients with quantifiable PD-L1 expression level status at baseline included 117 (87%) patients in the nivolumab group and 108 (79%) patients in the docetaxel group. Baseline PD-L1 expression level status can be seen in Table 13. PD-L1 expression level is discussed in more detail in the sub-group analysis (Section 4.8).

Table 13: Baseline characteristics for patients in the CheckMate 017 trial

Trial name	**CheckMate 017**	
Baseline characteristic	**Nivolumab (N=135)**	**Docetaxel (N=137)**
Median age, years (range)	62 (39-85)	64 (42-84)
<65, n (%)	79 (59)	73 (53)
65 - 74, n (%)	45 (33)	46 (34)
≥75, n (%)	11 (8)	18 (13)
Gender, n (%) Male	111 (82)	97 (71)
Race, n (%) White	122 (90)	130 (95)
Patients with quantifiable PD-L1 status at baseline, n (%)	117 (87)	108 (79)
PD-L1 expression level[a] n (%)		
<1%	54 (46)	52 (48)
≥1%	63 (54)	56 (52)
<5%	75 (64)	69 (64)
≥5%	42 (36)	39 (36)
<10%	81 (69)	75 (69)
≥10	36 (31)	33 (31)
Not quantifiable at baseline[b]	18 (13)	29 (21)
Smoking status, n (%)		
Current/Former	121 (90)	129 (94)
Never smoked	10 (7)	7 (5)
Unknown	4 (3)	1 (1)
ECOG PS, n (%)		
0	27 (20)	37 (27)
1	106 (79)	100 (73)
Not reported	2 (1)	0
Disease stage, n (%)		
IIIB	29 (21)	24 (18)
IV	105 (78)	112 (82)
Not reported	1 (1)	1 (1)
CNS metastases, n (%) Yes	[redacted]	[redacted]
Median time from initial diagnosis, years (range)	0.74 (0.1-10.0)	0.73 (0.1-4.6)
Number of prior systemic cancer therapies received, n (%)		
1	134 (99)	137 (100)
2	1 (1)	0
≥3	0	0
Prior radiotherapy, n (%)		
Yes	71 (53)	73 (53)

Trial name Baseline characteristic	CheckMate 017	
	Nivolumab (N=135)	Docetaxel (N=137)
Type of prior systemic cancer therapy, n (%)		
Prior platinum based therapy	135 (100)	137 (100)
Prior ALK inhibitor	0	0
Prior EGFR TKI	0	3 (2)
Other – chemotherapy	135 (100)	136 (99)
Other – experimental drugs	9 (7)	2 (1)
Time from completion of most recent prior systemic therapy regimen to randomisation, n (%)		
<3 months	64 (47)	59 (43)
3-6 months	35 (26)	40 (29)
>6 months	35 (26)	37 (27)
Best response to most recent prior regimen, n (%)		
CR or PR	48 (36)	43 (31)
SD	33 (24)	47 (34)
PD	44 (33)	41 (30)
Unknown/Not reported	10 (7)	6 (4)

Source: (Brahmer 2015a; Brahmer 2015b)

Abbreviations: ALK = Anaplastic Lymphoma Kinase; CNS = Central Nervous System; CR = Complete Response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = Epidermal Growth Factor Receptor; PD = Progressive Disease; PD-L1= Programmed Cell Death Ligand 1; PR = Partial Response; SD = Stable Disease; [a] Percent membranous staining in ≥100 tumour cells; [b] No quantifiable PD-L1 expression level

4.6 Quality assessment of the relevant randomised controlled trials

The quality assessment of RCT results for the CheckMate 017 trial can be found in Table 14.

Table 14: Quality assessment of the CheckMate 017 trial

Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? **If so, was this appropriate and were appropriate methods used to account for missing data?**	Yes
How closely do the RCT(s) reflect routine clinical practice*	Patients included in CheckMate 017 are thought to reflect patients seen in UK clinical practice • Comparator in the trial is docetaxel which represents standard of care in pre-treated patients in the UK • First-line treatment in the UK is a platinum-based chemotherapy; patients who had received a platinum-based therapy were included in the trial • Doses for both nivolumab and docetaxel used in the trial are reflective of UK clinical practice • Baseline characteristics are those of the patients seen in clinical practice (male, ex-smokers, etc.)

RCT = Randomised Controlled Trial

*If the trials do not reflect clinical practice please provide further details

4.7 Clinical effectiveness results of the relevant randomised controlled trials

- CheckMate 017 met its primary objective, demonstrating a statistically significant and clinically meaningful improvement in OS with nivolumab vs. docetaxel in previously treated patients with advanced squamous NSCLC:
    - 41% reduction in risk of death with nivolumab (HR 0.59, p<0.001)
    - 1-year OS: 42% (95% CI: 34, 50) vs. 24% (95% CI: 17, 31)
    - Median OS: 9.2 months (95% CI: 7.3, 13.3) vs. 6.0 months (95% CI: 5.1, 7.3).
- The trial was stopped early, as the assessment conducted by the independent DMC concluded that the study had met its primary endpoint: demonstrating superior OS in patients treated with nivolumab compared with docetaxel.
- The study demonstrated consistent, statistically significant superiority of nivolumab over docetaxel across the secondary endpoints of ORR and PFS:
    - ORR: 20% (95% CI: 14, 28) vs. 9% (95% CI: 5, 15) (p = 0.008)
    - 1-year PFS: 21% (95% CI: 14, 28) vs. 6% (95% CI: 3, 12)
    - Median PFS: 3.5 months (95% CI: 2.1, 4.9) vs. 2.8 months (95% CI: 2.1, 3.5) (HR 0.62, p<0.001).
- Similar survival outcomes were observed regardless of tumour PD-L1 expression level
    - No detriment was observed in PD-L1 low-expressors
- The current standard of care in the UK for second-line squamous NSCLC patients is docetaxel, and this was used as the comparator in the trial. It is associated with modest efficacy and poor tolerability.
- The results of the CheckMate 017 study demonstrates that nivolumab offers a significantly improved and meaningful clinical efficacy over the current standard of care, providing an effective option for pre-treated patients with locally advanced or metastatic squamous NSCLC in an area of high unmet medical need

CheckMate 017

As detailed in Section 4.4, on 15th December 2014, the clinical database was locked for the planned interim OS analysis. The independent DMC reviewed the interim OS data and declared that the trial reached its primary endpoint, demonstrating superior OS in patients receiving nivolumab as compared with docetaxel. The results for this trial presented here are based on this database lock.

Results presented in this section represent all patients relevant to the decision problem. Subgroup analyses, including analysis by PD-L1 expression level, are given in Section 4.8.

Primary outcome

Overall Survival

OS was the primary outcome in the CheckMate 017 trial.

Nivolumab demonstrated clinically superior OS compared with docetaxel in patients with advanced or metastatic squamous cell NSCLC after failure of prior platinum doublet-based chemotherapy, with a clinically and statistically significant improvement observed (Brahmer 2015a; Bristol-Myers Squibb 2015a) (Table 15). Treatment with nivolumab reduced the risk of death by 41% when compared with docetaxel (HR: 0.59; 95% CI: 0.44, 0.79; p<0.001) (Brahmer 2015a). The median OS at 1-year for nivolumab was 9.2 months (95% CI: 7.3, 13.3) compared with 6.0 months (95% CI: 5.1, 7.3) for the docetaxel treatment arm (Brahmer 2015a). The OS rate was higher at both 6 and 12 months in the nivolumab treatment arm compared with the docetaxel arm (6 months: 64% versus 50%; 12 months: 42% versus 24%) (Table 15) (Brahmer 2015a; Bristol-Myers Squibb 2015a). As shown in Figure 8, a separation of the Kaplan-Meier curves for OS was observed early in the treatment period, and was maintained throughout the trial (Brahmer 2015a).

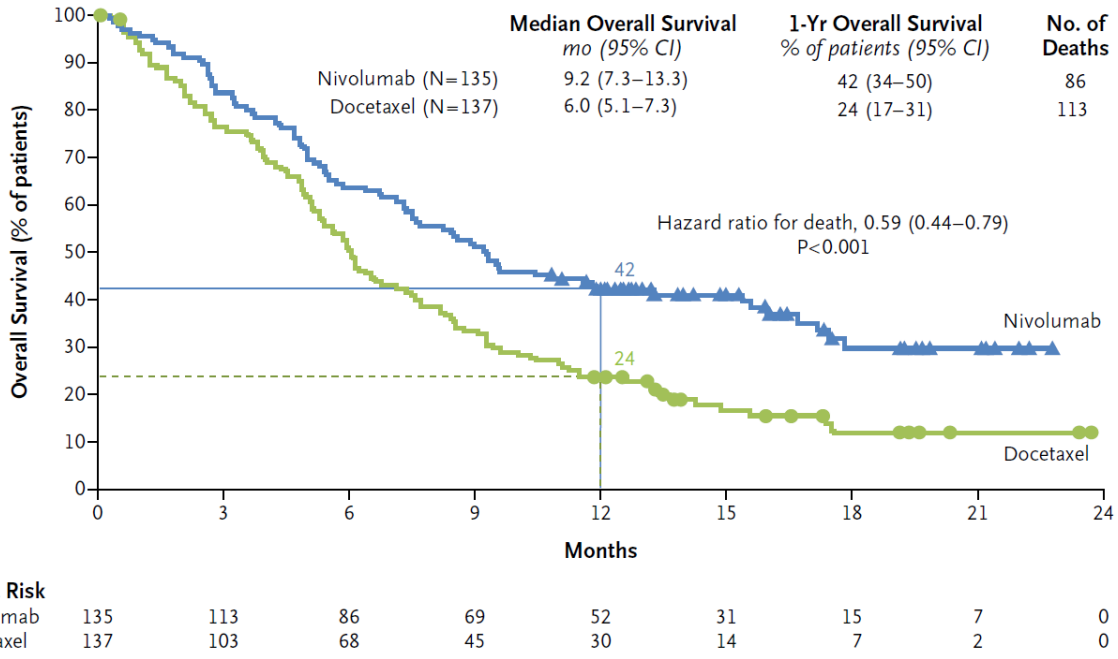
Table 15: CheckMate 017 - OS results from all randomised patients in the trial

OS	CheckMate 017	
	Nivolumab (N = 135)	**Docetaxel (N = 137)**
Events, n (%)	86 (63.7)	113 (82.5)
Stratified log-rank test p-value	p<0.001	
HR for death (95% CI)	0.59 (0.44, 0.79)	
Median OS, months (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
OS rate at 6 months (95% CI)	63.7 (55.0, 71.2)	50.4 (41.7, 58.4)
OS rate at 12 months (95% CI)	42 (34, 50)	24 (17, 31)

Source: (Brahmer 2015a; Bristol-Myers Squibb 2015a)

Abbreviations: CI = Confidence Interval; HR = Hazard Ratio; OS = Overall Survival

Figure 8: CheckMate 017 - Kaplan-Meier OS plot – all randomised patients in the trial



Source: (Brahmer 2015a)

Abbreviations: CI = Confidence Interval; mo = Months; OS: Overall Survival. The analysis included all the patients who underwent randomisation. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Secondary outcomes

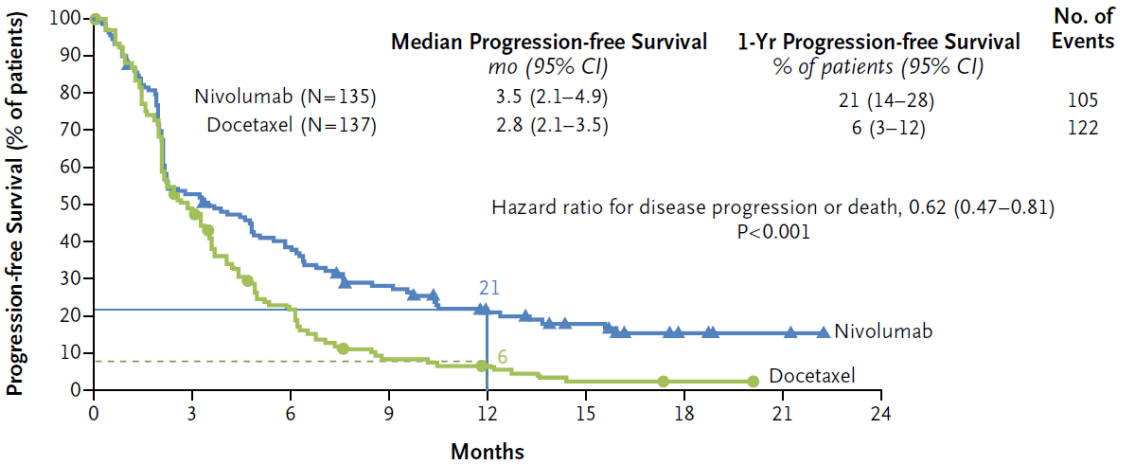
Progression-free survival

The clinical effect observed in the OS analysis can also be seen in the Kaplan–Meier survival curve for PFS (Figure 9), where treatment with nivolumab resulted in a clinically meaningful and statistically significant improvement in PFS compared with docetaxel.

Treatment with nivolumab reduced the risk of death or disease progression at 6 months by 38% when compared with docetaxel (HR: 0.62; 95% CI: 0.47, 0.81; p<0.001) (Brahmer 2015a). The median PFS was 3.5 months (95% CI: 2.1, 4.9) for patients receiving nivolumab compared with 2.8 months (95% CI: 2.1, 3.5) for patients receiving docetaxel (Brahmer 2015a). While the rate of PFS was already higher for nivolumab at 6 months and at 12 months, the rate of PFS was over three times higher at 12 months compared with the docetaxel arm (21% versus 6%, respectively; Table 16) (Brahmer 2015a).

Separation of the Kaplan-Meier curves for PFS for nivolumab and docetaxel starts at approximately 3 months: over time this separation continues to increase and is sustained (Figure 9). Radiographic assessments of tumour response were performed at Week 9 (+/- 5 days) and every 6 weeks (+/- 5 days) thereafter until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond progression) or other protocol defined reasons.

Figure 9: CheckMate 017 - Kaplan-Meier PFS – all randomised patients in the trial



Source: (Brahmer 2015a)

Abbreviations: CI = Confidence Interval; PFS = Progression-Free Survival

Table 16: CheckMate 017 - Summary of PFS results from all randomised patients in the trial

PFS	CheckMate 017	
	Nivolumab (N = 135)	Docetaxel (N = 137)
Events, n (%)	105 (77.8)	122 (89.1)
Stratified log-rank test p-value	<0.001	
HR for progression or death (95% CI)	0.62 (0.47, 0.81)	
Median, months (95% CI)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)
PFS rate at 6 months (95% CI)	38.4 (30.0, 46.8)	21.9 (15.1, 29.5)
PFS rate at 12 months (95% CI)	21 (14, 28)	6 (3, 12)

Source: (Brahmer 2015a; Bristol-Myers Squibb 2015a)

CI = Confidence Interval; HR = Hazard Ratio; PFS: Progression-free survival

Response

Nivolumab demonstrated benefits compared with docetaxel, namely, ORR, DOR, and TTR (Table 17). A greater number of responders were observed in the nivolumab treatment group compared with the docetaxel treatment group (Figure 10). One patient in the nivolumab group (1%) achieved a CR compared with no patients in the docetaxel group.

In both treatment arms, responders (patients who achieved a PR or CR) achieved response early, approximately 2 months from randomisation (Figure 10), while the median TTR was also similar in both treatment groups (Table 17).

However, in patients responding to treatment with nivolumab, the response was sustained, durable, and longer than in patients responding to treatment with docetaxel (Table 17). Patients achieving response demonstrated a longer DOR (Figure 10), where median DOR was not reached in the nivolumab group compared to 8.4 months in the docetaxel group.

Table 17: CheckMate 017 - Summary of response analyses from all randomised patients in the Phase III trial

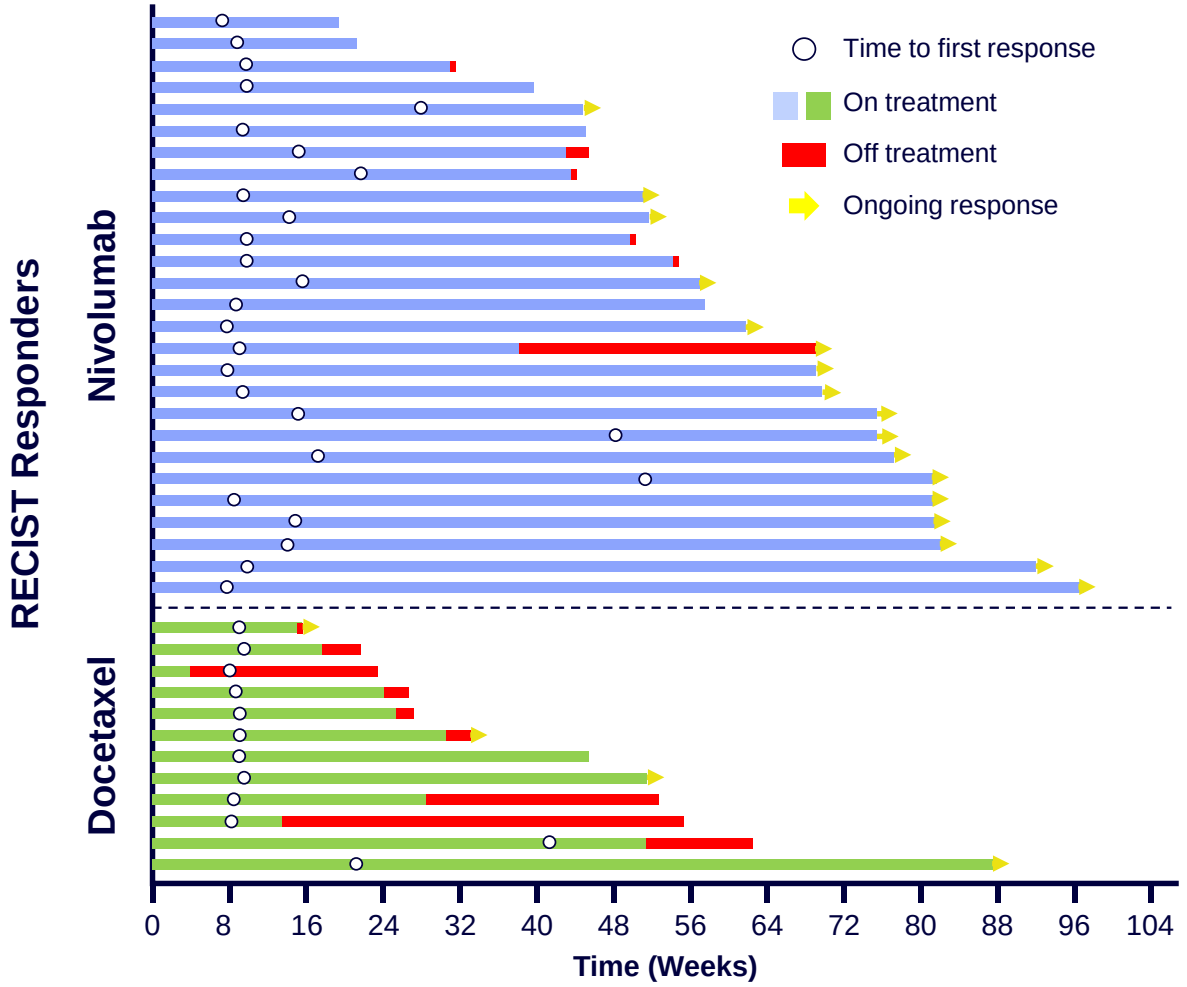
	CheckMate 017	
	Nivolumab (N = 135)	**Docetaxel (N = 137)**
ORR		
n, responders	27	12
% of patients (95% CI)	20 (14, 28)	9 (5, 15)
Odds ratio estimate (95% CI)	2.6 (1.3, 5.5)	
p value	0.008	
TTR		
Median, months	2.2	2.1
Min-Max (months)	1.6 - 11.8	1.8 - 9.5
DOR		
In responders, n/N, (%)	17/27 (63.0)	4/12 (33.3)
Median, months (95% CI)	NtR [redacted]*	8.41 [redacted]*
Min-Max (months)	2.9 - 20.5+	+1.4 - 15.2+

Source: (Brahmer 2015a; Bristol-Myers Squibb 2015a)

Abbreviations: CI = Confidence Interval; DOR = Duration of Response; NtR = Not Reached; ORR = Objective Response Rate; TTR = Time To Response

*All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb 2015a)

Figure 10: CheckMate 017 - Response analyses swimmer plot for both the nivolumab and docetaxel treatment groups in the trial



Source: Adapted from the NEJM publication (Brahmer 2015a; Bristol-Myers Squibb 2015a).

The figure shows the characteristics of response and disease progression as assessed by the investigator, according to the RECIST criteria, Version 1.1. Bars indicate the DOR. Arrows indicate ongoing response at the time of data censoring. GRAPH INTERPRETATION: Each 'lane' in this swimmer plot represents a responder (y axis) in either the nivolumab (blue) or docetaxel (green) treatment group. The DOR (weeks) can be seen on the x axis. For each responder, the time to first response is indicated by the circle on each lane. The arrow at the tail of a responder lane (yellow) represents ongoing response at the time of data censoring

Treatment beyond progression

For the nivolumab treatment group, 28 out of 135 patients were treated beyond progression, defined by RECIST criteria (Version 1.1), (Brahmer 2015a), as allowed within the protocol. Of these 28 patients, 9 (32.1%) were considered to derive clinical benefit from treatment beyond progression ('non-conventional' benefiters).

A non-conventional benefit was defined as patients who had one of the following:

- Appearance of a new lesion followed by decrease from baseline of at least 10% in sum of target lesions (five patients).
- Initial increase from nadir ≥20% in sum of target lesions followed by reduction from baseline of at least 30% (one patient).

- Initial increase from nadir ≥20% in sum of target lesions followed by at least two tumour assessments showing no further progression defined as 10% additional increase in sum of target lesions and new lesions (three patients) (Bristol-Myers Squibb 2015a).

Health-related quality of life

In CheckMate 017, the effect of nivolumab treatment on patients' HRQoL was measured according to the Lung Cancer Symptom Scale (LCSS) and EuroQol 5-Dimensions (EQ-5D).

Lung Cancer Symptom Scale

The LCSS includes six symptom-specific questions that address cough, dyspnoea, fatigue, pain, haemoptysis, and appetite. The scores range from 0 to 100, with zero representing the best possible score and 100 being the worst possible score. Disease-related symptom improvement rate is defined as a 10 points or more decrease from baseline in average symptom burden by Week 12.

Results of the LCSS Average Symptom Burden Index (ASBI) score, which is the mean computed from the six symptom-specific questions of the LCSS, demonstrated similar scores at baseline for nivolumab (29.6 ± 16.4) and docetaxel (29.6 ± 14.7) (Gralla 2015). Patients receiving nivolumab demonstrated statistically significant improvements in HRQoL, as measured by a reduction in mean ASBI score from baseline, at each assessment from Week 12 through Week 54 (Gralla 2015). These improvements exceeded the pre-defined minimally important difference (MID) of 10mm at assessments from Week 42 to Week 54 (Gralla 2015), indicating that the improvements were clinically meaningful (Hollen 1994; Sarna 2008). In comparison, mean LCSS scores in the docetaxel group remained relatively stable with no statistically significant change in ASBI mean score from baseline through Week 18, after which the sample size was fewer than 10 patients (Gralla 2015).

The overall ASBI score while on nivolumab improved from baseline over most of the year of available follow up, while ASBI score for docetaxel patients remained stable relative to baseline during their shorter time on treatment. These results show statistically and clinically significant reductions (improvements) from baseline in lung cancer symptoms for patients with squamous NSCLC treated with second-line nivolumab. Treatment discontinuation was observed to be associated with a worsening in HRQoL as measured by the LCSS burden index scores at the two follow-up visits (visit 1: 30 days following last dose, visit 2: 100 days following last dose) (Gralla 2015).

EQ-5D Visual Analogue Scale and Utility Index

The patients' overall health was assessed using the EuroQol 5-Dimensions Visual Analogue Scale (EQ-VAS) and utility index at each assessment point. The EQ-VAS elicits patients' ratings of their health status on a 0 to 100 scale with 0 being the worst imaginable health state and 100 being the best imaginable health state. The MID for the EQ-VAS has been estimated to be 7 points (Reck 2015). The EQ-5D utility index is computed using the EQ-5D descriptive system comprising the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The utility index score ranges from -0.594 (worst imaginable health state) to 1 (best imaginable health state), with -0.594 representing an "unconscious" health state. The MID for the EQ-5D utility index has been estimated to be 0.08 points.

Results from CheckMate 017 indicated that a better overall health status was achieved while on treatment. In the nivolumab group, the mean EQ-VAS score was statistically significantly higher (improved) from baseline ($p \leq 0.05$) at Week 12, Week 20 to Week 36, and at Week 48; nivolumab also exceeded the mean baseline score by more than the pre-defined 7-point MID, showing improvement at Weeks 24 to 36, and at Week 48 (Reck 2015). Similarly, the

EQ-5D utility index improved significantly from baseline at Week 16 to Week 30 assessments and Week 42 to Week 54 ($p \leq 0.05$), with the changes at Week 42 to Week 54 also exceeding the MID of 0.08 (Reck 2015). Neither the EQ-5D utility index nor EQ-VAS were statistically significantly different from baseline after nivolumab discontinuation at both follow-up assessments (30 days and 100 days post-last dose) (Reck 2015).

EQ-5D utility index and EQ-VAS scores did not differ significantly from baseline in the docetaxel arm while on treatment to Week 18 assessment, after which the sample size was fewer than 10 patients (Reck 2015). Following discontinuation of treatment, patients in the docetaxel arm experienced a clinically meaningful and statistically significant decline in health status from baseline as measured using the EQ-VAS at the first follow-up visit (30 days post-last dose), but there was not a significant decline in EQ-5D utility index (Reck 2015). At the second follow-up visit (100 days post-last dose), neither the EQ-VAS nor the EQ-5D utility index were statistically significantly different from baseline values (Reck 2015).

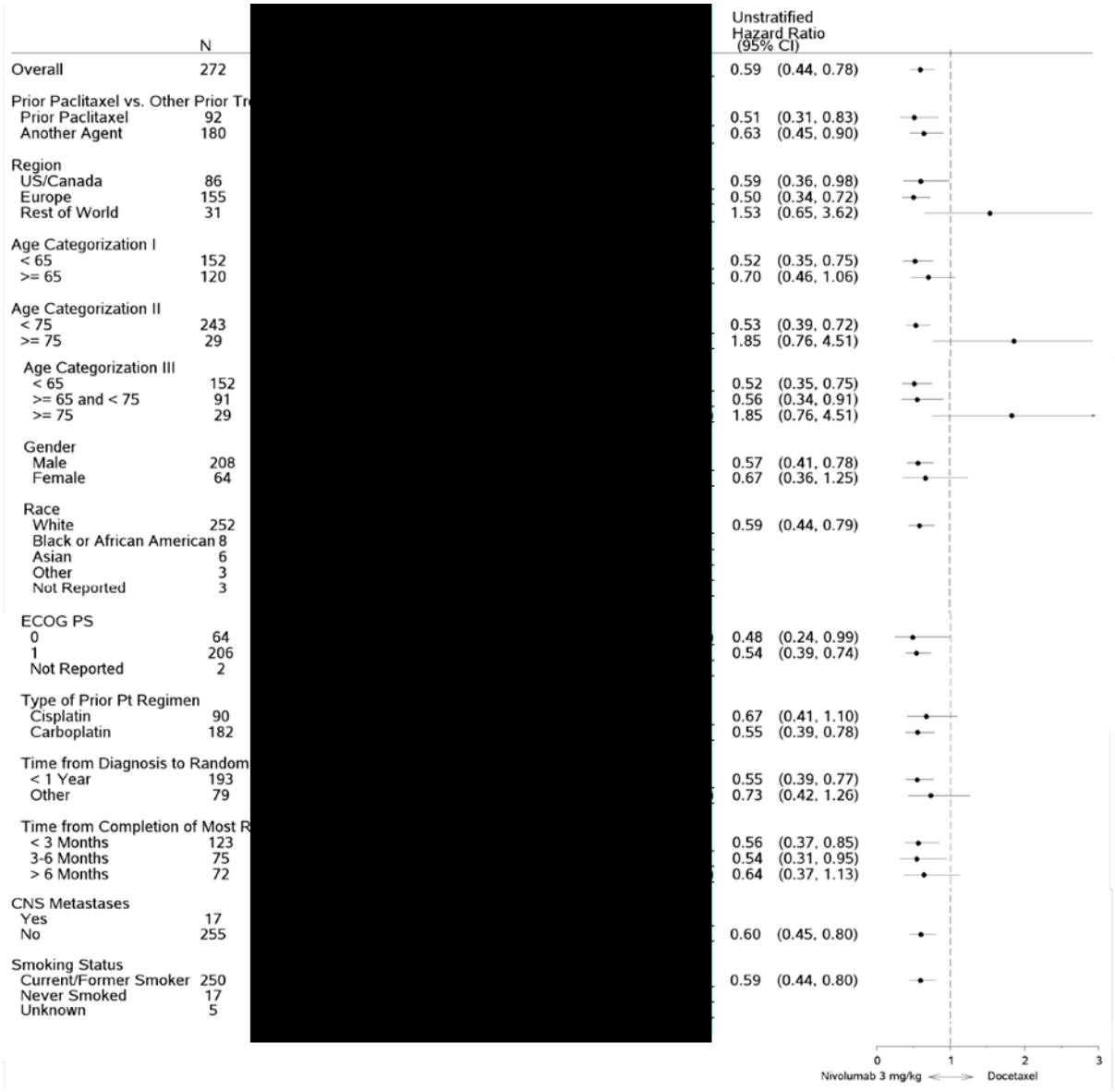
4.8 Subgroup analysis

Efficacy results by demographic subgroups in the CheckMate 017 trial

The OS benefit observed for nivolumab compared with docetaxel in the whole trial population (Section 4.7) was also observed across all but two of the pre-defined demographic subgroups (Figure 11). There were two exceptions; patients aged ≥75 years and patients in the Rest of the World region (i.e. Argentina, Australia, Chile, Mexico, and Peru) (Brahmer 2015a). In these two subgroups, confidence intervals were wide due to the small number of events within each group ($N<20$ in each treatment arm).

Similarly, the PFS HR favoured nivolumab versus docetaxel for all pre-defined subgroups, except patients ≥75 years of age. Similarly, the confidence intervals for this subgroup were wide due to the small subgroup size (Brahmer 2015a).

Figure 11: CheckMate 017 - Forest plot of treatment effect on OS in pre-defined subsets



Source: (Bristol-Myers Squibb 2015a; Brahmer 2015b)

Abbreviations: CI = Confidence Interval; CNS = Central Nervous System; ECOG PS = Eastern Cooperative Oncology Group Performance Status; mOS = Median Overall Survival; OS = Overall Survival

*All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb 2015a)

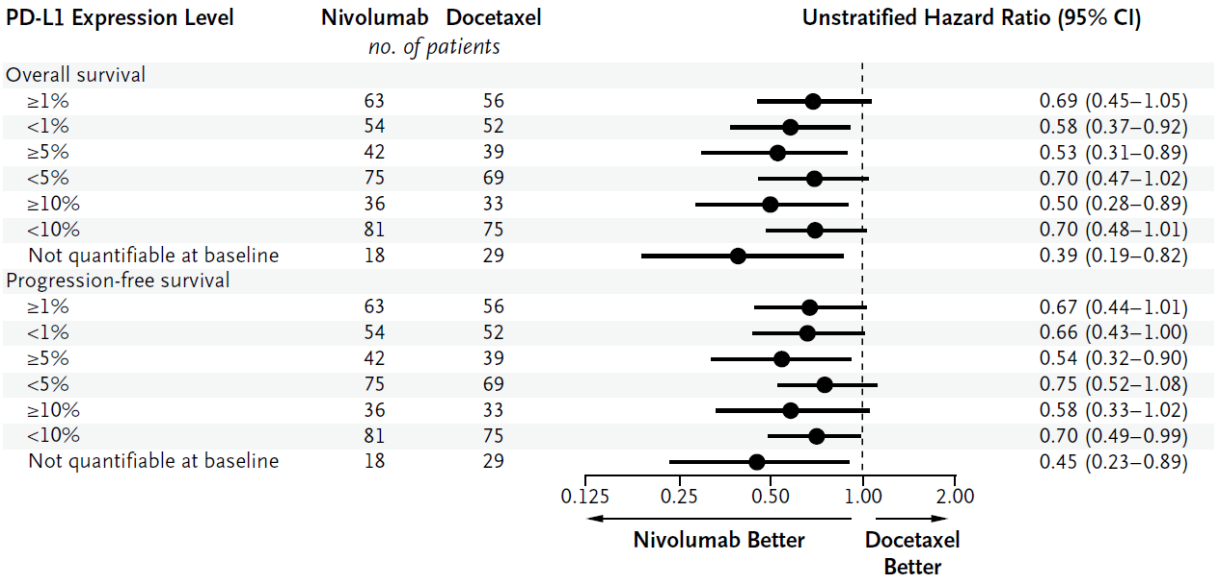
Efficacy results by PD-L1 expression level in CheckMate 017

Availability of archival or fresh tissue for evaluation of PD-L1 status was required for trial entry. 86.7% (117/135) of patients had an evaluable PD-L1 status in the nivolumab group and 78.8% (108/137) of patients in the docetaxel group. PD-L1 expression levels were balanced between the two treatment groups at each of the pre-defined PD-L1 expression level cut-offs (1%, 5%, and 10%).

Nivolumab was observed to be effective across all PD-L1 expression level subgroups, and so PD-L1 expression level was not considered predictive of outcome (Figure 12) (Brahmer 2015a; Brahmer 2015b):

- No statistically significant differences in OS were observed across the pre-defined PD-L1 expression levels of 1%, 5%, or 10%. The OS HRs for nivolumab versus docetaxel among all PD-L1 subgroups were similar to the HR in the primary population.
- The ORR observed in nivolumab-treated patients was numerically higher in PD-L1 high expressors, than low expressors, but responses were also seen in PD-L1 low expressors. Furthermore, responses in the PD-L1 low expressors were above those typically seen with docetaxel. PD-L1 expression level was not predictive of OS outcome.
- No meaningful differences in PFS were observed across the pre-defined PD-L1 expression levels of 1%, 5%, or 10%.

Figure 12: CheckMate 017 - Forest plot of OS and PFS according to PD-L1 expression level



Source: (Brahmer 2015a)

Abbreviations: CI = Confidence Interval; OS = Overall Survival; PD-L1 = Programmed Cell Death-Ligand 1; PFS = Progression-Free Survival

4.9 Meta-analysis

A meta-analysis was not possible as only one study included nivolumab. A meta-analysis requires two or more studies that contain the invention of interest.

4.10 Indirect and mixed treatment comparisons

- The clinical systematic review identified 14 studies that met the inclusion criteria for the review. In line with the final NICE scope, two studies (Smit 2009; Kim 2015) did not include comparators relevant to the decision problem, nor did they contribute to the evidence network. Relevant comparators were therefore assessed in 12 studies:
    - Nivolumab (n=1); Docetaxel (n=6); Erlotinib (n=8); and BSC (n=1)*.
    - Only three trials, CheckMate 017, TAILOR and Br.21 contributed to ITC
- An indirect comparison between nivolumab and erlotinib was possible using data from a subgroup analysis of the TAILOR trial; however, the heterogeneity between the studies means that results should be interpreted with caution
- An indirect comparison of nivolumab to BSC was only possible by expanding the inclusion criteria of the ITC to include all pre-treated population i.e. patients currently receiving second- or further-line therapy
- Although there are the limitations of the analysis due to paucity and heterogeneity of the available data, the results of the ITC suggests a [redacted]% probability that OS is better with nivolumab compared with erlotinib with a statistically significant improvement in PFS, and that nivolumab offers a significant improvement in OS compared with BSC
    - OS: nivolumab vs. erlotinib – HR: [redacted]; 95% CI: [redacted] p=[redacted]; note that this analysis did not reach statistical significance by a very small margin
    - PFS: nivolumab vs. erlotinib - HR: [redacted]; 95% CI: [redacted]; p<[redacted]
    - OS: nivolumab vs. BSC - HR: [redacted]; 95% CI: [redacted]; p=[redacted] in heavily pre-treated patients

*Note that the total number of studies does not total 12 as more than one comparator may have been included in a single study

Search strategy

The systematic review detailed in Section 4.1, was used to identify trials included in the indirect comparison and network meta-analysis for both the treatment under consideration (nivolumab) and relevant comparator treatments.

Study selection

The systematic review detailed in Section 4.1, was used to identify trials relevant to the decision problem i.e. for nivolumab and comparators included by NICE; docetaxel, erlotinib, and BSC. It should be noted that the clinical evidence for nivolumab is in those patients who have locally advanced or metastatic squamous NSCLC who have been previously been treated with at least one prior therapy, including a platinum-based chemotherapy.

Methods and outcomes of included studies

The clinical systematic review identified 14 studies that met the inclusion criteria of the review. The systematic review used a broad inclusion criteria to allow the identification of all studies that might be relevant to the decision problem. Two studies (Smit 2009; Kim 2015) did not include comparators included in the NICE scope nor did these studies contribute data to the ITC analysis. Of the remaining 12 studies, one study (CheckMate 017) included nivolumab; six studies included docetaxel monotherapy; and eight studies included erlotinib monotherapy and one study evaluated the use of BSC (Shepherd 2005). It should be noted

that the number of studies does not sum to 12 as one study may include more than one comparator. Although not explicitly stated in the Br.21 study (Shepherd 2005), it is assumed that the patients randomised to placebo continued to receive palliative BSC. For this analysis it is therefore assumed that results of the Br.21 study represent patients receiving BSC.

Three studies (Br.21, TAILOR, and CheckMate 017) contributed to the ITC. A full description of the ITC analysis is given in Appendix 7, including network diagrams (Appendix 7.15). A brief overview of the three studies included in the ITC analysis is given in Table 18; baseline characteristics of the patients included in these studies are provided in Table 19 and Table 20.

A brief overview of the studies included in the systematic review, baseline characteristics of the patients included in these studies and reported outcomes are given in the Appendix 7.12, Appendix 7.13 and Appendix 7.14, respectively.

Table 18: Summary of RCTs reporting data for pre-treated squamous NSCLC population and included in analysis

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
Br.21	(Shepherd 2005)	Randomised, multicentre international, double-blind, placebo-controlled Phase III study	15 countries worldwide	Erlotinib (488) BSC (243)	NR	• Age ≥18 years • Stage IIIB or IV NSCLC • PS 0 to 3 • 1 or 2 prior chemotherapy • Ineligible for further chemotherapy • Adequate haematologic and biochemical values
CheckMate 017	(Brahmer 2015a)	Randomised, multicentre international, open-label, active-controlled Phase III study	21 countries worldwide	Nivolumab (135) Docetaxel (137)	Duration of the study from start of randomisation to final analysis: approximately 38 months (14 months of accrual + 24 months of follow-up) Minimum follow-up: 10.6 months	• Age >18 years • Histologically- or cytologically-documented squamous cell NSCLC (stage IIIB/IV) • Recurrent or PD following multimodal therapy • Recurrence or progression during or after 1 prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease • Measurable disease by CT or MRI per RECIST 1.1 criteria • ECOG PS ≤1
TAILOR	(Garassino 2013)	Randomised, multicentre, open-label, active-controlled Phase III study	105 sites in Italy	Docetaxel (110) Erlotinib (109)	Median follow-up: 33 months	• Age ≥18 years • Histological or cytological confirmation of NSCLC • Locally advanced or metastatic NSCLC in second-line treatment • Wild-type EGFR • Recurrence or progression after platinum-based chemotherapy • No previous treatment with taxanes or anti-EGFR drugs • ECOG PS ≤2 • Adequate vital function

Abbreviations: CT = Computerised Tomography; ECOG = European Cooperative Oncology Group; EGFR = Epidermal Growth Factor Receptor; MRI = Magnetic Resonance Imaging; PS = Performance Status; NR = Not Reported; NSCLC = Non-Small Cell Lung Cancer; PD = Progressive Disease; RECIST= Response Evaluation Criteria in Solid Tumors

Table 19: Summary of baseline characteristics of studies reporting data for pre-treated squamous NSCLC population and included in analysis

Trial ID (Acronym)	Primary author, year (reference)	Treatment arm	N	Smokers n (%)				PS (ECOG*/WHO**) n (%)			
				Current	Former	Never	Current or former	PS 0	PS 1	PS 2	PS 3
Br.21	(Shepherd 2005)	Erlotinib	488	-	-	104 (21.3)	358 (73.4)	64* (13.1)	256* (52.5)	126* (25.8)	42* (8.6)
		Placebo	243	-	-	42 (17.3)	187 (77)	34* (14)	132* (54.3)	56* (23)	21* (8.6)
CheckMate 017	(Brahmer 2015a)	Nivolumab	135	-	-	10 (7.4)	121 (89.6)	27* (20)	106* (78.5)	-	-
		Docetaxel	137	-	-	7 (5.1)	129 (94.2)	37* (27)	100* (73)		-
TAILOR	(Garassino 2013)	Docetaxel	110	-	-	30 (27)	80 (73)	53* (48)	50* (45)	7* (6)	-
		Erlotinib	109	-	-	19 (17)	90 (83)	52* (48)	48* (44)	9* (8)	-

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSCLC = Non-Small Cell Lung Cancer; PS = Performance Status; WHO = World Health Organisation

Table 20: Summary of baseline characteristics of studies reporting data for pre-treated squamous NSCLC population and included in analysis

Trial ID (Acronym)	Primary author, year (reference)	Treatment arm	N	Disease stage (%)			EGFR mutation status	Histology	Age (range) in years, Median/Mean*	Male, %
				Stage III	Stage IV	Stage III/ IV				
Br.21	(Shepherd 2005)	Erlotinib	488	-	-	100%	EGFR mutation test, Overall: N=177 - EGFR wild-type: 77% - EGFR +ve: 23%	SQ: 30.5% NSQ: 69.5%	62 (34-87)	64.5%
		Placebo	243	-	-	100%			70 (31-81)	65.8%
CheckMate 017	(Brahmer 2015a)	Placebo		21.5%	77.8%	-	EGFR mutation status: - wild-type: 100% (assumed as all patients were squamous)	SQ: 100%	62 (39-85)	82.2%
		Docetaxel	137	17.5%	81.8%	-			64 (42-84)	70.8%
TAILOR	(Garassino 2013)	Docetaxel	110	-	-	-	EGFR wild-type: 100%	SQ: 34.7% NSQ: 75.3%	67 (35-83)	66%
		Erlotinib	109	-	-	-			66 (40-81)	71%

Abbreviations: EGFR = Epidermal Growth Factor Receptor; NSCLC = Non-Small Cell Lung Cancer; NSQ = Non-squamous; Sq = Squamous

Risk of bias

A detailed critical appraisal of the three studies that contributed to the analysis is given in Table 21 and a quality assessment of all the studies included in the systematic review (n=14) is given in Appendix 3.

- Only three trials (Br.21, CheckMate 017, and TAILOR) contributed to the ITC
- Two of these trials were open-label (CheckMate 017 and TAILOR); and one trial, despite stating it was double-blinded, did not report any details pertaining to blinding (Br.21)
- The patient populations included in these trials also differed; CheckMate 017 recruited pre-treated patients with only squamous advanced and/or metastatic NSCLC, whereas both the TAILOR and Br.21 trials included patients with both squamous and non-squamous NSCLC with subgroup data provided for the squamous population
- Furthermore, the CheckMate 017 and TAILOR trials recruited patients who had failed a platinum-based chemotherapy and had PS 0-1 and PS 0-2, respectively; however, the Br.21 study included patients who had failed one or two lines of chemotherapy and had a PS 0-3
- Due to the paucity of the available evidence, it was not possible to control for this heterogeneity in the analysis

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Table 21: Summary of quality assessment of RCTs included in the analysis

Trial ID (Acronym)	Primary author, year (reference)	JADAD score	Allocation concealment grade	Was randomisation carried out appropriately	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Br.21	(Shepherd 2005)	3	A	Not clear; This was a randomised study but the method of randomisation was not reported: Low risk; patients were centrally allocated to the respective treatment	Low risk; The baseline characteristics between the two treatment arms were well balanced	Not clear; Although this was double-blinded, however the details of blinding were not reported	Not clear; Withdrawals and reasons for withdrawals were not reported	Low risk; the authors measured all outcomes as reported in the protocol (NCT00036647)	Low risk; The safety and efficacy analysis was performed using ITT population
CheckMate 017	(Brahmer 2015a)	3	A	Low risk; the patients enrolled in the trial were randomised using IVRS. Allocation concealment was adequate.	Low risk; the baseline characters in the two groups were well balanced	High risk; this was an open-label trial	Low risk; study withdrawals were adequately reported	Low risk; the authors measured all outcomes as reported in the protocol (NCT01642004)	Low risk; ITT was used for efficacy analysis while mITT was used for safety analysis
TAILOR	Garassino 2013	2	B	Not clear; Treatment was randomly allocated in a 1:1 ratio with a minimisation algorithm, which stratified treatment allocation by centre, stage, type of first-line platinum-based chemotherapy and ECOG status(0–1 vs 2)	Low risk; There was no significant difference in the baseline characteristics reported between the two treatment arms	High risk; This was an open label study	Low risk; The withdrawals and the specific reasons for withdrawal were reported	High risk; Author has not measured all the outcomes that have been listed in clinical trial registry (NCT00637910)	Low risk; The primary efficacy and safety analysis was done using mITT population

Abbreviations: ECOG = Eastern Cooperative Oncology Group; HR = High Risk; LR = Low Risk; NR = Not Reported; IVRS: Interactive Voice Response System; ITT: Intention To Treat; mITT: Modified Intention to Treat

Methods of analysis and presentation of results

A summary of the outcomes data from the three studies that contributed to the ITC is presented in Table 22.

A summary of the outcomes data from all the studies included in the systematic review (n=14) is provided in the Appendix 7.14. A list of studies excluded from the analysis, along with the rationale for exclusion, is given in the Appendix 7.10.

Table 22: Summary of data from trials reporting data for pre-treated squamous NSCLC population and included in analysis

Trial ID (Acronym)	Primary reference	Treatment (N)	ORR, n (%)	DCR, n (%)	OS rate at 12 months, n (%)	OS (Reported as median (95% CI), months	OS (Reported as HR) (95% CI)	PFS (Reported as median (95% CI), months	PFS (Reported as HR) (95% CI)	Withdrawals due to treatment related AE, n (%)
Br.21 trial	(Shepherd 2005)	Erlotinib: Squamous	-	-	-	-	0.67, (0.5-0. 9)	-	-	-
		Placebo: Squamous	-	-	-	-		-	-	-
Checkmate 017	(Brahmer 2015a)	Nivolumab (135)	27 (20%)	66 (49%)	57 (42%)	9.23 (7.33-13.27)	0.59, (0.43-0.81)	3.48 (2.14-4.86)	0.62, (0.47-0.81)	4 (3%), Evaluable n= 131
		Docetaxel (137)	12 (9%)	59 (43%)	32 (23%)	6.01 (5.13-7.33)		2.83 (2.1-3.52)		13 (10%), Evaluable n= 129
		Erlotinib: Squamous (13)	-	-	-	-				-
TAILOR trial	(Garassino 2013)	Docetaxel (Squamous) (23)	-	-	-	-	0.90, (0.49-1.65)	-	0.57, (0.32-1.03)	-
		Erlotinib (Squamous) (31)	-	-	-	-		-		-

Abbreviations: AE = Adverse Event; CI = Confidence Interval; DCR = Disease Control Rate; HR = Hazard Ratio; PFS = Progression-Free Survival; ORR = Overall Response Rate; OS = Overall Survival

An ITC, comparing nivolumab and erlotinib, was possible in pre-treated patients with advanced squamous NSCLC. The TAILOR study and CheckMate 017 comprising of a total of 326 patients contributed to this analysis. It should be noted that the TAILOR study was an Italian study, which included a broad metastatic NSCLC patient population who had failed platinum-based chemotherapy, and subgroup data was available for 54 patients (25%) with squamous histology. HR was reported for both OS and PFS for the subgroup of squamous NSCLC patients.

A comparison of nivolumab with BSC was only possible if the patient population was expanded to include those squamous patients who had received one or more prior therapy. Therefore, this analysis included patients receiving treatment at third-line. By expanding the patient population three trials contributed to the analysis (Br.21, TAILOR and CheckMate 017). It should be noted that the CheckMate 017 study included patients with only one line of prior therapy (mainly a platinum-based combination therapy) and a PS of 0 or 1. Only one patient, included in the nivolumab group had received two lines of prior therapy. However, the inclusion criteria for the Br.21 study allowed the recruitment of patients with NSCLC with PS between 0 and 3 who had received two or more lines of therapy and who were not eligible for further chemotherapy.

Expanding the evidence base to patients who had received more than two lines of therapy did not increase the evidence base for the comparison of nivolumab and erlotinib.

A summary of the ITC results is given in Table 23. A full description of the analysis, along with network diagrams, is given in the Appendix 7.15. The ITC methodology is given in the Appendix 7.

Table 23: Results of the ITC

Outcome	**Nivolumab vs. erlotinib**	**Nivolumab vs. BSC**
	HR (95% CI); p-value	**HR (95% CI); p-value**
Patient population: squamous NSCLC in patients with one prior therapy only		
OS	[redacted]	
PFS	[redacted]	
Patient population: squamous NSCLC in patients with at least one prior therapy		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: BSC = Best Supportive Care; CI = Confidence Interval; HR = Hazard Ratio; ITC = Indirect Treatment Comparison; NSCLC = Non-Small Cell Lung Cancer; OS = Overall Survival; PFS = Progression-Free Survival

These results suggested a [redacted]% probability that OS is better with nivolumab compared with erlotinib (HR: [redacted]; 95% CI: [redacted]; p=[redacted]). Also, nivolumab offers a significant improvement in OS compared with BSC (HR: [redacted]; 95% CI: [redacted]; p=[redacted]) in heavily pre-treated patients.

Furthermore, a statistically significant improvement was observed in PFS on comparing nivolumab with erlotinib ([redacted]).

Due to paucity of available evidence and heterogeneity among the studies, these analysis results should be interpreted with caution.

4.11 Non-randomised and non-controlled evidence

List of relevant non-randomised and non-controlled evidence

In addition to the Phase III RCT (CheckMate 017), a single-arm Phase II non-RCT (CheckMate 063) and a single-arm, Phase I, dose-escalation non-RCT (CheckMate 003) also evaluated the safety and/or efficacy of nivolumab in pre-treated patients with squamous NSCLC (Table 24).

CheckMate 063 and CheckMate 003 are included in this submission as they provide clinical data that are directly relevant to the NICE decision problem: nivolumab for pre-treated patients with locally advanced or metastatic squamous NSCLC who had progressed after receiving platinum-based doublet chemotherapy. CheckMate 063 included patients who had received prior treatment with both platinum-based doublet chemotherapy and at least one additional systemic therapy (third-line setting) (Rizvi 2015), while CheckMate 003 included patients who had received at least one prior systemic therapy, including a platinum-based or taxane-based chemotherapy (although the majority of patients had multiple previous cycles of chemotherapy) (Gettinger 2015).

CheckMate 063 and CheckMate 003 are the only non-RCT nivolumab trials with available data for squamous NSCLC. See Section 4.14 below for further information about on-going RCT and non-RCT nivolumab trials.

Summary of methodology of the relevant non-randomised and non-controlled evidence

A summary of the study methodology is provided in Table 24.

Table 24: List of relevant non-RCTs

Study number (acronym)	Objectives	Population	Intervention	References	Justification for inclusion
CheckMate 063 (CA209-063)	To assess the clinical activity of nivolumab, as measured by the IRC, using assessed ORR	Adult patients with advanced or metastatic squamous cell NSCLC who had received both platinum doublet chemotherapy and at least one additional systemic therapy	Nivolumab 3 mg/kg Q2W until disease progression*	Primary reference (Rizvi 2015) Secondary reference (Bristol-Myers Squibb 2014b; Bristol-Myers Squibb 2014a)	Examines the efficacy of nivolumab in a heavily pre-treated (third-line and later line) squamous NSCLC population
CheckMate 003 (MDX110603, CA209-003)	To determine if nivolumab is safe and tolerable at the dose levels investigated and, in addition, to conduct a preliminary assessment of anti-tumour activity.	Adult patients with advanced or recurrent malignancies, including a subset of patients with squamous NSCLC, who had received at least one and up to five previous therapies and had experienced progression through at least one platinum- or taxane-based regimen	Nivolumab 1-, 3-, 10-mg/kg Q2W for up to 96 weeks**	Primary reference (Gettinger 2015)† Secondary reference (Topalian 2012)‡	Examines the efficacy of nivolumab in a heavily pre-treated (up to five prior treatments) squamous and non-squamous NSCLC population

Abbreviations: IRC = Independent Radiology Review Committee; kg = Kilograms; Mg = milligrams; NSCLC = Non-Small Cell Lung Cancer; ORR = Objective Response Rate; Q2W = Every 2 Weeks; RCT = Randomised Controlled Trial

* Each 2-week treatment period was considered 1 cycle. ** Each treatment cycle is comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43 with a response assessment between Days 52 and 56. †Gettinger et al (2015) provided clinical and demographic data for the NSCLC patient sub-set. ‡Data in Topalian et al (2012) included patients with all included cancers (including but not limited to NSCLC). This paper was used to obtain methodological characteristics of the study.

CheckMate 063

CheckMate 063 was a Phase II, single-arm, multicentre, global, open-label trial conducted at 27 sites in four countries (France, Germany, Italy, and the US). The trial included 117 heavily pre-treated patients with locally advanced or metastatic squamous NSCLC. To be included in the study, patients had to have received both platinum-based doublet chemotherapy and at least one additional systemic therapy (third- and later-line setting) as this was a pre-specified inclusion criterion (Rizvi 2015). Patients (N=117) received 3mg/kg nivolumab as an IV infusion every 2 weeks, with allowances for a delay of nivolumab treatment for a maximum of 6 weeks due to an AE (delays of nivolumab dose were allowed for protocol defined Grade 2 or Grade 3 AEs) (Rizvi 2015). A 2-week treatment period was considered one treatment cycle and comprised of one dose of study drug administered on Day 1 of the treatment cycle.

The primary endpoint of the study was the proportion of patients with a confirmed OR as assessed by the Independent Radiology Review Committee (IRC) using RECIST 1.1 criteria (ORR). The secondary endpoint of this study was the proportion of patients with investigator-assessed confirmed OR using RECIST 1.1. Further exploratory endpoints included: the characterisation of immunogenicity of nivolumab, the safety and tolerability of nivolumab, PFS and OS of all treated patients, and the association between ORR and PD-L1 expression level in all patients.

Results for CheckMate 063 are based on two interim data analyses: an interim clinical database lock that occurred on 23rd July 2014, and an IRC database lock that occurred on 15th August 2014. [redacted] (Bristol-Myers Squibb 2014b). The CheckMate 063 study will end when analysis of survival is completed, up to 5 years beyond analysis of the primary endpoint.

CheckMate 003

CheckMate 003 was a Phase I, open-label, multicentre study across 12 sites in the US. It was a multi-dose, dose escalation study of nivolumab in patients with selected advanced or recurrent malignancies, and included 129 patients with NSCLC (54 squamous and 74 non-squamous patients, and 1 patient with unknown tumour cell histology). Patients were heavily pre-treated, having received at least one, and up to five, prior systemic therapies for advanced/recurrent and progressing disease, including either a platinum-based or taxane-based chemotherapy. In the study, patients received nivolumab 1, 3, or 10mg/kg every 2 weeks for up to 96 weeks (12 treatment cycles). Each treatment cycle was comprised of four doses of study drug administered on Days 1, 15, 29, and 43, with a response assessment between Days 52 and 56.

The primary endpoint was safety. Secondary (efficacy) outcomes included ORR, DOR, and TTR. OS and PFS were included as an exploratory efficacy outcome. Treatment was discontinued at 96 weeks and the median follow-up was 39 months (range: 32 to 66 months).

Statistical analysis of the relevant non-randomised and non-controlled evidence

Further detail on the methodology and statistical analyses of the two studies are provided in the Appendix 16.1 and 16.2.

Participant flow

CheckMate 063

Of the 140 patients enrolled, 117 (83.6%) were treated with nivolumab 3mg/kg Q2W. As of 15 August 2014 clinical database lock, the minimum follow-up for response was approximately 11 months.

The study population and baseline characteristics were representative of heavily pre-treated squamous NSCLC patients for whom no approved or established treatment options exist. The majority (83%) of the patients had stage IV NSCLC while 17% had stage IIIB disease. Around 65% of the patients had three or more prior therapies, and ECOG PS was 1 in 78% of patients, and 0 in all other patients (Rizvi 2015).

Detailed baseline characteristics of this trial are provided in Appendix 16.3.1.

CheckMate 003

From November 2008 through January 2012, 129 patients with advanced NSCLC were enrolled across 12 sites in the United States, with a median follow-up of 39 months (range: 32 to 66 months). Within the advanced squamous NSCLC patient subgroup (n=54/129), 15, 18, and 21 patients received 1, 3, and 10mg/kg nivolumab Q2W, respectively.

Baseline demographics and disease characteristics were in line with those expected of a NSCLC population. The median age of patients was 65 years, and 98% had an ECOG PS of 0 or 1. The patients in this trial were heavily pre-treated; 54% had received three or more prior systemic treatments for advanced NSCLC. All except one patient (99.2%) had previously received platinum-based chemotherapy (Gettinger 2015).

Detailed baseline characteristics of this trial, for the NSCLC subset are provided in Appendix 16.3.2.

Quality assessment of the relevant non-randomised and non-controlled evidence

A detailed quality assessment of CheckMate 063 and CheckMate 003 is provided in the Appendix 8.

Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

CheckMate 063

Tumour Response

At the time of the August 2014 IRC database lock, the ORR was 14.5% (responders, n=17/117) as assessed by the IRC (Table 25) (Rizvi 2015). The ORR was 14.5% and TTR was 3.3 months. At the time of reporting, median DOR had not been reached.

The majority of patients' responses happened before the first scan and were durable. The median DOR was not reached at the point of the data lock as 77% of patients were still responding at the time of analysis (n=13/17) (Rizvi 2015), further suggesting a durability of response (Table 25).

The rate of stable disease (SD) was 26% and the median duration of SD was 6.0 months (Rizvi 2015). Of these [redacted] who experienced SD, [redacted] Additional evidence of a therapeutic benefit was noted in the form of durable stable disease in many patients, clinical activity for CNS disease and non-conventional responses in patients who continued

nivolumab after disease progression suggesting an immune-related pattern of anti-tumour activity.

A high concordance between IRC and investigator-assessed responses was observed (Rizvi 2015). Results for the investigator-assessed ORR and ORR by PD-L1 expression levels are presented in Appendix 16.4.1.

Survival Outcomes

From analysis of IRC-assessed PFS (August 2014 database lock), a median PFS of 1.9 months (95% CI: 1.8, 3.2) was observed. Median OS was 8.2 months (95% CI: 6.1, 10.9) (Rizvi 2015). The 6-month and 1-year survival rates are presented in Table 25 and Kaplan-Meier curves are provided in Appendix 16.4.1.

Table 25: CheckMate 063 - Summary of efficacy results

Efficacy parameter	**Nivolumab 3 mg/kg N=117**
Primary Endpoint: IRC-Assessed ORR[a] Number of responders (%) Exact 95% CI	 17 (14.5) 8.7, 22.2
DOR[b] Median (95% CI), months Range, months	 NtR (8.3, NtR) 1.9+, 11.5+*
SD No. (%) of SD Median (95% CI), months	 30 (26) 6.0 (4.7, 10.9)
PFS[c] Median PFS (95% CI), months 6-month PFS rate (95% CI) 1-year PFS rate (95% CI)	 1.9 (1.8, 3.2) 25.9 (18.0, 34.6) 20.0 (12.7, 28.5)
OS No. of events (%) Median OS (95% CI), months 6-month OS rate (95% CI) 1-year OS rate (95% CI)	 72 (62) 8.2 (6.1, 10.9) 60.1 (50.5, 68.4) 40.8 (31.6, 49.7)

Source: (Bristol-Myers Squibb 2014b; Rizvi 2015)

Abbreviations: CI = Confidence Interval; DOR = Duration of Response; IRC = Independent Radiology Review Committee; kg = Kilograms; mg = Milligrams; NtR = Not Reached; ORR = Objective Response Rate; OS = Overall Survival; PFS = Progression-Free Survival; SD = Stable Disease

Note: [a]Confirmed CR + PR as per RECIST v1.1 criteria (after imaging plus clinical review by the IRC); [b]Determined for patients with IRC-assessed confirmed CR or PR; [c]Based on IRC assessment

Subgroup analyses (PD-L1 expression level)

No clear association between PD-L1 expression level and OS was observed at any expression level (1%, 5% and 10%) (Rizvi 2015). Results ORR by PD-L1 expression level status are presented in Appendix 16.4.1.

In summary, the results of both the ORR and survival outcomes show the value of nivolumab in meeting the unmet clinical need for this hard-to-treat, refractory, pre-treated (third-line) squamous NSCLC patient population.

CheckMate 003

Tumour response

The confirmed ORR was 17.1% (n=22/129) in all patients with NSCLC treated at any nivolumab dose level (1, 3, or 10 mg/kg Q2W) (Table 26) (Gettinger 2015). Specifically, for NSCLC patients treated at the 3 mg/kg Q2W dose, the confirmed ORR was 24.3% (n=9/37) (Gettinger 2015).

In patients with squamous histology who were treated with 3mg/kg nivolumab (the subset of patients directly relevant to the population defined by the NICE decision problem), the ORR observed was 22.2% (n=4/18) (Table 26) (Gettinger 2015).

[redacted] was observed in [redacted] of patients with NSCLC pooled across all doses of nivolumab. The median duration of [redacted] for all treated patients was [redacted], with a range of [redacted] . SD rates and durations were similar across dose levels and NSCLC histologies (Table 26) (Gettinger 2015; Bristol-Myers Squibb 2013).

Table 26: CheckMate 003 - Summary of tumour response outcomes in all treated patients with NSCLC

Efficacy Parameter	All NSCLC All doses N=129	Squamous NSCLC All doses N=54	Squamous NSCLC 3 mg/kg N=18
ORR[a] n (%) **(95% CI)**	22 (17.1) (11.0, 24.7)	9 (16.7) (7.9, 29.3)	4 (22.2) (6.4, 47.6)
[redacted]*			
[redacted]*	[redacted]*	[redacted]*	[redacted]*
[redacted]*	[redacted]*	[redacted]*	[redacted]*
[redacted]*	[redacted]*	[redacted]*	[redacted]*
[redacted]*	[redacted]*	[redacted]*	[redacted]*
[redacted]*	[redacted]*	[redacted]*	[redacted]*

Source: (Gettinger 2015; Bristol-Myers Squibb 2013)

Abbreviations: BOR= Best Objective Response; CI = Confidence Interval; CR = Complete Response; kg = kilograms; mg = Milligrams; NSCLC = Non-Small Cell Lung Cancer; ORR = Objective Response Rate; PD = Progressive Disease; PR = Partial Response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = Stable Disease

[a] Confirmed PR or CR per sponsor using RECIST v1.0 criteria based on investigator-assessed tumour measurements. [b] BOR was derived by the Sponsor using RECIST v1.0 criteria on investigator-assessed tumour measurements.

*All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb 2014b)

The sponsor-assessed TTR ranged from 7.4 to 31.4 weeks (median TTR was not reached as the analysis was conducted in the overall population). Long-term (minimum 2 years) follow-up indicated a durability of response in the 22 confirmed responders treated with any

nivolumab dose. Additional information on the DOR, by NSCLC histology, is provided in Appendix 16.4.2.

Survival outcomes

Median OS was 9.9 months (95% CI: 7.8, 12.4) for all 129 patients with NSCLC (Rizvi 2015). In the 37 patients who received nivolumab 3mg/kg, the median OS was 14.9 months (95% CI: 7.3, 30.3) (Rizvi 2015). In the total population of patients with NSCLC and across all dose levels, 1-, 2-, and 3-year survival rates were 42% (95% CI: 33, 50), 24% (95% CI: 17, 33), and 18% (95% CI: 11, 25), respectively (Gettinger 2015). At the 3mg/kg dose, 1-, 2-, and 3-year OS rates were 56% (95% CI: 38, 71), 42% (95% CI: 24, 58), and 27% (95% CI: 12, 43), respectively. Median OS and survival rates were similar in patients with squamous and non-squamous histologies (1-, 2-, and 3-year OS rate for squamous NSCLC at 3mg/kg: 49%, 35%, and 28%, respectively) (Gettinger 2015).

Median PFS across doses was 2.3 months (95% CI: 1.8, 3.7). Long-term follow-up across doses indicated a slowing of PFS events rates consistent with a sustained clinical effect. PFS rates across doses at 6 months, 1 year, and 2 years were 33%, 22%, and 9%, respectively. PFS across doses was comparable across NSCLC histologies (Gettinger 2015).

The Kaplan-Meier curves for all NSCLC patients by histology are provided in Appendix 16.4.2.

4.12 Adverse reactions

- Clinical trial data show that nivolumab is well tolerated
- The current standard of care, docetaxel, is generally poorly tolerated and many patients are not suitable for treatment with this agent
- The overall safety profile of nivolumab is consistent across studies in terms of type, frequency, and severity of adverse events
- Nivolumab, as with other immuno-oncology treatments, has AEs that are immune-related or immunological in origin.
    - These are termed 'Select' AEs and specific treatment algorithms for these Select Adverse Events have been defined during the nivolumab development program

CheckMate 017

- Nivolumab demonstrated a more favourable safety profile vs. docetaxel (SOC) (in both haematologic and non-haematologic AEs)
- There were fewer Grade 3-4 treatment-related AEs in the nivolumab group vs. docetaxel arm (7% vs. 55%)
- Grade 3-4 AEs were less frequent in nivolumab arm compared with the docetaxel arm
- Serious AEs that were drug-related were less frequent in nivolumab arm compared with the docetaxel arm
- Treatment-related AEs leading to discontinuation were less common in the nivolumab vs. docetaxel arm (3.1% vs. 10.1%, respectively)
- Immune-related AEs were manageable with established treatment algorithm guidelines (SmPC in Appendix 1)
- No deaths were attributed to nivolumab toxicity; three deaths were attributed to docetaxel toxicity

Introduction

Select AEs are a category of immune-related adverse events (irAEs) with immune-related aetiology, defined as AEs that require more frequent monitoring or intervention with immune suppression. Select AEs are primarily caused by the inflammatory mechanism of the immune system and are due to the immunologic mode of action of nivolumab.

Select AEs require more frequent monitoring when compared to 'any AEs'; however, these are usually manageable and reversible with interruption of drug treatment and, for moderate/high grade Select AEs, treatment with steroid or other immunosuppressants. Hormone replacement therapy may be used depending on the specific nature of the Select AE. For Select AEs of low grade, treatment with nivolumab can be resumed once the Select AE has been resolved. For moderate/high grade Select AEs, withdrawal of nivolumab is recommended (Bristol-Myers Squibb 2015c). There are treatment algorithms for each Select AE category to guide management of these types of AE (Bristol-Myers Squibb 2015c).

The Select AEs are based on the types of AEs observed across all nivolumab monotherapy studies. As the reporting of AEs is based on individual preferred terms this can often underestimate the frequency of similar types of organ-related AEs. Select AEs are therefore grouped by the most commonly reported preferred terms by organ category as shown below:

1. Pulmonary toxicity
2. Gastrointestinal toxicity
3. Endocrinopathy
4. Hepatic toxicity
5. Renal toxicity
6. Skin toxicity
7. Infusion reaction

Hypersensitivity/infusion reactions are analysed along with the Select AE categories because multiple event terms may be used to describe such events, and pooling of terms is therefore necessary for full characterisation. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered Select AEs. Special guidance and precautions for use of nivolumab are provided for the management of Select AEs in the SmPC (Appendix 1).

Safety of nivolumab

Nivolumab is the subject of an extensive clinical trial programme across a number of different tumour types, and the safety of nivolumab has been assessed in a number of clinical trials. The safety data from all these studies are consistent across tumour types and histologies.

In this submission we present nivolumab safety data from three NSCLC trials (CheckMate 017, CheckMate 063, and CheckMate 003).

Safety in squamous NSCLC

The overall safety and tolerability of nivolumab in the squamous NSCLC population is based on patients who received the licensed dose of nivolumab 3mg/kg in two NSCLC studies (CheckMate 017 and CheckMate 063) and described below. The safety profile of nivolumab in the Phase I dose-escalation CheckMate 003 trial is also briefly described.

Overall, nivolumab is a well-tolerated therapy for squamous NSCLC with an acceptable AE profile.

CheckMate 017

The methodology and baseline characteristics for this study are given in Section 4.2 and Section 4.5, respectively.

Overall safety summary

Comparative safety data from CheckMate 017 demonstrated that nivolumab monotherapy has a more favourable safety profile compared to docetaxel, including both haematologic and non-haematologic toxicities, in patients with previously-treated locally advanced or metastatic squamous NSCLC. Toxic effects normally reported with traditional chemotherapies were lower for the nivolumab group when compared to the docetaxel group. The frequency of both haematological and non-haematological AEs, including severe toxic events, was substantially lower with nivolumab compared with docetaxel (Table 27).

Treatment-related AEs occurred less frequently in the nivolumab group compared to the docetaxel group. In the nivolumab group, 58% of patients had treatment-related AEs of any

grade, 7% had Grade 3 or 4 treatment-related AEs, and no patients died from a treatment-related AE (Brahmer 2015a). In comparison, 86% of patients treated with docetaxel had treatment-related AEs, 55% had Grade 3 or 4 treatment-related AEs, and three (2%) docetaxel patients died from a treatment-related AE. Treatment-related Serious AEs of Grade 3 or 4 also occurred less frequently in the nivolumab group compared with the docetaxel group: 2% and 19% respectively (Brahmer 2015a).

There were fewer treatment-related AEs leading to treatment discontinuation in the nivolumab group compared with the docetaxel group (% and 10%, respectively), with 2% of patients experiencing a Grade 3 or 4 treatment-related AE leading to treatment discontinuation in the nivolumab group compared to 6% in the docetaxel group (Brahmer 2015b).

All occurrences of Select AEs were managed with the use of established treatment algorithm guidelines (Brahmer 2015a).

The overall safety profiles of both nivolumab and docetaxel were consistent with expectations based on prior data with respect to the type, frequency, and severity of reported events. There were no new safety concerns with nivolumab monotherapy treatment and no deaths were attributed to nivolumab therapy in CheckMate 017.

Table 27: CheckMate 017 - Summary of deaths (All treated subjects) and AEs

	Nivolumab, n (%) (N = 131)		Docetaxel, n (%) (N = 129)	
All Deaths	[redacted]*		[redacted]*	
Reason for death:				
Disease progression	73 (55.7)		86 (66.7)	
Study drug toxicity	0		3 (2)	
Unknown	[redacted]*		[redacted]*	
Other	[redacted]*		[redacted]*	
Deaths within 30 days of last dose	[redacted]*		[redacted]*	
Deaths within 100 days of last dose	[redacted]*		[redacted]*	
	Any grade n (%)	**Grade 3-4 n (%)**	**Any grade n (%)**	**Grade 3-4 n (%)**
All causality AEs	127 (96.9)	[redacted]*	125 (96.9)	[redacted]*
Treatment-related AEs	76 (58)	9 (7)	111 (86)	71 (55)
All causality Select AEs	[redacted]*	n/a	[redacted]*	n/a
All treatment-related Select AEs	[redacted]*	n/a	[redacted]*	n/a
All causality SAEs	[redacted]*	[redacted]*	[redacted]*	[redacted]*
All treatment-related SAEs	9 (7)	3 (2)	31 (24)	25 (19)
All causality AEs leading to discontinuation	[redacted]*	[redacted]*	[redacted]*	[redacted]*
All treatment-related AEs leading to discontinuation	4 (3)	2 (2)	13 (10)	8 (6)

Source: Table 8.1-1, Table 8.2-1, Table 8.3.1-1, Table 8.4.1-1, Table 8.4.2-1, Table 8.3.2-1, Table 8.7-1, Table 8.5.1-1, and Table S.6.5 in (Bristol-Myers Squibb 2015a) and (Brahmer 2015b)

Abbreviations: AE = Adverse Event; n/a = data not available; SAE = Serious Adverse Event

*All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb 2015a)

Deaths

For [redacted], there were [redacted] deaths in the nivolumab treatment arm, but none were treatment-related. In the docetaxel group, there were [redacted] (Bristol-Myers Squibb 2015a).

[redacted] was the most common cause of death: 73 (55.7%) patients in the nivolumab group and 86 (66.7%) patients in the docetaxel group (Bristol-Myers Squibb 2015a). No patients in the nivolumab group died due to study drug treatment, whereas in the docetaxel group, there were three (2%) treatment-related deaths, ([redacted]) (Table 27) (Brahmer 2015a; Bristol-Myers Squibb 2015a).

AEs leading to discontinuation

All causality AEs led to treatment discontinuation less frequently in the nivolumab group than in the docetaxel group (in 10.7% vs. 20.2% of the patients, respectively) (Bristol-Myers Squibb 2015a). Treatment-related AEs led to treatment discontinuation less frequently in the nivolumab group than in the docetaxel group (in 3% vs. 10% of the patients, respectively) (Brahmer 2015a).

In the nivolumab group, the most frequently reported (≥1%) treatment-related AEs leading to the discontinuation was pneumonitis (n=2; 2%) (Brahmer 2015a; Brahmer 2015b). Two additional patients in the nivolumab group discontinued treatment owing to pneumonitis (one for whom the relationship was changed from not treatment-related to treatment-related after database lock, and one who discontinued >30 days after the most recent dose).

In the docetaxel group, the most frequently reported (≥1%) treatment-related AEs leading to discontinuation was peripheral neuropathy (3%) and fatigue (2%) (Brahmer 2015a).

Treatment-related AEs

The rates of all treatment-related AEs and treatment-related serious adverse events (SAEs), including both haematologic and non-haematologic toxic events, occurred less frequently with nivolumab than with docetaxel (Table 27 and Table 28).

In the nivolumab group, 58% of the patients had treatment-related AEs of any grade, 7% had treatment-related AEs of Grade 3 or 4, and no patients had Grade 5 treatment-related AEs (i.e. death). In the docetaxel group, 86% of the patients had treatment-related AEs of any grade, 55% had treatment-related AEs of Grade 3 or 4, and 2% had treatment-related AEs of Grade 5 (i.e. died) (Brahmer 2015a).

[redacted] (Bristol-Myers Squibb 2015a). A number of treatment-related AEs (any grade) occurred more commonly in the docetaxel group than the nivolumab group, which included: neutropenia, febrile neutropenia, fatigue, neutrophil count decreased, white blood cell count decreased, asthenia, leukopenia, anaemia, diarrhoea, and peripheral neuropathy (Table 28). In comparison, the only treatment-related AE (any grade) that occurred in a higher number of patients in the nivolumab group, compared to the docetaxel group, was pneumonitis (5% versus 0%). The majority of AEs were Grade 1-2. The higher rates of both all-grade and Grade 3-4 treatment-related AEs and SAEs in the docetaxel group were mainly attributable to haematological toxicities and infections, consistent with the myelosuppressive profile of docetaxel. The most frequently reported treatment-related AEs with nivolumab were: fatigue (16%); decreased appetite (11%); and asthenia (10%). In docetaxel treated patients, the most frequently reported treatment-related AEs were: neutropenia (33%); fatigue (33%); nausea (23%); alopecia (22%) and anaemia (22%) (Table 28).

Table 28: CheckMate 017 - Summary of treatment-related AEs, reported in ≥5% of treated patients

	Nivolumab (N = 131)		Docetaxel (N = 129)	
	Any grade n (%)	**Grade 3-4 n (%)**	**Any grade n (%)**	**Grade 3-4 n (%)**
Total patients with an event	76 (58)	9 (7)	111 (86)	71 (55)
General disorders and administration site conditions	41 (31.3)	1 (0.8)*	68 (52.7)	14 (10.9)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Asthenia	13 (10)	0	18 (14)	5 (4)
Pyrexia	6 (5)	0	10 (8)	1 (1)
Mucosal inflammation	3 (2)	0	12 (9)	0
Oedema peripheral	2 (2)	0	8 (6)	0
Gastrointestinal disorders	24 (18.3)	1 (0.8)	61 (47.3)	7 (5.4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhoea	10 (8)	0	26 (20)	3 (2)
Vomiting	4 (3)	0	14 (11)	1 (1)
Abdominal pain	2 (2)	0	7 (5)	1 (1)
Constipation	2 (2)	0	8 (6)	0
Skin and subcutaneous tissue disorders	19 (14.5)	0*	39 (30.2)	5 (3.9)
Rash	5 (4)	0	8 (6)	2 (2)
Alopecia	0	0	29 (22)	1 (1)
Metabolism and nutrition disorders	18 (13.7)	1 (0.8)	36 (27.9)	5 (3.9)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Musculoskeletal and connective tissue disorders	17 (13.0)	0*	29 (22.5)	3 (2.3)
Arthralgia	7 (5)	0	9 (7)	0
Myalgia	2 (2)	0	13 (10)	0
Respiratory, thoracic and mediastinal disorders	17 (13.0)	1 (0.8)	13 (10.1)	2 (1.6)
Pneumonitis	6 (5)	1 (1)	0	0
Nervous system disorders	13 (9.9)	1 (0.8)	43 (33.3)	6 (4.7)
Dizziness	2 (2)	0	7 (5)	0
Paraesthesia	2 (2)	0	7 (5)	0
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Investigations	12 (9.2)	2 (1.5)	21 (16.3)	9 (7.0)
Neutrophil count decreased	0	0	8 (6)	6 (5)
White blood cell count decreased	0	0	7 (5)	5 (4)

	Nivolumab (N = 131)		Docetaxel (N = 129)	
	Any grade n (%)	**Grade 3-4 n (%)**	**Any grade n (%)**	**Grade 3-4 n (%)**
Blood and lymphatic system disorders	4 (3.1)	1 (0.8)	68 (52.7)	50 (38.8)
Anaemia	2 (2)	0	28 (22)	4 (3)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)

Source: (Brahmer 2015a; Bristol-Myers Squibb 2015a)

Abbreviations: AE = Adverse Event

NOTE: a patient may be recorded as having more than one adverse event within a category

Select AEs

The majority of nivolumab Select AEs were manageable and resolved using the recommended treatment algorithm guidelines (SmPC – Appendix 1) for early identification and intervention.

In the nivolumab group, all-causality Select AEs (Any grade) were most frequently reported (≥10% of patients) in the [redacted] and [redacted] categories ([redacted]). Grade 3-4 Select AEs were reported by ≤3% of patients in the nivolumab group in all Select AE categories (Brahmer 2015a). Across categories, there were only three Grade 3 treatment-related Select AEs reported in the nivolumab group: one event of tubulointerstitial nephritis, one event of colitis, and one event of pneumonitis, which was changed from “not treatment-related” to “treatment-related” after database lock; no Grade 4 Select AEs were reported (Table 29) (Brahmer 2015a).

Time to onset and time to resolution of Select AEs were also analysed. Median time to onset of Select treatment-related AEs ranged from 0.3 to 17.6 weeks in the nivolumab group versus 1.0 to 17.7 weeks in the docetaxel group. The median times to resolution of treatment-related Select AEs ranged from 0.3 to 5.0 weeks in the nivolumab group and 0.7 to 5.6 weeks in the docetaxel group.

Immune-modulating medication was administered for management of a proportion of AEs in each Select AE category in both treatment groups. Most immune-modulating medications used were systemic corticosteroids, except for the skin events where topical dermatological corticosteroid preparations were also used, and for pulmonary events, where inhaled anti-asthmatic agents were also used (Brahmer 2015a).

Across Select AE categories, the majority of events were manageable, with resolution occurring even when immunosuppressive medication was needed (Brahmer 2015a).

Table 29: CheckMate 017 - Summary of treatment-related Select AEs

	Nivolumab (N = 131)		Docetaxel (N = 129)	
	Any grade n (%)	Grade 3-4 n (%)	Any grade n (%)	Grade 3-4 n (%)
Endocrine	5 (4)	0	0	0
Hypothyroidism	5 (4)	0	0	0
Gastrointestinal	11 (8)	1 (1)	26 (20)	3 (2)
Diarrhoea	10 (8)	0	26 (20)	3 (2)
Colitis	1 (1)	1 (1)	0	0
Hepatic	2 (2)	0	2 (2)	1 (1)
Alanine aminotransferase increased	2 (2)	0	1 (1)	1 (1)
Aspartate aminotransferase increased	2 (2)	0	1 (1)	1 (1)
Blood bilirubin increased	0	0	1 (1)	0
Pulmonary	7 (5)	1 (1)	1 (1)*	0
Pneumonitis	6 (5)	1 (1)	0	0
Lung infiltration	1 (1)	0	0	0
Interstitial lung disease	0	0	1 (1)*	0
Renal	4 (3)	1 (1)	3 (2)	0
Blood creatinine increased	4 (3)	0	2 (2)	0
Tubulointerstitial nephritis	1 (1)	1 (1)	0	0
Renal failure acute	0	0	1 (1)	0
Skin	12 (9)	0	11 (9)	2 (2)
Rash	5 (4)	0	8 (6)	2 (2)
Pruritus	3 (2)	0	0	0
Erythema	1 (1)	0	2 (2)	0
Rash maculopapular	1 (1)	0	0	0
Skin exfoliation	1 (1)	0	2 (2)	0
Urticaria	1 (1)	0	0	0
Palmar-Plantar erythrodysaesthesia syndrome	0	0	1 (1)	0
Hypersensitivity/infusion reaction	1 (1)	0	3 (2)	1 (1)
Infusion-related reaction	1 (1)	0	1 (1)	0
Hypersensitivity	0	0	2 (2)	1 (1)

Source: (Brahmer 2015b) Abbreviations: AE = Adverse Event

NOTE: a patient may be recorded as having more than one adverse event within a category

*Grade 5 event

CheckMate 063

Study methodology and baseline characteristics for this study are given in Section 4.11.

Overall safety summary

This single-arm study demonstrated that nivolumab monotherapy (3mg/kg) has a reasonably well-tolerated safety profile in patients with locally advanced or metastatic squamous NSCLC.

Two (1.7%) deaths were attributed to nivolumab; both deaths occurred in patients with multiple comorbidities and in the setting of PD (Rizvi 2015).

Almost three-quarters of patients reported a treatment-related AE of any grade; most commonly, fatigue, decreased appetite and nausea. The nature, frequency and severity of treatment-related AEs, SAEs, Select AEs, and AEs leading to discontinuation are consistent with prior nivolumab trials in squamous NSCLC.

The majority of Select AEs were manageable and resolved, including those for which corticosteroids were initiated. The treatment-related pneumonitis rate was low (5%) and consistent with that reported in prior nivolumab studies (Rizvi 2015). All pneumonitis cases were manageable with corticosteroids and none required infliximab.

Deaths

There were 72 deaths (62%), of which two were assessed by the investigator to be related to nivolumab treatment. One death was as a result of treatment-related hypoxic pneumonia at 28 days following the last nivolumab dose, and the other was a treatment-related ischaemic stroke 41 days after the first and only administered nivolumab dose. Both deaths occurred in patients with multiple comorbidities and in the setting of progressive disease (Rizvi 2015).

Table 30: CheckMate 063 - Summary of all AEs and deaths

	Nivolumab (N = 117) n (%)	
All Deaths	72 (62)	
Reason for death:		
Disease progression	[redacted]*	
Study drug toxicity	2 (1.7)	
Unknown	[redacted]*	
Other	[redacted]*	
Deaths within 30 days of last dose	[redacted]*	
Deaths within 100 days of last dose	[redacted]*	
	Any grade n (%)	**Grade 3-4 n (%)**
All AEs	[redacted]*	[redacted]*
Treatment-related AEs	87 (74)	20 (17)
All SAEs	[redacted]*	[redacted]*
All treatment-related SAEs	[redacted]*	[redacted]*
All AEs leading to discontinuation	[redacted]*	[redacted]*
All treatment-related AEs leading to discontinuation	14 (12.0)	[redacted]*

Source: (Bristol-Myers Squibb 2014b; Rizvi 2015)

Abbreviations: AE = Adverse Event; SAE = Serious Adverse Event

*All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb 2014b)

AEs leading to discontinuation

Treatment-related AEs led to discontinuation for 14 (12%) of 117 patients: five (4%) for pneumonitis, five (2%) for fatigue, and one (1%) for each of anaphylactic reaction, hypersensitivity, adrenal insufficiency, diarrhoea, polyneuropathy, rash, and sensory neuropathy in both hands (Rizvi 2015).

Treatment-related AEs

At least one treatment-related AE and treatment-related SAE was reported during treatment in 87 (74%) and [redacted] patients, respectively, on treatment or within 30 days of last nivolumab dose (Rizvi 2015; Bristol-Myers Squibb 2014a). The majority of patients experienced treatment-related AEs that were Grade 1-2 in severity.

Grade 3-4 treatment-related AEs and treatment-related SAEs were reported by 20 (17%) and [redacted] of nivolumab patients, respectively (Rizvi 2015; Bristol-Myers Squibb 2014a). The most frequent Grade 3-4 treatment-related AE (≥ 5% of patients) was fatigue (4%) (Table 31) (Rizvi 2015). The most frequent treatment-related Grade 3-4 SAE was [redacted] of which none were Grade 4 (Bristol-Myers Squibb 2014a).

[redacted] After the clinical database lock, one additional treatment-related SAE of Grade 3

pneumonitis was reported, and one patient died of a treatment-related SAE of pneumonia within 30 days of last dose and one patient died from a treatment-related ischaemic stroke within 100 days of last nivolumab dose of treatment.

Table 31: CheckMate 063 - Summary of treatment-related AEs reported in ≥5% all treated patients

	Nivolumab (N = 117)	
	Any Grade n (%)	**Grade 3-4 n (%)**
General disorders and administration site conditions	55 (47.0)	5 (4.3)
Fatigue	38 (33)	5 (4)
Asthenia	14 (12)	0
Gastrointestinal disorders	37 (31.6)	3 (2.6)
Nausea	18 (15)	0
Diarrhoea	12 (10)	3 (3)
Dry mouth	7 (6)	0
Vomiting	7 (6)	0
Constipation	6 (5)	0
Metabolism and nutrition disorders	30 (25.6)	2 (1.7)
Decreased appetite	22 (19)	0
Skin and subcutaneous disorders	24 (20.5)	2 (1.7)
Rash	13 (11)	1 (1)
Pruritus	7 (6)	1 (1)
Musculoskeletal and connective tissue disorder	18 (15.4)	1 (0.9)
Myalgia	6 (5)	1 (1)
Respiratory, thoracic and mediastinal disorders	16 (13.7)	4 (3.4)
Dyspnoea	6 (5)	0
Pneumonitis	6 (5)	4 (3)
Blood and lymphatic system disorders	9 (7.7)	3 (2.6)
Anaemia	7 (6)	1 (1)
Infections and infestations	7 (6.0)	1 (0.9)

Source:(Rizvi 2015; Bristol-Myers Squibb 2014a)

Abbreviations: AE = Adverse Event

NOTE: a patient may be recorded as having more than one adverse event within a category

Select AEs

Most Select AEs were of low grade, with the most frequently reported Select AE categories being: [redacted]
(Table 32) (Bristol-Myers Squibb 2014a).

Across Select AE categories, the majority of events were manageable, with resolution occurring even when immunosuppressive medications were needed. Corticosteroids were the most common immunosuppressive concomitant medication administered.

A treatment-related pneumonitis Grade 3-4 rate of 3% was observed, of which no cases were Grade 4 or 5 (Rizvi 2015). All pneumonitis cases were manageable with corticosteroids and none required infliximab. All patients with pneumonitis had a median time to resolution of 3.4 weeks (range 1.6–13.4). Four low-grade, treatment-related renal AEs were reported (Rizvi 2015).

Three patients had treatment-related Grade 3 diarrhoea, which resolved with either corticosteroid treatment (one patient) or supportive care (Rizvi 2015). Six patients had treatment related pneumonitis (none Grade 4 or 5); and one additional event of Grade 3 pneumonitis was reported between 30 and 100 days after the last dose of nivolumab (Rizvi 2015).

Time to onset and time to resolution of Select AEs were also analysed. Median time to onset of Select AEs ranged from [redacted], with a median time to onset in the [redacted] AE category of [redacted] weeks (Bristol-Myers Squibb 2014a).

Table 32: CheckMate 063 - Summary of Select AEs

	Nivolumab (N = 117)	
	Any grade n (%)	**Grade 3-4 n (%)**
Endocrine		
Any causality	[redacted]*	[redacted]*
Treatment-related	[redacted]*	[redacted]*
Gastrointestinal		[redacted]*
Any causality	[redacted]*	[redacted]*
Treatment-related	[redacted]*	[redacted]*
Hepatic		[redacted]*
Any causality	[redacted]*	[redacted]*
Treatment-related	[redacted]*	[redacted]*
Pulmonary		
Any causality	[redacted]*	[redacted]*
Treatment-related	[redacted]*	[redacted]*
Renal		
Any causality	[redacted]*	[redacted]*
Treatment-related	[redacted]*	[redacted]*
Skin		
Any causality	[redacted]*	[redacted]*
Treatment-related	[redacted]*	[redacted]*
Hypersensitivity/infusion reaction		
Any causality	[redacted]*	[redacted]*
Treatment-related	[redacted]*	[redacted]*

Source: (Bristol-Myers Squibb 2014a)

Abbreviations: AE = Adverse Event

*All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb 2014a)

CheckMate 003

In the nivolumab dose-escalation portion of this trial, the highest planned dose of 10mg/kg was not reached. Subsequently, the 1, 3, and 10mg/kg cohorts were expanded in patients with NSCLC. At the time of the March 2013 safety analysis, the median duration of therapy was 13.6 weeks (range, 2 to 104 weeks) (Gettinger 2015).

Overall safety summary

Among the NSCLC treated patients across all doses and histologies, 71% had experienced treatment-related AE of any grade (Gettinger 2015). The most common treatment-related AEs were: fatigue (24%); decreased appetite (12%); and diarrhoea (10%) (Gettinger 2015).

Eighteen patients who responded to nivolumab discontinued treatment for reasons other than PD. Grade 3 or 4 treatment-related AEs occurred in 14% of patients. Nivolumab treatment-related deaths occurred in three patients (2%); all were associated with pneumonitis (Gettinger 2015).

Death

Three nivolumab treatment-related deaths occurred in patients with NSCLC, each associated with pneumonitis (two with unresolved Grade 4 pneumonitis, and one with Grade 5 pneumonitis). Two of the deaths occurred early in the trial before AE management guidelines were established, and the third occurred after the March 2013 safety analysis (Gettinger 2015).

Treatment-related AEs and SAEs

Among the treated patients with NSCLC, 71% had experienced treatment-related AEs of any grade (Table 32 in Appendix 17). The most common AEs were fatigue (24%), decreased appetite (12%), and diarrhoea (10%) (Table 32 in Appendix 17) (Gettinger 2015). Eighteen patients (14%) experienced Grade 3 or 4 treatment-related AEs, and the most common was fatigue (3%) (Table 232 in Appendix 17).

Select AEs

Treatment-related Select AEs of any grade were observed in 41.1% of 129 patients with NSCLC, and the most common included skin, gastrointestinal, and pulmonary events (15.5%, 11.6%, and 7.0%, respectively (Table 33). Four patients (3%) had treatment-related Grade 3 or higher pneumonitis, including one with Grade 5 pneumonitis (Table 33). No clear relationships between the occurrence of pneumonitis and dose level or treatment duration were noted.

Table 33: CheckMate 003 - Summary of Select AEs

	Nivolumab all patients (N = 129)	
	Any Grade n (%)	**Grade 3 or 4 n (%)**
All Select AEs	53 (41.1)	6 (4.7)
Skin	20 (15.5)	0
GI	15 (11.6)	1 (0.8)
Pulmonary	9[‡§] (7.0[§])	3[‡] (2.3)
Endocrinopathies	8 (6.2)	0
Hepatic	6 (4.7)	1 (0.8)
Infusion reaction	5 (3.9)	1 (0.8)
Renal	4 (3.1)	0

Source: (Gettinger 2015)
Abbreviations: AE = Adverse Event; GI = Gastrointestinal
Select AEs were those requiring more frequent monitoring or intervention with immune suppression or hormone replacement, based on pre-specified list of Medical Dictionary for Regulatory Activities terms.16 March 2013 data analysis. †Grades 1 to 5. ‡Eight patients had pneumonitis (Grades 1 to 2, n = 5; Grades 3 to 4, n = 3), and one patient had Grade 2 interstitial lung disease. §Two additional patients had treatment-related Grade 2 pneumonitis, which occurred before date of safety analysis, but they were not included, because these data were not available until after this analysis. A third additional patient had treatment-related Grade 5 pneumonitis (detailed in Data Supplement) but was not included because event occurred after date of safety analysis.

Summary

Overall, the safety profile of nivolumab presented in this submission is consistent with the safety profile seen in other clinical trials evaluating nivolumab in tumours other than squamous NSCLC.

Docetaxel, the current standard of care in this NSCLC patient population, has a number of adverse events, with many patients discontinuing use due to treatment-related toxicities.

The most frequently reported nivolumab treatment-related AEs across trials were the immuno-oncology AEs of: fatigue, pruritus; nausea; diarrhoea; and rash. The majority of Select AEs were mild, transient, and generally manageable using the established safety management algorithm guidelines outlined in the SmPC (Appendix 1).

In CheckMate 017, the rate of treatment-related AEs of Any Grade in the nivolumab vs. docetaxel arm was 58% vs. 86% (Brahmer 2015a). The rate of treatment-related Grade 3-4 AEs was much lower in the nivolumab group (7%) compared with the docetaxel group (55%) (Brahmer 2015a). There were 3% discontinuations due to drug toxicity in the nivolumab group compared to 10% in the docetaxel group. There were no treatment-related deaths in the nivolumab treatment group compared with three treatment-related deaths in the docetaxel treatment group (Brahmer 2015a).

Similar rates of AEs were seen in CheckMate 063, a refractory third-line squamous NSCLC population. The rate of treatment-related AEs in nivolumab treated patients was 74%, and the rate of Grade 3-4 treatment-related AEs was 17% (Rizvi 2015).

Nivolumab is generally well tolerated by patients with locally advanced or metastatic squamous NSCLC. Nivolumab which has a significantly improved AE profile compared to docetaxel.

4.13 Interpretation of clinical effectiveness and safety evidence

Squamous NSCLC is a disease associated with a poor prognosis. Docetaxel, the current standard of care, offers only modest efficacy and poor tolerability. Checkmate 017 demonstrates nivolumab to have a superior clinical efficacy and tolerability profile compared with docetaxel, and offers a step change in the management of locally advanced or metastatic squamous NSCLC after prior chemotherapy.

Principal findings of the clinical evidence base

1. Nivolumab offers a clinically significant survival benefit in patients with locally advanced or metastatic squamous NSCLC after prior chemotherapy, in an area of unmet need:

    - Nivolumab resulted in a 41% lower risk of death in CheckMate 017, nivolumab was compared with docetaxel in the second-line setting after platinum doublet chemotherapy. Nivolumab significantly increased 1-year survival (42% vs. 24%), HR 0.59 ($p<0.001$), with a median OS benefit of 9.2 months vs. 6.0 months.
    - In CheckMate 063, a single-arm study of nivolumab in a refractory third-line population, nivolumab showed 1-year OS of 41% with a median OS of 8.2 months. This is a significant improvement on historical cohorts (Rizvi 2015).
    - These data are consistent with a Phase I study of nivolumab in heavily pre-treated patients with NSCLC (CheckMate 003), where 1-year and 3-year survival of patients with NSCLC was 56% and 27%, respectively, in those patients treated with 3mg/kg nivolumab. 1-year and 3-year survival rates in patients with squamous NSCLC was 41% and 19% respectively in patients treated across all doses of nivolumab.
    - The nivolumab survival benefit across these studies is similar in pre-treated patients, and hence nivolumab may offer clinical benefit to all patients with locally advanced or metastatic squamous NSCLC regardless of line of therapy.
    - 3-year follow up data from CheckMate 003 indicate that there may be a long-term survival benefit from nivolumab in NSCLC.
    - There were no subgroups in CheckMate 017 that demonstrated different clinical efficacy to the main population, and clinical benefit was seen regardless of PD-L1 expression status.

2. Nivolumab demonstrates durable response across lines of therapy:

    - In CheckMate 017, patients treated with nivolumab had an ORR of 20% vs. 9% in the docetaxel group ($p<0.008$). Responses typically occurred before the first assessment (median duration of onset was 2.2 months for nivolumab). At the time of reporting median DOR had not been reached in the nivolumab group and was 8.4 months for the docetaxel group. This pattern was also seen in CheckMate 063, with an ORR of 14.5% and a TTR of 3.3 months. At the time of reporting, median DOR had not been reached.
    - In CheckMate 017, 28 nivolumab patients were treated beyond progression. Of these, nine patients continued to benefit from treatment beyond disease progression ('non-conventional' benefiters). This is typically seen in nivolumab studies and is due to the immunological mechanism of action of nivolumab. The ORR in these studies may therefore underestimate the true clinical benefit observed with nivolumab.

3. In squamous NSCLC, nivolumab shows significant clinical efficacy regardless of PD-L1 expression levels:

    - In CheckMate 017, tissue samples from each patient were examined for PD-L1 expression level. There was an observed benefit in OS and PFS, regardless of the PD-L1 expression level. Nivolumab has significant survival benefit regardless of PD-L1 expression level.

4. Nivolumab is well tolerated and offers a significant improvement in toxicity against current standard of care (docetaxel):

    - Docetaxel, the current standard of care in this patient population, is poorly tolerated resulting in some patients discontinuing treatment.
    - The most frequently reported nivolumab treatment-related AEs in CheckMate 017 were the immuno-oncology AEs of fatigue, asthenia, decreased appetite, nausea and diarrhoea.
    - The majority of Select AEs were mild, transient, and generally manageable using the established safety management algorithm guidelines outlined in the SmPC (Appendix 1).
    - In CheckMate 017, the rate of treatment-related Grade 3-4 AEs was less in the nivolumab group (7%) compared with the docetaxel group (55%). There were fewer discontinuations due to toxicity in the nivolumab group (3%) compared with the docetaxel group (10%). There were no treatment-related deaths in the nivolumab treatment group compared with three treatment-related deaths in the docetaxel treatment group.
    - Similar rates of treatment-related AEs were seen in CheckMate 063, a refractory third-line squamous NSCLC population; the rate of treatment-related Grade 3-4 AEs was 17%.
    - The AE profile of nivolumab is well understood and consistent across nivolumab studies.

Strengths of the current evidence base

1. The nivolumab clinical development programme in NSCLC investigated squamous and non-squamous populations separately in the pre-treated setting in two separate large randomised controlled trials- CheckMate 017 (squamous) and CheckMate 057 (non-squamous).

2. CheckMate 017 was a well-designed Phase III study, which provides comparative evidence against the most appropriate standard of care:

    - Docetaxel is the recognised standard of care in patients with pre-treated advanced NSCLC, at the time of study design of 017 and also at the time of analysis.
    - This is still the case - making the results of this study directly relevant to current UK clinical practice.
    - CheckMate 063 was a single-arm study and CheckMate 003 was a Phase I expansion cohort study. Although these are not RCTs, they provide useful data in addition to the CheckMate 017 RCT and show a consistent 1-year OS rate with similar benefit across lines of therapy.

- All studies are being conducted in line with Good Clinical Practice guidelines, with steps taken to minimise the risk of bias.
- Independent DMCs were established in each of these studies to provide independent oversight of safety and efficacy considerations and study conduct.

3. Study endpoints are clinically relevant:

- The CheckMate 017 RCT has endpoints that are most relevant to patients and physicians in the UK:
    - The study was powered for OS as the primary end point which is the most informative and robust clinical end point; the consequence is that CheckMate 017 therefore provides a high level of clinical evidence.
    - OS is particularly important with immuno-oncology treatments given that ORR may not capture the true benefit of the drug. Although immune response criteria have been developed, these are not yet widely used in clinical practice or clinical trials.
    - HRQoL were collected as a secondary endpoints.
- CheckMate 063 and CheckMate 003 also provide OS data
    - CheckMate 063 shows an overall 1-year OS rate of 40.8%.
    - CheckMate 003 shows an Overall 3-year OS rate of 18%, with a 3-year OS rate of 27% in the 3mg/kg dose group.

Limitations of the current evidence base

- CheckMate 017
    - The minimum follow up time of patients in this study at the point of analysis was approximately 11 months. In addition, there were many censoring events after 12 months. Continued collection of follow-up data will further support the survival benefit of nivolumab beyond 1 year.
    - While the baseline characteristics of patients were well balanced between the two treatment groups, and are typical of those seen in other lung cancer clinical trials, aspects of these patients may not be typical of real world patients with lung cancer. The median age in this trial was 63 years and proportion of patients with PS1 was 76% and thus may not reflect the real world UK clinical population.
    - There was insufficient power in subgroup analysis to identify whether the relative benefit in some groups was statistically significant (e.g. patients older than 75 years).
    - The results from PD-L1 expression level is not predictive of outcomes and there were some limitations that need to be recognised:
        - Patients were not prospectively stratified by PD-L1 expression level
        - Though tissue was required for study entry, ascertainable PD-L1 expression level status was not required, and so only 83% of patients had an expression level available.
        - Many of the samples used were taken before patients received first-line chemotherapy (i.e. archival).
    - This study only used docetaxel as a comparator. This is appropriate as it is the current standard of care in the UK. Although, erlotinib can also be used in

the wild type EGFR (mutation negative) patients, there is no direct comparison with this agent in RCTs.

- Whilst an indirect comparison was possible, the results should be interpreted with caution given the paucity and heterogeneity of the data across the evidence available for this comparison.

- CheckMate 063
  - This was a single-arm study with no comparator, hence data to support the use of nivolumab in pre-treated patients who had received two of more previous chemotherapies, came from this non-RCT. Results from this study were comparable to those seen in CheckMate 017. However, there is no evidence to suggest that the relative clinical efficacy of nivolumab would be different in the second vs. third-line squamous NSCLC populations.
  - The patient population was refractory to other treatments, as the majority of patients having had two (35%), three (44%) or four (21%) previous cycles of chemotherapy. Only five (4%) patients achieved a CR or PR to previous therapy, with the majority of patients (n=71, 61%) having PD. Eighty-nine (76%) patients moved to nivolumab within 3 months of completing their previous chemotherapy.
- CheckMate 003
  - This is a Phase I study with small patient numbers in a heavily pre-treated cohort (54% had received three or more prior systemic treatments).
  - Despite these limitations, data from CheckMate 003 provide useful 3-year follow-up and long-term safety data for nivolumab when interpreted appropriately, bearing in mind that this is a large Phase 1 trial.

The CheckMate 017 study was stopped early, as the assessment conducted by the independent DMC concluded that the study had met its endpoint, demonstrating superior OS in patients treated with nivolumab compared with patients treated with docetaxel. The results from this trial showed that the median OS rate was 9.2 months for nivolumab compared with 6.0 months for docetaxel, and an increase of over 3 months survival benefit. Furthermore, there was a 41% reduction in the risk of death with nivolumab. We believe, therefore, that Nivolumab will fulfil the Institute's end of life criteria.

Table 34: End of life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Patients with advanced or metastatic NSCLC have a short life expectancy of less than 24 months (Health and Social Care Information Centre 2014b).
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	Median OS data from the CheckMate 017 trial is 9.2 months vs. 6.0 months for docetaxel (Brahmer 2015a). This means that nivolumab extends life by greater than 3 months compared with docetaxel.
The treatment is licensed or otherwise indicated for small patient populations	The patient population eligible for nivolumab treatment is expected to be very small (estimated 853 patients in England).

	Nivolumab is also indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. The expected number of eligible patients for which nivolumab is being appraised in that submission is 1,304.

4.14 Ongoing studies

Study	Study description	Data availability
CheckMate 017	RCT study described in this submission	[redacted]
CheckMate 063	Non-RCT study described in this submission	[redacted]
CheckMate 003	Non-RCT study described in this submission	[redacted]
CheckMate 153	Title: A Safety Trial of Nivolumab (BMS-936558) in Subjects With Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Progressed During or After Receiving At Least One Prior Systemic Regimen (CheckMate 153) Phase IIIB/IV safety study. Study includes to nivolumab treated cohort. Cohort A is treated until disease progression, unacceptable toxicity or withdrawal of informed consent. Cohort B is treated until 1 year (52 weeks).	[redacted]

5 Cost-effectiveness

- A *de novo* cost-utility analysis was undertaken to assess the cost-effectiveness of nivolumab in pre-treated patients with locally advanced or metastatic squamous NSCLC from a UK NHS and PSS perspective
- The health economic model was a standard three health state cohort model (progression-free, progressed disease and death), which used a partitioned survival (AUC) approach to determine the proportion of patients in each of the three health states. The model structure and health states have been routinely used in previous HTAs in advanced NSCLC and oncology in general
- The base case time horizon of 20 years (equivalent to lifetime) was applied to ensure the full extent of relevant costs and benefits were captured. The economic analysis was therefore consistent with the NICE reference case
- In line with the NICE decision problem, the base case comparator was docetaxel; a sensitivity analysis was performed comparing nivolumab to erlotinib using an ITC
- Efficacy, resource use, costs and utilities were estimated based on information from the CheckMate 017 trial, previous technology appraisals to NICE, published sources and clinical experts. EQ-5D-based utilities were collected in CheckMate 017 and applied in the model
- In the base case analysis, OS from CheckMate 017 was modelled using the log-logistic curve as it provided the optimal balance between statistical fit within the trial period and long-term clinical plausibility based on RWD; PFS from CheckMate 017 was modelled using the spline 2-knots function, which provided the best fit to the trial data
- The base case ICER is £85,950 per QALY gained
- A scenario analysis is presented where a spline 2-knots distribution is used to model OS, which generated an ICER of £108,096 per QALY gained
- There is uncertainty of the length of the long term duration of therapy. Sensitivity analyses of treatment stopping rules at 1 year and 2 years that limited the duration on treatment (DOT) were also undertaken, which resulted in ICERs of £45,470 and £60,923, respectively. This suggests that as DOT is reduced, the ICER approaches a cost-effective range
- Deterministic sensitivity analysis revealed that the model was most sensitive to the choice of curve used to extrapolate the overall survival, treatment efficacy (hazard ratio on overall survival on nivolumab), body weight, discount rate and utility in the progressive disease state. These factors should be considered in the context of NICE's End of Life criteria and the innovative nature of the technology in an area of high unmet need

5.1 Published cost-effectiveness studies

Identification of studies

A systematic literature review was conducted to identify evidence to support the development of cost-effectiveness and budget impact models for nivolumab. A single review was carried out to identify studies reporting economic evaluations, resource use and costs, as well as studies reporting utility values for health states within a model. While the decision problem is relevant to a squamous-only NSCLC population, the published economic literature is often reported as NSCLC, so the focus of the review was to identify evidence in pre-treated locally advanced or metastatic NSCLC.

Literature was searched in biomedical electronic literature databases recommended by HTA agencies (CADTH 2014; IQWIG 2008; NICE 2015d; NICE 2015e). MEDLINE® In-process was searched to ensure that non-indexed citations were retrieved. The following databases were searched (Table 35).

Table 35: Data sources for the economic systematic review

Search strategy component	Sources	Date limits
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies	MEDLINE® MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL)	01 JAN 2000 to 23 FEB 2015
Conference proceeding	HTA International	2012, 2013, 2014
	International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	
	Society for Medical Decision Making	

The search strategy is presented in Appendix 11. The first screening of the literature included or excluded citations on the basis of the abstract and title using pre-defined inclusion/exclusion criteria. The second stage of screening was based on review of the full texts. All citations meeting the inclusion criteria after the second stage of screening were extracted. The extractions were independently verified and validated by a second reviewer.

The inclusion/exclusion criteria for the systematic review are summarised in Table 36. The range of comparators included in the search is broader than the scope of the decision problem, and this is to allow additional analysis outside in the future. The studies assessed to have met the inclusion criteria are described in Table 37.

Table 36: Inclusion/exclusion criteria for the economic review in non-small cell lung cancer

	Economic evaluations	Rationale
Patient population (P)	• Adults diagnosed with locally advanced or metastatic non-small cell lung cancer pre-treated with at least one previous line of chemotherapy	• To ensure that evidence related to economic evaluations of NSCLC will be captured as the studies specifically in squamous NSCLC may be limited
Intervention (I)	• Nivolumab	• This is the intervention of interest within the decision problem
Comparator (C)	• Any pharmacological intervention • Placebo • Best supportive care • Afatinib • Docetaxel • Erlotinib • Gefitinib • Nintedanib (in combination with docetaxel) • Pemetrexed monotherapy • Ceritinib • Crizotinib • Platinum therapy in combination with gemcitabine, vinorelbine, pemetrexed, or a taxane	• These treatment options are broader than the scope, but are included to allow further analysis in the future if required
Outcome (O)	• Studies will not be excluded based on the reported outcomes	• The aim of the review was to identify relevant economic evaluations that also reported costs
Study design 1 (S1)*	• All economic evaluation studies based on models • Cost-effectiveness analysis • Cost-utility analysis • Cost-minimisation analysis • Budget impact models	• The aim of the review was to identify relevant economic evaluations that also reported costs
Study design 2 (S2)*	• Randomised Controlled Trials • Database studies • Prospective observational studies • Retrospective observational studies	• The aim of the review was to identify relevant studies that reported quality of life data
Line of therapy	• Second- or further-line of therapy	• This is the relevant line of treatment

	Economic evaluations	Rationale
Search timeframe	• 2000 to 2015 (last 15 years)	• This period was deemed relevant to reflect models that are representative of the current NSCLC landscape
Language	• Only studies with the full-text published in English language will be included	• It is expected that the majority of evidence in this disease area will be available in the English language
Exclusion criteria	• Reviews, letter to the editors, and editorials • Studies reporting only cost and resource use data where no formal economic analysis has been undertaken	• These types of articles were not relevant
	• Animal/*in vitro* studies • Single-arm studies • Studies with no subgroup data for disease and adult population • Studies investigating first-line treatment for non-small cell lung cancer • Studies assessing included intervention as an adjuvant or neo-adjuvant therapy • Studies evaluating included intervention in combination with radiotherapy • Studies comparing different doses of the same intervention (i.e. dose-ranging studies), two formulations of the same intervention, and intervention with two different routes of administration	• The design of such studies was not relevant to the decision problem
	• Conference abstracts prior to 2012 will be excluded.	• Studies are published within 3 years of results presentation in conference abstracts. Studies of trials that are terminated or are not of good quality are generally not published within this timeframe

*NOTE: Within the single systematic review, two sets of study design criteria were used to identify relevant economic evaluations and relevant studies reporting data on quality of life in second-line or later-line patients with NSCLC

Description of identified studies

The literature search yielded a total of 5190 studies, of which 35 met the inclusion/exclusion criteria. Of these, 11 studies were modelling studies (Figure 13). An overview of the two UK-based studies is provided in Table 37. Both of these studies were in a broad NSCLC population. No study evaluated the cost-effectiveness of treatments in a squamous only population and no study evaluated nivolumab.

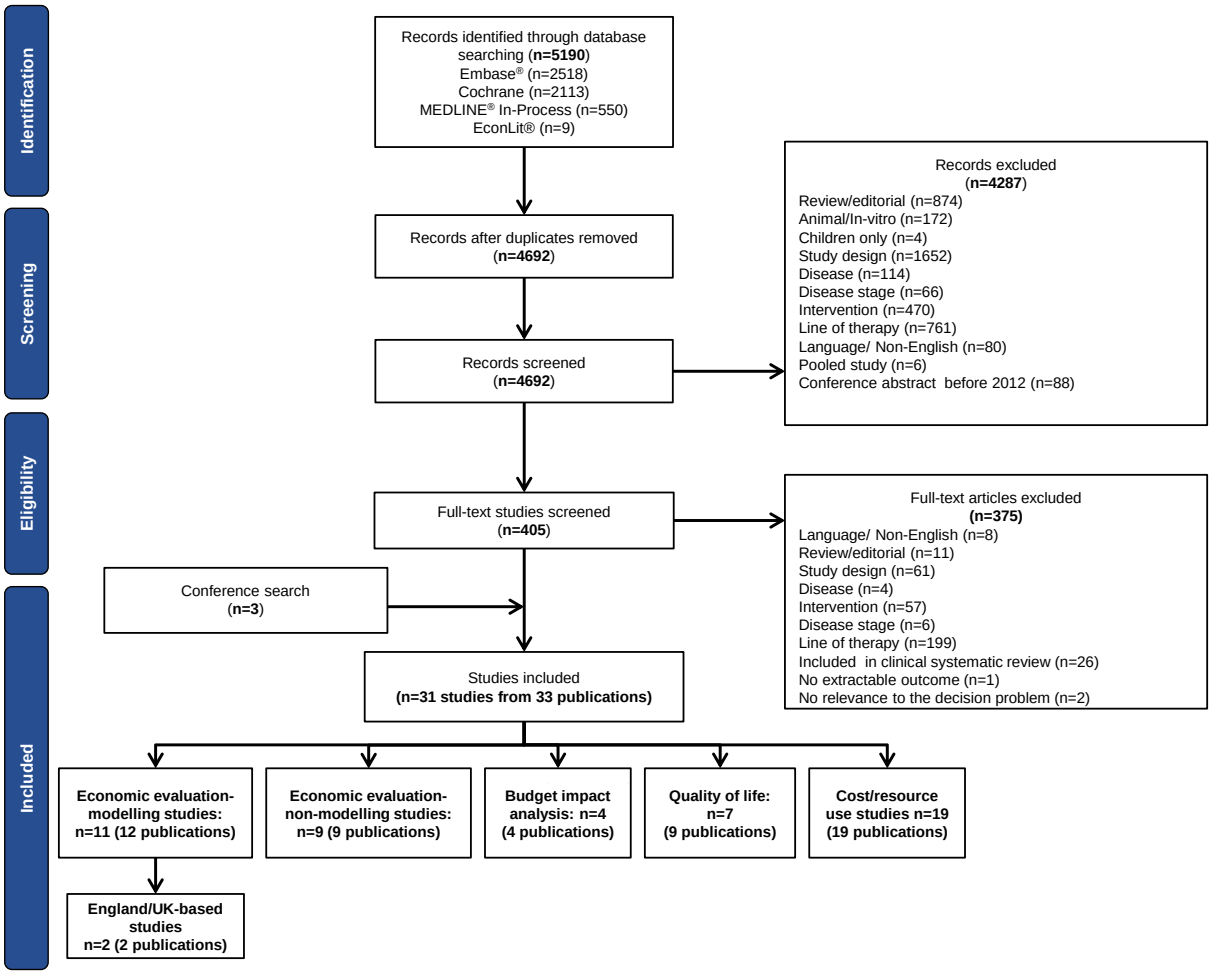
A review was also undertaken of published NICE technology appraisals to identify appraisals in pre-treated NSCLC with the aim of identifying the structure of previous models in this area

and potential sources of resource use or utility values. An overview of the four relevant appraisals identified in this review is provided in Table 38.

The two UK-based publications (Table 36) compared docetaxel and BSC or erlotinib and docetaxel in a pre-treated population of patients with NSCLC. Holmes (2004) reports an incremental cost per LYG for docetaxel versus BSC of £13,863. Lewis (2010) reports erlotinib dominant versus docetaxel. Both of these models and all of the models submitted to the NICE technology appraisals use a three-state Markov structure representing progression free (PF) disease, PD and death.

A quality assessment for each of the cost-effectiveness studies is included in Appendix 12.

Figure 13: Identification of economic evaluations identified in the systematic literature review



Abbreviations: UK: United Kingdom

Table 37: Summary list of published cost-effectiveness studies

Author	Patient population (Mean age in years [range])	NSCLC type (NSQ, SQ, or NR)	Disease stage	Line of therapy (2L, 3L)	Treatments being compared	Evaluation type, cost year	Perspective	Model design	QALYs	Total costs	ICER
(Holmes 2004)	Previously treated with platinum-based chemotherapy, taxane-naïve, with PS≤2 Age: NR	NR	NR	2L	D vs BSC	CEA Costs: 2000/2001	UK NHS	Difference in weighted mean survival estimated by calculating the area under the survival curves (AUC)	LYG vs BSC: 3.82 months (0.32 years)	Net incremental cost: £4432	Incremental cost per LYG for D vs BSC: £13,863
(Lewis 2010)	Previously treated stage IIIB – IV NSCLC with PS≤3 E: 62 (34-87), D: 61 (37-73)	NR	IIIB, IV	2L	E vs D	CUA Cost year varies: 2004-2009	UK NHS	Three health state transition model	E vs D: 0.238 vs 0.206	E vs. D: £13,730 vs £13,956	E vs D: (E dominant)

Abbreviations: BSC = Best Supportive Care; CEA Cost-Effectiveness Analysis; CU = Cost-Utility; D = Docetaxel; E = Erlotinib; ICER = Incremental Cost Effectiveness Ratio; NHS = National Health System; NSCLC = Non-Small Cell Lung Cancer; NR = Not Reported; NSQ = Non-Squamous; QALY = Quality-Adjusted Life Year SQ = Squamous

Table 38: Summary list of published NICE technology appraisals

Intervention and NICE TA	NSCLC treatment indication	Status	Comparator	Study Type	Model Design	No. of States	Time Horizon	Cycle	QALYs	Total costs	ICER
Crizotinib TA296 (NICE 2013)	2nd line ALK+ patients with advanced NSCLC	NR	D and BSC	CUA	Semi-Markov model	3 state: PFS, PD, Death	15 years	30 days	C: 1.949 D: 0.981 BSC: 0.592	C: £54,149 D: £13,922 BSC: £6021	C vs D: £41,544 C vs BSC: £35,455
Erlotinib TA 162 (NICE 2012b)	2nd line patients with NSCLC	R	D	CUA	Markov model	3 state: PFS, PD, Death	2 years	Per month	E: 0.201 D: 0.176	E: £12,707 D: £12,621	E vs D: £3354
Nintedanib (in combination with docetaxel) GID-TAG449* (NICE 2015c)	2nd line patients with locally advanced, metastatic, or locally recurrent NSCLC	R (Final appraisal determination)	D	CUA	Partitioned survival (area under curve) approach	3 state: PFS, PD, Terminal	15 years	3 weeks	Manufacturer values: Confidential (incremental N/D vs D: 0.22) ERG report and NICE guidance values (incremental reported only): N/D vs D: 0.22	Manufacturer values: Confidential (incremental N/D vs D: £10,932) ERG report and NICE guidance values (incremental reported only): N/D vs D: £11,051	Manufacturer values: N/D vs D: £50,234 ERG report and NICE guidance values: N/D vs D: £50,776

Intervention and NICE TA	NSCLC treatment indication	Status	Comparator	Study Type	Model Design	No. of States	Time Horizon	Cycle	QALYs	Total costs	ICER
Erlotinib and gefitinib (MTA) (rev TA162, TA175) [ID620] (NICE 2015a)	2nd line patients with locally advanced or metastatic NSCLC	D favoured over E	D and BSC No Assessment Group analysis for gefitinib	CUA	Markov model	3 state: PFS after second-line chemotherapy, post progression, Death	5 years	21 days	EGFR M-population D: 0.5939 E: 0.4863 EGFR unknown population BSC: 0.3452 E: 0.4484 No Assessment Group analysis for gefitinib	EGFR M-population D: £15,701.64 E: £14,049.00 EGFR unknown population BSC: £8132.79 E: £14,446.38 No Assessment Group analysis for gefitinib	EGFR M-population D vs E: £15,359 EGFR unknown population E vs BSC: £61,132 No Assessment Group analysis for gefitinib

* Final appraisal determination; ALK = Anaplastic Lymphoma Kinase fusion gene; BSC = Best Supportive Care; C = Crizotinib; CUA = Cost-utility Analysis; D = Docetaxel; D/Cis = Docetaxel/cisplatin; DSA = Deterministic Sensitivity Analysis; E = Erlotinib; EGFR-TK+ = Epidermal Growth Factor Receptor Mutation Positive; G/Car = Gemcitabine/carboplatin; G/Cis = Gemcitabine/cisplatin; N = Nintedanib; NR = Not recommended; NSCLC = Non-Small Cell Lung Cancer; P/Cis = Pemetrexed/cisplatin; PD = Progressive Disease; PSA = Probabilistic Sensitivity Analysis; QALY = Quality-Adjusted Life Year; R = Recommended; SD = Stable Disease; TR = Treatment Response

5.2 De novo analysis

Patient population

The economic evaluation considers pre-treated adult patients with advanced or metastatic squamous NSCLC, which is consistent with the trial population of CheckMate 017 (Section 4.3). This population is also consistent with the marketing authorisation for nivolumab and the decision problem (Section 2.2 and Section 1.1).

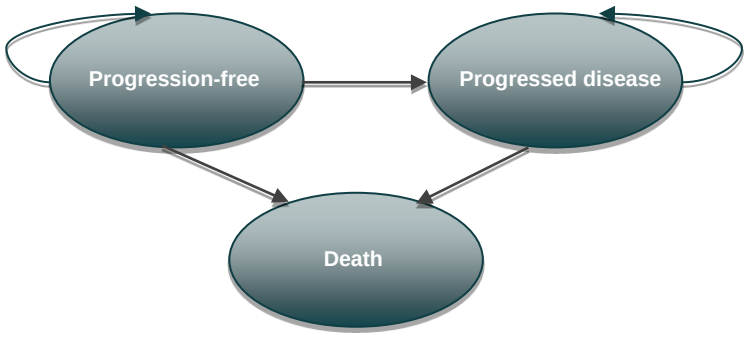
Model structure

The economic evaluation was developed in Microsoft Excel and is a cohort-based partitioned survival model consisting of three mutually exclusive health states – PF, PD, and death (Figure 14). The model structure is in line with the clinical pathway of care for the treatment of pre-treated squamous NSCLC in the UK and is consistent with previous economic evaluations submitted to NICE in advanced NSCLC and other metastatic cancers (Nintedanib GID-TAG449, Erlotinib TA258, Bevacizumab TA212; Table 38).

The base case evaluates the cost-effectiveness of nivolumab compared with docetaxel. Docetaxel is the current standard of care in the second-line setting in the UK (for squamous NSCLC), and is the treatment most likely to be displaced from UK clinical practice following the introduction of nivolumab. The CheckMate 017 trial evaluates the efficacy, safety and tolerability of nivolumab in pre-treated patients with squamous NSCLC (Section 4.3); docetaxel was the comparator in this trial. Clinical parameters in the economic evaluation are derived from the CheckMate 017 clinical trial, and this reflects the decision problem.

The three health states in the model represent the primary stages of disease in advanced NSCLC. It is recognised that radiographic progression alone may not be a particularly good marker for a decline in HRQoL, but the approach here is consistent with previous models in NSCLC. The number of patients in each health state was estimated using the partitioned survival method.[1] The proportion of patients in the PD health state is calculated as the difference between OS and PFS. The partitioned survival approach allows for direct modelling of OS and PFS based on trial observed events, which is expected to accurately reflect disease progression and the long-term expected survival profile of patients treated with nivolumab.

Figure 14: Health states in the economic model



[1] The number of patients occupying each state in the model is derived directly from the cumulative survival probabilities for progression-free and overall survival. The proportion of patients occupying the progressed disease state was calculated as the proportion alive (OS) minus the progression-free proportion alive (PF).

Patients with locally advanced or metastatic squamous NSCLC who have failed platinum therapy enter the model in the PF health state. Patients who remain progression free are treated with either nivolumab or docetaxel. At the end of each cycle a patient can remain in the same health state or transition to PD or death (Figure 14). A restriction in the model is that patients cannot transition to an improved health state, which reflects disease progression and is consistent with previous economic modelling in NSCLC. Disease progression is defined by RECIST v1.1 criteria (as in the CheckMate 017 trial).

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. Cycle length is 1 week to accommodate the different dosing regimens of nivolumab (every 2 weeks) and docetaxel (every 3 weeks). A half-cycle correction is implemented to mitigate bias.

It is assumed that all patients are treated until progression, consistent with the CheckMate 017 trial protocol, and treatment costs include costs of drug acquisition, administration, and monitoring. Costs and disutilities associated with AEs are estimated per episode, and are applied once at the beginning of the simulation based on the proportion of patients in each treatment arm experiencing each AE.

Table 39: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	20 years	Considered to be appropriate as the lifetime of patients with advanced NSCLC taking into account typical age at diagnosis and advanced nature of disease; consistent with previous NICE STAs in this disease area and validated by expert clinical opinion
Cycle length	1 week (7 days)	The smallest common denominator between the different cycle lengths of comparators in the economic model and allows adequate granularity when assessing progression and survival
Half-cycle correction	Yes	Mitigate bias due to cycle length
Were health effects measured in QALYs; if not, what was used?	QALYs (as well as LYs)	NICE Reference Case
Discount of 3.5% for utilities and costs	Yes	NICE Reference Case
Perspective (NHS/PSS)	Yes	NICE Reference Case

Abbreviations: LYs = Life-years; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NSCLC = Non-Small Cell Lung Cancer; PSS = Personal Social Services; QALYs = Quality-Adjusted Life Years

Intervention technology and comparators

In line with the decision problem, the base case comparator in the economic analysis is docetaxel. Docetaxel is the current standard of care in pre-treated patients with squamous NSCLC in the UK and is the treatment most likely to be displaced by the introduction of nivolumab. The use of erlotinib in this patient population in the UK is limited and declining. A comparison of nivolumab and erlotinib is presented as a scenario analysis (Appendix 20).

Although BSC has been included as a relevant comparator in this evaluation despite a lack of comparative data, it should be recognised that in UK clinical practice, BSC, which comprises a range of supportive measures, is given to all patients with locally advanced or metastatic squamous NSCLC regardless of whether they receive systemic therapy. Furthermore, the economic case of docetaxel versus BSC has been established (Holmes 2004).

The dosing and administration frequencies for all treatments in the evaluation are in line with their marketing authorisations.

5.3 Clinical parameters and variables

Overall method of modelling survival

The primary data source for the economic model was patient level data from the CheckMate 017 clinical trial. The follow-up period in CheckMate 017 was shorter than the required length of the economic analysis (a lifetime equivalent), and extrapolation of the PFS and OS data from CheckMate 017 was required for the partitioned survival (AUC) approach. This involved identifying parametric survival models for both OS and PFS.

The guidance from the NICE DSU and from Royston and colleagues was followed to identify the best fitting parametric survival model for OS and PFS (Latimer 2013; Royston 2002). Figure 15 provides a visual depiction of the guidance recommended by the DSU. In summary, the steps required include:

1. Testing the proportional effects assumption – the log cumulative hazards, log cumulative odds, and standardised normal curve plots were assessed to determine if the data from Checkmate 017 indicate proportional effects. This was done by visual inspection to determine if the survival curves for nivolumab and docetaxel arms were parallel
2. In the event proportional effects held, a comprehensive range of parametric survival distributions were explored. These included the standard exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma models, as well as a series of spline-based models (additional details around spline-based models are given in Appendix 19)[2]
3. In the event proportional effects did not hold, both independent survival models and single survival models adjusted for shape and scale were assessed
4. Within the various parametric survival distributions explored (whether single or independent models), the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit statistics were assessed to identify the best fitting survival models
5. Lastly, the choice of parametric model needs to be validated in terms of clinical plausibility of both short-term and long-term extrapolations

The final choice of parametric survival model adopted for the base case model was a balance between both statistical fit (as per AIC/BIC values) within the period when patient

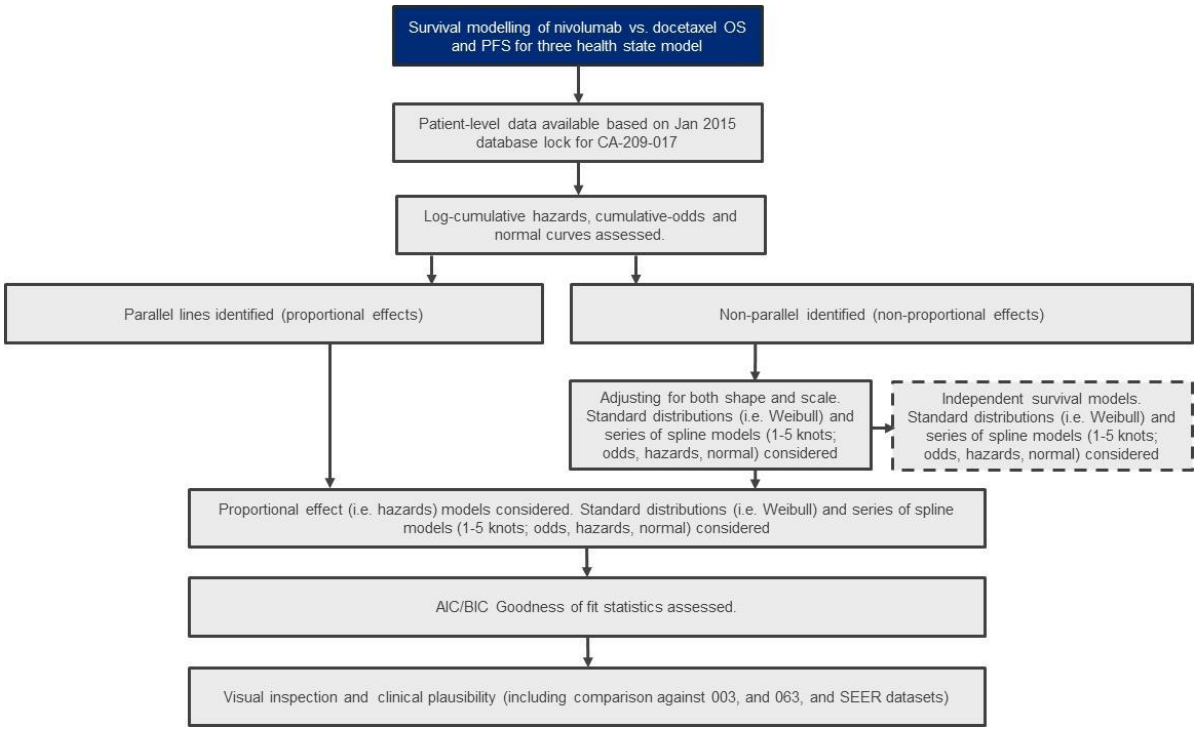
[2] Whilst spline-based models have not formally been assessed in previous oncology technology appraisals, they are recommended by the NICE DSU guidance document on parametric survival analysis as an alternative to standard parametric and piecewise modelling approaches. Accordingly, if spline-based models provided the best fit to the data, they were explored in full to determine their appropriateness to the economic model.

level data were available, and long-term clinical plausibility of the extrapolated model where there is a high-level of uncertainty because no trial data were available. Specifically, the long term clinical plausibility of the extrapolated model was based on validation against available nivolumab clinical trial data with longer follow-up than CheckMate 017 (in-trial validation) and RWD where available.

The data sets available for validation were:

- Clinical trial data: survival data were available for nivolumab-treated patients from CheckMate 003 (Phase I study – Table 24) and CheckMate 063 (Phase II study – Table 24), for up to 3 years and 1 year, respectively
- RWD: two sources of RWD were also available for analysis - the NLCA registry (UK) and the SEER registry (US). Further details on both registries and the comparability of SEER with UK survival estimates are given later in this section

Figure 15: Identifying parametric survival models based on NICE DSU guidelines



Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CA-209-017 = CheckMate 017; DSU = Decision Support Unit; NICE = National Institute for Health and Care Excellence; OS = Overall Survival; PFS = Progression-Free Survival; SEER = Surveillance, Epidemiology, and End Results Program

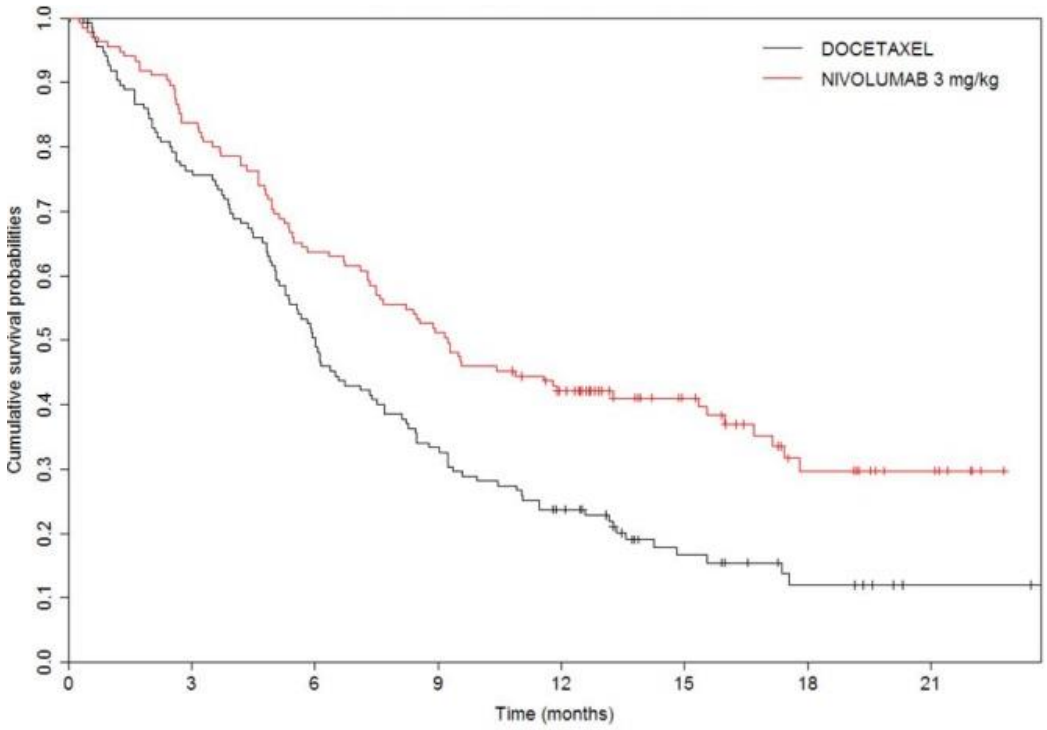
Extrapolation model for OS

Figure 16 shows the cumulative survival plot for OS based on CheckMate 017. Using the patient level data from CheckMate 017, log-cumulative hazards, log-cumulative, odds, and standardised normal curve plots were generated to determine if parallel lines were evident (Appendix 19, Figure 34). In addition, the Grambsch and Therneau's correlation test was applied, which confirmed the null hypothesis that proportional hazards could be demonstrated for OS (p=0.559). Therefore, it was assumed that proportional hazards held for OS.

Table 40 summarises the AIC/BIC values for the variety of parametric distributions assessed to determine the best fitting parametric survival model. Spline based models can increase in complexity based on the number of intermediate knots defined within the distribution. The implicit assumption within these models is that the number of knots represents the potential heterogeneous subgroups of patients – that is, 2-knot, 3-knot, 4-knot models represent 3, 4, and 5 subgroups, respectively, because the distributions segment the curve into different polynomial functions. Based on consultation with health economists and clinicians, it was determined that as with other parametric distributions, when using spline based models, the model should balance goodness of fit alongside clinical plausibility. It was agreed that any models above 2-knots would be considered over-fitting the data without a clinical justification. Likewise, it was agreed that within the 1-knot and 2-knot models, the model with the best fit in the short and long term should be utilised. In light of this, only 1-knot and 2-knot models were explored within the survival analysis.

It is evident from Table 40 that in terms of statistical fit, the two best fitting parametric survival models are the 2-knot spline hazards and a log-logistic distribution. Figure 17 and Figure 18 show the fit of each distribution to the CheckMate 017 OS data. Figure 19 and Figure 20 show the long term extrapolation of each distribution.

Figure 16: Cumulative survival plot for OS based on CheckMate 017



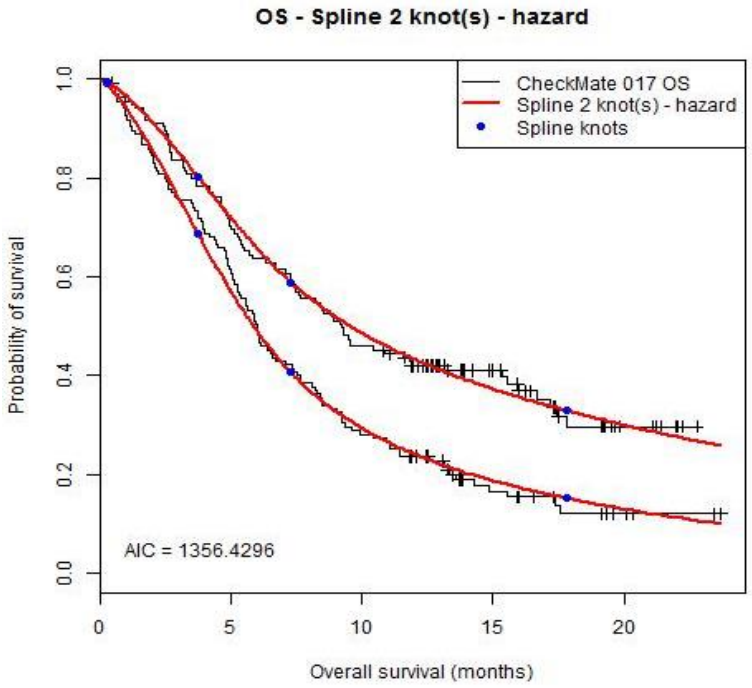
Abbreviations: OS = Overall Survival

Table 40: Summary of goodness-of-fit data for single survival model for OS

Distribution	AIC	BIC
Spline 4 hazard	1356.04	1381.28
Spline 2 hazard	**1356.43**	**1374.46**
Spline 3 hazard	1357.07	1378.71
Log-logistic	**1357.61**	**1368.43**
Spline 4 normal	1358.51	1383.75
Spline 1 hazard	1358.71	1373.13
Spline 4 odds	1358.80	1384.04
Spline 3 normal	1358.86	1380.49
Spline 5 hazard	1359.02	1387.87
Generalised gamma – treatment on scale	1359.28	1377.31
Spline 1 odds	1359.46	1373.89
Spline 2 normal	1359.51	1377.54
Spline 3 odds	1359.52	1381.15
Lognormal	1359.71	1370.53
Generalised gamma	1359.87	1374.30
Spline 2 odds	1360.02	1378.04
Spline 1 normal	1360.44	1374.87
Generalised gamma - treatment on shape	1360.90	1378.93
Generalised gamma – treatment on scale and shape	1361.23	1382.86
Spline 5 normal	1361.80	1390.65

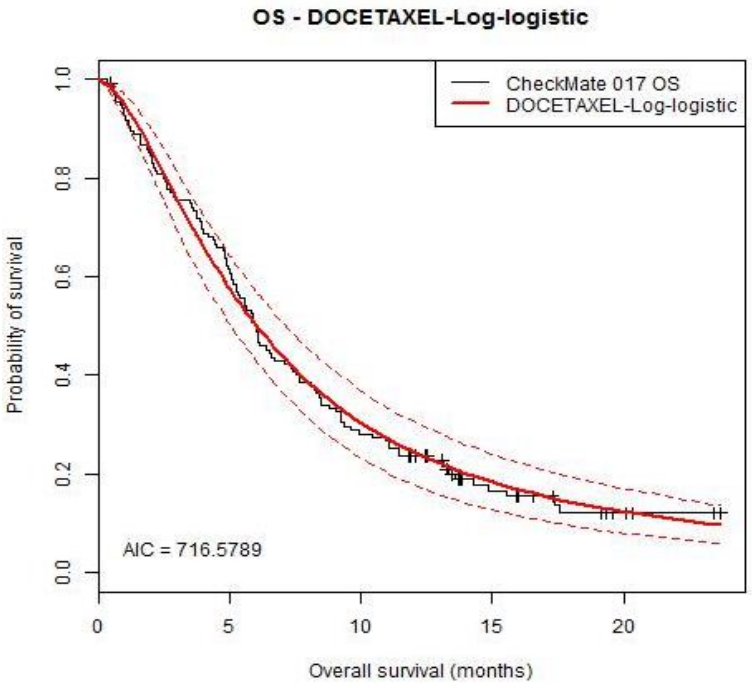
Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = Overall Survival

Figure 17. Plot of 2-knot spline-based hazard model for OS



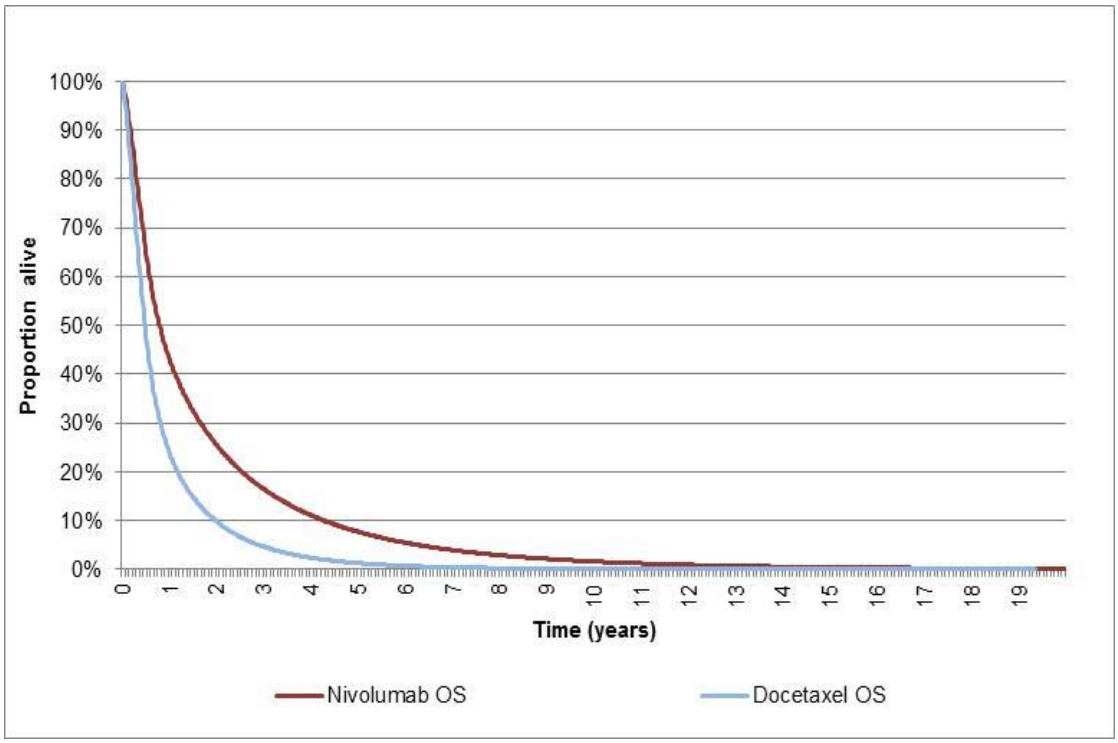
Abbreviations: AIC = Akaike Information Criterion; OS = Overall Survival

Figure 18: Plot of log-logistic for OS based on CheckMate 017



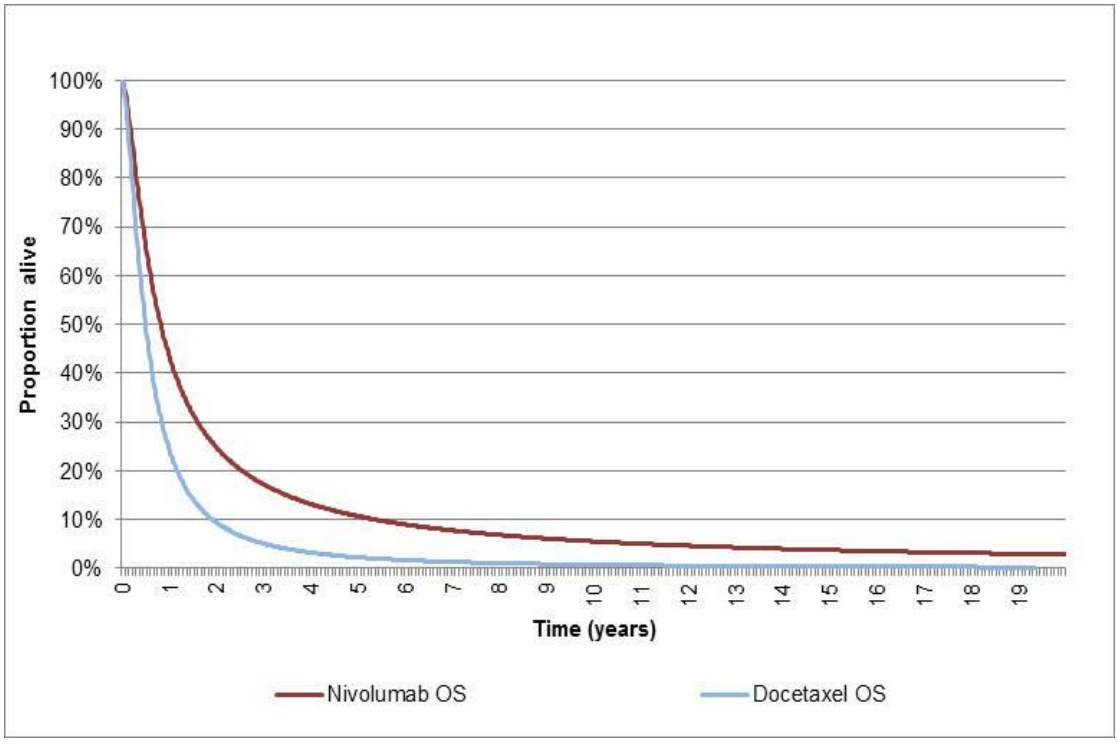
Abbreviations: AIC = Akaike Information Criterion; OS = Overall Survival

Figure 19: Plot of long-term extrapolation using 2-knot spline hazards model for OS



Abbreviations: OS = Overall Survival

Figure 20: Plot of long-term extrapolation using log-logistic model for OS



Abbreviations: OS = Overall Survival

Selection of base case OS parametric distribution

Determining the base case parametric model for OS was based on validating the best fitting curves (in terms of AIC/BIC values) against both clinical trial data and RWD to ensure the

clinical plausibility of the extrapolation. It is evident from Figure 17 and Figure 18 that both the spline 2-knot and log-logistic models provide a good fit to the observed trial data from CheckMate 017. In addition, both distributions were validated against additional data on OS with nivolumab from CheckMate 003 and CheckMate 063, and these comparisons are reported in Table 41. Though the population groups are heterogeneous across the three CheckMate trials, it is clear that patients on nivolumab experience comparable survival rates at both 6 months and 1 year across all three trials. The only clinical data for nivolumab at 3 years is from CheckMate 003. Both the 2-knot spline and log-logistic functions generate consistent estimates of survival at 3 years which are comparable with CheckMate 003 data, providing further validation of the extrapolation.

Table 41: Survival estimates from nivolumab trials compared with extrapolations

Data source	Curve	Proportion alive			
		6 months	1 year	2 years	3 years
Log-logistic	Nivolumab OS	68.0%	44.3%	25.1%	17.4%
	Docetaxel OS	52.0%	25.2%	9.6%	5.2%
Spline-2 knots	Nivolumab OS	67.3%	44.0%	25.9%	16.7%
	Docetaxel OS	51.0%	24.7%	10.1%	4.8%
CheckMate 017	Nivolumab OS	63.7%	42%	n/a	n/a
	Docetaxel OS	50.4%	24%	n/a	n/a
CheckMate 003	Nivolumab OS	n/a	42.0%	24.0%	18.0%
CheckMate 063	Nivolumab OS	60.1%	41%	n/a	n/a

Abbreviations: OS = Overall Survival

Beyond 3 years there is no clinical survival evidence on nivolumab to facilitate long-term validation. Therefore, RWD from two registries were utilised. Specifically, NLCA data were available for up to 5 years and SEER data were available for up to 15 years. These datasets are comparable in terms of epidemiological and survival statistics, as reported below in Table 43 and Table 44. NLCA and SEER were therefore utilised to ensure the long term extrapolations of each model reflected clinical expectations. Both the NLCA and SEER datasets provided OS rates from diagnosis. In comparison, in the CheckMate 017 study, patients were nearly 1 year from diagnosis when entering the study; median duration of time from initial diagnosis to randomisation was [redacted] years for patients on nivolumab and [redacted] years for patients on docetaxel. Therefore, predicted OS rates from the economic model were compared against NLCA and SEER OS rates for the year after. For example, conditional survival from year 2 to year 3 in the economic model was compared against conditional survival from year 3 to year 4 in NLCA and SEER.

A comparison of the conditional survival estimates from CheckMate 017, NLCA, and SEER are provided in Table 42, which compares the likelihood that a patient is still alive at the “end-year” if they survive to the “start-year”. When comparing conditional survival, it is clear that both the NLCA and SEER datasets have comparable conditional survival estimates. In

addition, it is clear that the spline model extrapolation consistently under-predicts conditional survival seen in the real world, which is clinically difficult to justify. In comparison, the log-logistic model is more closely aligned with real-world conditional survival estimates (Table 42).

Table 42: Comparison of conditional survival estimates predicted from OS parametric distributions vs. RWD

OS parametric distributions	**Curve**	**Conditional survival**				
	Start-year	**Yr 2**	**Yr 3**	**Yr 4**	**Yr 5**	**Yr 10**
	End-year	**Yr 3**	**Yr 4**	**Yr 5**	**Yr 10**	**Yr 15**
Spline – 2 knot	Nivolumab OS	64.5%	67.4%	69.4%	20.9%	26.4%
	Docetaxel OS	47.4%	51.1%	53.8%	7.0%	10.4%
Log-logistic	Nivolumab OS	69.4%	76.6%	81.0%	51.6%	67.7%
	Docetaxel OS	53.9%	63.6%	70.0%	32.6%	51.6%
RWD*	**Start-year**	**Yr 3**	**Yr 4**	**Yr 5**	**Yr 6**	**Yr 11**
	End-year	**Yr 4**	**Yr 5**	**Yr 6**	**Yr 11**	**Yr 16**
SEER stage IIIb/IV	Treatment not specified	69.3%	79.1%	81.3%	53.4%	57.0%
NLCA stage IV	Treatment not specified	78.6%	90.9%	N/A	N/A	N/A

* Both the NLCA and SEER datasets measure absolute survival rates of patients diagnosed with NSCLC, therefore they inherently capture “all-cause” mortality. Both datasets also include squamous and non-squamous NSCLC.

Abbreviations: NLCA = National Lung Cancer Audit; OS = Overall Survival; RWD = Real World Data; SEER = Surveillance, Epidemiology, and End Results Program

Based on all of the evidence considered, it was determined that the log-logistic survival model should be used as the base case for OS extrapolation. To summarise, the log-logistic curve was selected as the base case survival function for OS based on the following criteria:

- Goodness-of-fit statistics
- Clinical plausibility
- Visual inspection of fit
- Internal validation against all available nivolumab clinical trial data
- External validation using conditional survival estimates available from NLCA and SEER

The comparability of UK and US data

The economic analysis utilises both NLCA and SEER registry data to assess the clinical plausibility and validity of the long-term extrapolation methods for overall survival. The NLCA looks at the care delivered for people diagnosed with lung cancer and mesothelioma in England, Wales and Scotland, and therefore, survival estimates reported in NLCA can be considered representative of UK clinical practice (Health and Social Care Information Centre 2014b). SEER is a co-ordinated system of population based cancer registries located across the US; data are collected on cancer incidence and survival from 18 geographic areas comprising nearly 25% of the US population, and the population covered by SEER is comparable to the general US population (Howlader 2015).

Given that NLCA data were only available for up to 5 years, SEER registry data were an important source of validation for the long-term survival projections. The comparability of US and UK cancer statistics were assessed by undertaking a comparison of key epidemiological and mortality trends, as reported in Table 43 and Table 44. This assessment revealed that, in general, epidemiological and survival statistics are consistent across the UK and US for lung cancer. Specifically, for incidence, deaths, mortality, and proportion alive by year, as well as the stage distributions at diagnosis and trends in age at diagnosis (Appendix 21) are consistent across populations in the UK and the US.

Additionally, baseline characteristics of patients registered in the CheckMate 017 trial were compared with those of patients in the SEER and NLCA registries, and this comparison is presented in Table 45. Specifically for median age, age range, and male to female ratios, trial data appear to be well aligned with RWD from SEER and NLCA. In terms of disease stages, SEER data provide a better match than NLCA data to patients from CheckMate 017. A limitation in the comparison is the lack of data describing patients by line of therapy, type of therapy and performance status, however, the overall conclusion is that the baseline demographics of trial patients match those seen in the real world, and provides further justification for the long-term extrapolations based on these RWD.

Table 43: Comparison of UK and US data for lung cancer

	UK	**US**
Incidence	69.8 per 100,000	58.7 per 100,000
Estimated new cases/diagnoses	13% of all cancers (2012)	13% of all new cancers (2015)
Estimated deaths	35,371 (2012) - 22% of all cancer deaths	158,040 (2015) - 27% of all cancer deaths
Mortality	37.6 per 100,000	44.9 per 100,000
Proportion of patients alive at 1 year (IV UK, IIIB-IV US)	20%*	26%**
Proportion of patients alive at 2 years (IV UK, IIIB-IV US)	9%*	12%**
Proportion of patients alive at 5 years (IV UK, IIIB-IV US)	5%*	4%**

Source: (Cancer Research UK 2015c; Howlader 2015; Cancer Research UK 2015d; National Cancer Institute 2015a; Cancer Research UK 2015a; Cancer Research UK 2015b)

*Based on NLCA data from 2008-2012; personal communication

**Based on SEER 1973-2011

Table 44: Comparison of stage distribution for lung cancer across the UK and US

Stage, %	I	II	III	IV	Unknown
UK	12.9	7.3	19.4	47.6	12.7
US	16		22	57	5

Source: (Cancer Research UK 2015b; National Cancer Institute 2015b)

Table 45: Comparison of baseline characteristics from CheckMate 017, SEER and NLCA

	CheckMate 017[a]	SEER[b]	NLCA
Median age (years)	62	68	72[c]
Age range (years)	39 – 85	45 – 85	40 – 90[d]
Age categorisation (years)			
≤55	NR	15.5%	9.2%[e]
<65	59%	39.6%	35.8%[e]
≥70	NR	58%	44.7%[e]
≥75	8%	NR	24.5%[e]
% males	82% male	60% male	58% male[c]
Disease stage			
Stage IIIb	21%	33%	NR
Stage IV	78%	67%	32%[c]

NR: not reported

Source:

[a] CheckMate 017 (Brahmer 2015a)

[b] Long-term and conditional survival estimates for advanced NSCLC from SEER registry data (patients diagnosed in 1994 through end of 2011) (Bristol-Myers Squibb 2010)

[c] based on 120,745 patients with NSCLC in NLCA database seen from 2004 to 2014 (Khakwani 2013)

[d] NLCA report 2014 (Health and Social Care Information Centre 2014b)

[e] Data from 10,991 patients with NSCLC operated on between 2004 and 2010 from NLCA database (Powell 2013)

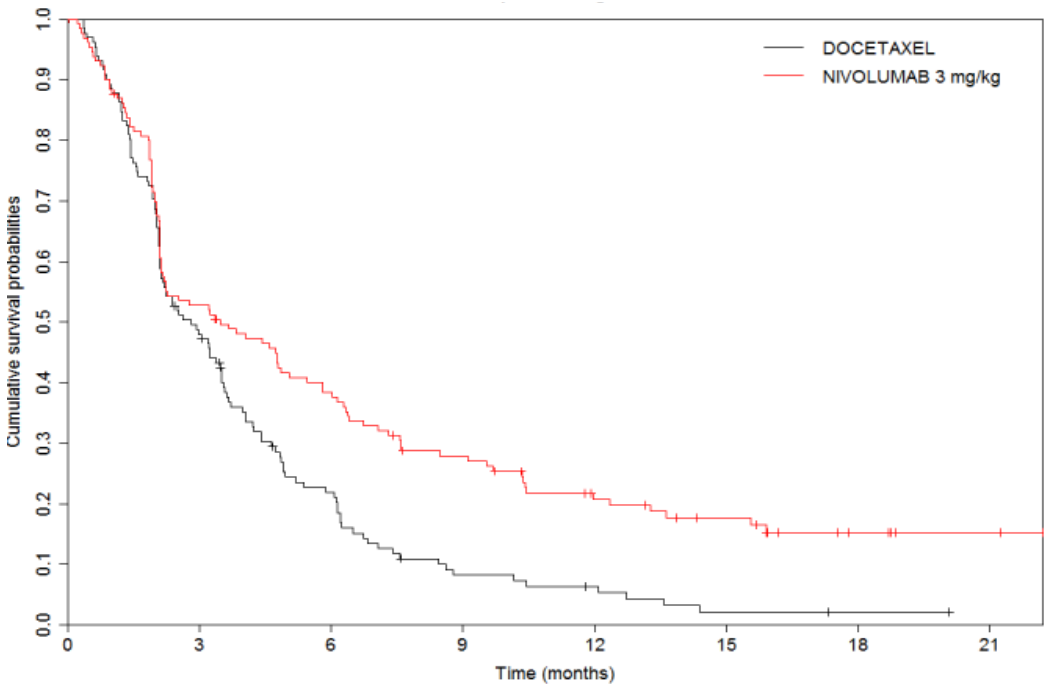
Selection of the extrapolation model for PFS

Similar to the OS extrapolation, the choice of a parametric survival model for PFS was informed by assessment of whether the assumption of proportional effects holds. This was done by visual inspection of the log-cumulative hazards, log-cumulative odds, and standardised normal curve plots (Figure 33 in Appendix 19). In addition, a Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time was used to test the proportional hazards assumption, which was highly significant (p=0.012), indicating that the null hypothesis for proportional hazards should be rejected.

Visual inspection suggested that the PFS curve and the proportional hazards assumption were heavily influenced by the steep drop observed within the first 9 weeks of follow-up (Figure 21), which is most probably due to the first follow-up being at 9 weeks after

randomisation. In the absence of further clinical information, curve fitting options were explored assuming non-proportional hazards.

Figure 21: Cumulative survival plot for PFS based on CheckMate 017



Abbreviations: PFS = Progression-Free Survival

Two approaches for parametric modelling were then considered:

- **Single survival model adjusted for shape and scale**: a single parametric curve was fitted to *both* the docetaxel and nivolumab arms (ITT population) with an adjustment factor (coefficient) to account for the effect of treatment on the scale and shape of the survival function
- **Independent survival models**: independent parametric survival curves were fitted *separately* to the docetaxel and nivolumab arms

A summary of the single survival models explored is given in Table 46. Similar to OS, spline models with more than 2 knots were not considered clinically plausible for PFS. Therefore, the best fitting parametric model in terms of AIC/BIC values was the 2-knot spline hazard model with an adjustment on gamma 1. Further details on the statistical parameters of the spline 2-knot model are provided in Appendix19, and Figure 22 shows the fitting of the spline 2-knot curve to PFS data from CheckMate 017.

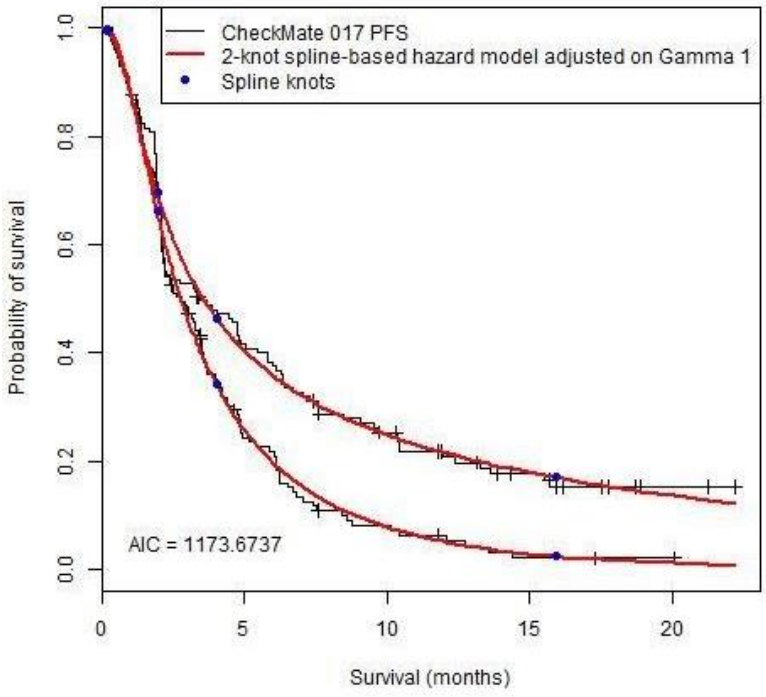
A summary of the independent survival models explored for PFS are in Table 47 and Table 48, for docetaxel and nivolumab, respectively. The best fitting parametric models in terms of AIC/BIC values were the log-normal distribution for docetaxel and 1-knot spline hazard model for nivolumab. Figure 23 shows the fitting of the log-normal and 1-knot spline models to the CheckMate 017 data for docetaxel and nivolumab.

Table 46: Summary of goodness-of-fit statistics for single survival models for PFS

Distribution	AIC	BIC
Spline 5 knot(s) – hazard	1158.49	1187.34
Spline 5 knot(s) – normal	1161.35	1190.20
Spline 5 knot(s) – odds	1162.85	1191.70
Spline 4 knot(s) – hazard	1172.93	1198.17
Spline 2-knot(s) hazard– interaction term on gamma 1	**1173.67**	**1195.31**
Spline 3 knot(s) – hazard	1174.93	1196.56
Spline 1 knot(s) – hazard	1175.95	1190.37
Spline 2 knot(s) – hazard	1178.34	1196.37
Spline 3 knot(s) – odds	1180.18	1201.82
Spline 3 knot(s) – normal	1180.24	1201.88
Spline 4 knot(s) – odds	1182.97	1208.21
Spline 1 knot(s) – odds	1183.04	1197.47
Spline 4 knot(s) – normal	1183.64	1208.88
Spline 2 knot(s) – odds	1185.25	1203.28
Spline 1 knot(s) – normal	1185.27	1199.69
Spline 2 knot(s) – normal	1185.32	1203.35
Log-normal	1187.10	1197.91
Generalised gamma	1187.43	1201.85
Log-logistic	1189.15	1199.97
Gamma	1216.93	1227.74

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PFS = Progression-Free Survival

Figure 22: Best fitting single survival function for PFS (2-knot spline hazard)



Abbreviations: AIC = Akaike Information Criterion; PFS = Progression-Free Survival

Table 47: Summary of goodness-of-fit statistics for PFS curve for docetaxel (independent survival model)

Distribution	AIC	BIC
Log-normal	**566.39**	**572.23**
Log-logistic	567.47	573.31
Generalised gamma	568.34	577.10
Spline 1 normal	568.37	577.13
Spline 1 hazard	568.92	577.68
Spline 1 odds	569.28	578.04
Spline 2 normal	570.28	581.96
Spline 2 odds	570.45	582.13
Spline 2 hazard	570.96	582.64
Spline 5 normal	571.20	591.64
Spline 3 normal	571.62	586.22
Spline 3 odds	571.64	586.24
Spline 5 odds	571.77	592.21
Spline 3 hazard	572.80	587.40
Spline 5 hazard	572.84	593.28
Spline 4 hazard	573.22	590.74
Spline 4 normal	573.31	590.83
Spline 4 odds	573.56	591.08
Gamma	579.24	585.08
Weibull	584.84	590.68
Exponential	590.20	593.12
Gompertz	592.15	597.99

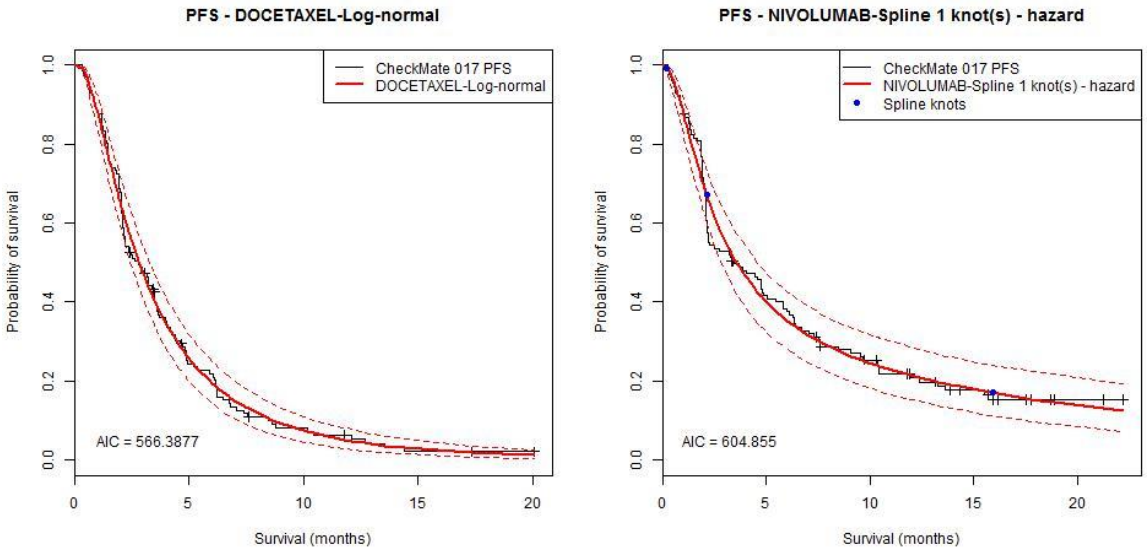
Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PFS = Progression-Free Survival

Table 48: Summary of goodness-of-fit statistics for nivolumab curve for PFS (independent survival model)

Distribution	AIC	BIC
Spline 5 odds	584.14	604.48
Spline 3 odds	598.27	612.80
Spline 3 normal	598.53	613.05
Spline 4 hazard	598.72	616.16
Spline 3 hazard	601.06	615.59
Spline 4 odds	601.67	619.10
Spline 4 normal	603.60	621.04
Spline 1 hazard	**604.86**	**613.57**
Spline 1 odds	604.88	613.60
Spline 1 normal	606.06	614.78
Generalised gamma	606.50	615.22
Spline 2 hazard	606.73	618.35
Spline 2 odds	606.95	618.57
Spline 2 normal	607.78	619.40
Log-normal	608.04	613.85
Log-logistic	610.37	616.18
Gompertz	625.31	631.12
Weibull	628.02	633.83
Exponential	628.28	631.18
Gamma	629.80	635.61

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PFS = Progression-Free Survival

Figure 23: Plot of selected independent curves fitted to docetaxel (left: log-normal) and nivolumab (right: 1-knot spline-based hazard model)



Abbreviations: AIC = Akaike Information Criterion; PFS = Progression-Free Survival

Visual inspection of the PFS curves (Figure 22 and Figure 23) revealed that both the dependent and independent survival model options provided a good fit to the data. As with OS, the survival parameters generated by these curves were compared with the in-trial survival estimates obtained from CheckMate 003 and CheckMate 063 (Table 49). It is evident from Table 49 that similar to OS, across the three CheckMate trials, there is a comparable proportion of patients alive in PFS at 6 months and 1 year. In addition, the survival estimates generated by both the single survival model and independent survival models match closely against all nivolumab clinical trials. The only estimates of PFS in year 2 are from CheckMate 003; it is apparent that both single and independent survival models match well against the 2-year survival rates predicted from CheckMate 003, providing further validation of these extrapolations. In terms of utilising long-term data to validate the extrapolation, PFS data were not available from RWD for comparison.

Table 49: In-trial survival estimates for PFS survival functions

Data source	Curve	Proportion alive		
		6 months	1 year	2 years
Single survival model adjusted for shape and scale	Nivolumab PFS	36.9%	22.0%	11.4%
	Docetaxel PFS	21.2%	5.5%	0.6%
Independent survival model	Nivolumab PFS	36.4%	21.8%	11.7%
	Docetaxel PFS	20.0%	6.4%	1.4%
CheckMate 017	Nivolumab PFS	38.4%	21%	NA
	Docetaxel PFS	21.9%	6%	NA
CheckMate 003	Nivolumab PFS	33%	22%	9%
CheckMate 063	Nivolumab PFS	25.9%	20%	NA

Abbreviations: PFS = Progression-Free Survival

Selection of the base case parametric distribution for PFS

As both dependent and independent survival functions provided a comparable and good fit to clinical trial data, and long-term RWD for PFS were not available to help validate long-term extrapolation, other factors were considered in selecting the base case distribution. To ensure randomisation was not broken by fitting independent curves to each treatment arm, and to account for a possible delayed response to treatment, the dependent curve option (2-knot spline hazards) was selected as the base case survival curve for PFS.

In summary, the single 2-knot spline hazards curve was selected as the best fitting survival function for PFS based on the following factors:

- Goodness-of-fit statistics
- Clinical plausibility
- Visual inspection of fit
- Compliant with trial randomisation
- Internal validation against all available nivolumab clinical trial data

Summary of survival analysis

Table 50 summarises the survival functions that were selected for the base case and scenario analyses.

Table 50: Summary of survival distributions for PFS and OS

Survival models explored	Best-fitting parametric curve
PFS	
Base case: single survival model adjusted for shape and scale	2-knot spline hazards
Scenario analysis: independent survival models	Docetaxel: Log-normal Nivolumab: 1-knot spline hazards
OS	
Base case: single survival model	Log-logistic
Scenario analysis: single survival model	2-knot spline hazards

Abbreviations: OS = Overall Survival; PFS = Progression-Free Survival

The use of the 2-knot spline hazard model for OS was explored as a sensitivity analysis not only because it was the second best fitting curve in terms of AIC/BIC values but also to address two general methodological points raised by the NICE DSU guidance on survival analysis for economic evaluations (Latimer 2013). Specifically:

- Proportional hazards makes the assumption that treatment effect is proportional over time, and therefore this assumption can be made for proportional hazards models such as the exponential, Gompertz, or Weibull, but not log-logistic and log normal models, which are accelerated failure time models
- Application of the HR obtained from the chosen parametric model to the control group in comparison to one derived from a Cox proportional hazards model is preferred

Both the application of HR to log-logistic and log normal curves, and the application of Cox proportional hazards model to independently derived parametric models have been accepted by NICE historically in several previous manufacturer submissions. However, the 2-knot spline hazards model addresses both points in the NICE DSU guidance. The spline model is a proportional hazards model. In addition, the 2-knot spline model utilises the HR derived from the parametric curve and not the Cox proportional hazards model reported in the CheckMate 017 CSR. The HR derived from the parametric model was identical to that of CheckMate 017 (OS HR = 0.59). This gives extra validity to the use of the spline-2 knots model as a sensitivity analysis for modelling OS.

Adverse events

The incidence of AEs was taken from the CheckMate 017 trial (Table 51). The inclusion criteria for AEs in the economic model were any Grade ≥3 severity with a ≥5% incidence in either treatment arm that were associated with a high cost or significant decrease in utility (Bristol-Myers Squibb 2015a). The inclusion of these events is a conservative assumption considering that the safety profile for nivolumab is favourable compared with docetaxel for both incidence of all AEs, and incidence of all Grade ≥3 AEs (Section 4). The inclusion criteria for all AEs were produced with the help of clinical experts.

Table 51: Grade ≥3 severity AEs included in the economic model based on CheckMate 017 data

Type of AE	Rate for nivolumab	Rate for docetaxel
Dyspnoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]

Source: (Bristol-Myers Squibb 2015a)

Abbreviations: AE = Adverse event; NA = Not applicable

Overall frequencies of AEs over the duration of CheckMate 017 are shown in Appendix 23. These were applied in the first cycle of the model for all patients. This method of calculation is to ensure the full cost and HRQoL impact associated with AEs is captured for both treatment arms (i.e. without discounting).

Transition probabilities

The economic model is defined on three health states: PF, PD and death (Figure 14). The proportion of patients in each health state per cycle is determined by the AUC or partitioned survival approach, based on parametric survival functions for PFS and OS. The proportion of patients in PD per cycle is defined as the difference between the OS and PFS for that cycle. As OS and PFS are defined by different parametric survival models, in instances where there is cross-over of curves, that is, PFS is greater than OS, the model has an adjustment factor to ensure that PFS is always equal to OS.

Subsequent treatment

PD is represented by a single health state; however, in order to reflect the treatment of patients after disease progression, and to ensure that the full cost of treatment for a progressed patient is accurately represented, patients in the PD health state were assumed

to incur costs of subsequent (post-progression) treatment which were calculated based on the proportion of patients who received subsequent systemic therapy as reported in the CheckMate 017 trial (Table 52). The possible impact of subsequent therapy on OS was not included in the model.

Considering the advanced nature of the disease, an assumption was made that patients could only receive one line of therapy following progression (third line therapy) on or after second line therapy. Data from CheckMate 017 were used to estimate the type and distribution of treatment patients could receive as third line therapy (Table 52). CheckMate 017 however did not provide details on duration of subsequent treatment, and therefore the duration of third-line therapy was derived from real world data, as reported in the observational study CA209-116, which investigated the treatment patterns, outcomes and healthcare resource use in patients with advanced NSCLC in Europe (Bristol-Myers Squibb 2015b). The time until treatment discontinuation in patients in a third-line setting for the overall population was [redacted] days (Bristol-Myers Squibb 2015b). A cost of subsequent treatment was calculated by weighting the cost of the different third-line treatments received by patients in the CheckMate 017 trial (Table 45), assuming an average duration of treatment of [redacted] days. This weighted cost was applied as a one-off cost to all patients who transitioned out of the PF health state.

Table 52: Type and distribution of subsequent (third-line) therapy based on CheckMate 017

	Nivolumab arm	Docetaxel arm
Platinum-based therapies	[redacted]	[redacted]
Docetaxel	17.36%	2.93%
Gemcitabine	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
Erlotinib	2.63%	4.69%
BSC	[redacted]	[redacted]

Source: adapted from CheckMate 017 data (Bristol-Myers Squibb 2015a)

Abbreviations: BSC = Best Supportive Care

5.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

HRQoL data were collected in the CheckMate 017 trial using the EuroQol 5D preference-based health state utility questionnaire (EQ-5D utility index) and visual analogue scale (EQ-VAS) for overall health status. The EQ-5D descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, severe problems. The EQ-5D utility index and EQ-VAS are scaled from 0–1 and 0–100, respectively; higher scores indicate better health status. The MID has been estimated to be 0.08 for the EQ-5D utility index and 7 for the EQ-VAS (Pickard 2007).

All randomised subjects from CheckMate 017 who had one baseline assessment and at least one post-baseline assessment were included in the analysis. The EQ-5D completion rates were similar between treatment arms, being 77.8% and 76.6% for nivolumab and docetaxel, respectively, at baseline; however, for patients with baseline and at least one post-baseline visit, the completion rates decreased to 71.9% and 64.2% for nivolumab and

docetaxel, respectively. No adjustments were made for missing data when scoring the EQ-5D index. Data from screening visits (up to 28 days before) were used in place of any missing baseline data.

The schedule of assessments is given in Table 53. Assessments were taken every other cycle (every 4 weeks) on Day 1 for first 6 months of study for nivolumab and every cycle (every 3 weeks) on Day 1 for first 6 months of study for docetaxel. Assessments were then taken every 6 weeks for the remainder of the trial period for both treatment arms.

The use of utilities as captured in the CheckMate 017 trial via the EQ-5D instrument is in line with the NICE reference case. The UK Measurement and Valuation of Health (MVH) study scoring algorithm was applied to patient-level data from the overall analysed trial population to generate EQ-5D utility index-based scores for the UK (Dolan 1997). These scores aggregated across treatment groups were applied for the base case analysis and are listed in Table 54.

The strength of this approach is that it is based on patient-level data from the pivotal CheckMate 017 clinical trial, making it directly relevant to the economic analysis.

Table 53: EQ-5D assessment schedule in CheckMate 017

	Nivolumab & Docetaxel		**Nivolumab: On-study assessments**	**Docetaxel: On-study assessments**	**Nivolumab & Docetaxel: Follow-up assessments**	**Nivolumab & Docetaxel: Follow-up assessments**
Assessments	**Screening Visit**	**Cycle 1 Day 1 Visit**	**Every other cycle (every 4 weeks) Day 1 (± 3 days)**	**Each cycle (every 3 weeks) Day1 (± 3 days)**	**Follow-up visits 1 (X01)a and 2 (X02)b**	**Further follow-up visits (beyond X02)c**
EQ-5D	✓	✓	✓	✓	✓	✓

[a] X01 to occur approximately 30 days (±5 days) after last dose or coinciding with the date of discontinuation (±5 days) if date of discontinuation is greater than 35 days after last dose

[b] X02 to occur approximately 70 days (±5 days) after X01

[c] Beyond 100 days from the last dose of study therapy, the EQ-5D will be administered every 3 months for the first 12 months, then every 6 months thereafter, as permitted by local law

Table 54: UK-specific mean EQ-5D values by health state

Tumour Response Category	**UK (Mean)**	**Standard deviation**	**95% CI**
Overall (N=1132)	0.719		
PD (N=219)	0.592	0.315	0.550-0.634
PFS - SD/PR/CR (N=913)	0.750	0.236	0.734-0.765

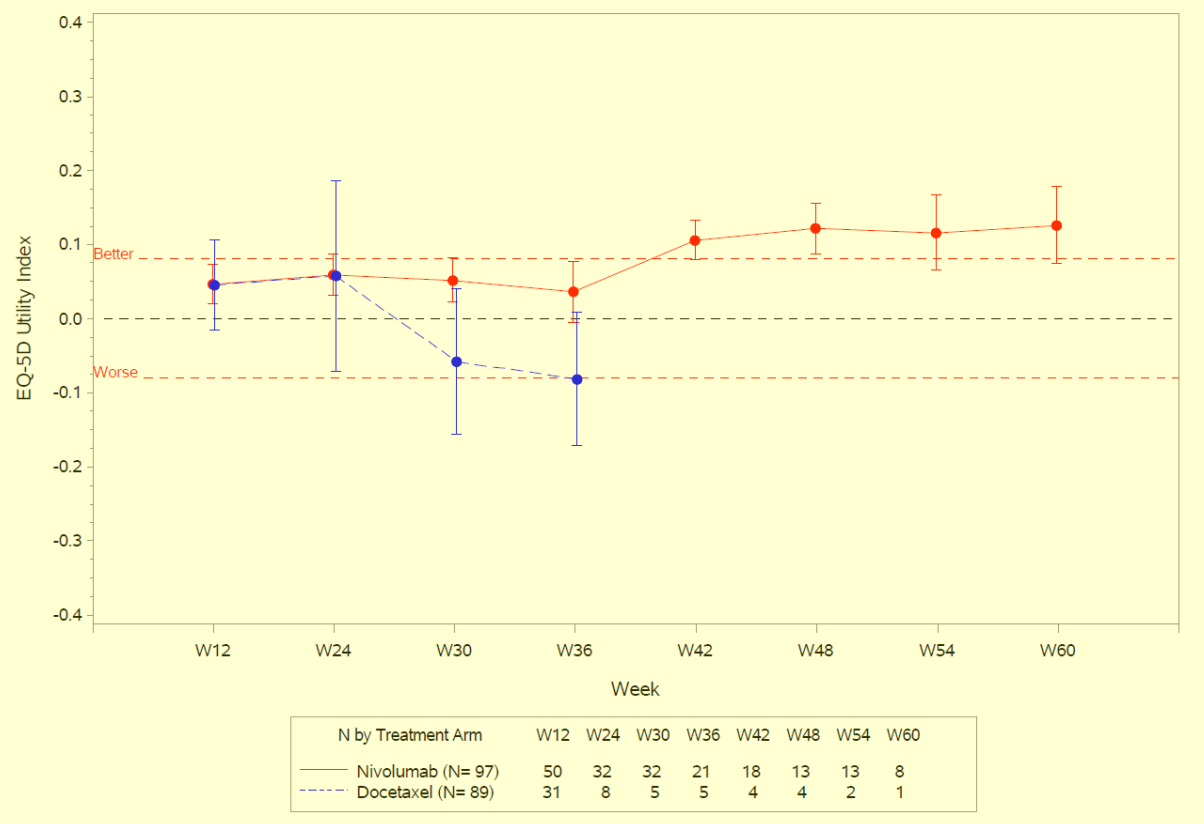
Abbreviations: CI = Confidence Interval; CR = Complete Response; EQ-5D = EuroQol 5-Dimensions; PD = Progressive Disease; PFS = Progression-Free Survival; PR = Partial Response; SD = Stable Disease; UK = United Kingdom

EQ-5D descriptive statistics based on CheckMate 017

Using the EQ-5D utility index, a significant improvement was observed from week 16 ([redacted]) to week 30 ([redacted]), and from week 42 ([redacted]) to week 54 ([redacted]) in the nivolumab-treated patients ([redacted]). The improvement through week 42 to week 54 was also considered clinically relevant (greater than MID of 0.08). Conversely, with docetaxel, no significant changes from baseline were observed.

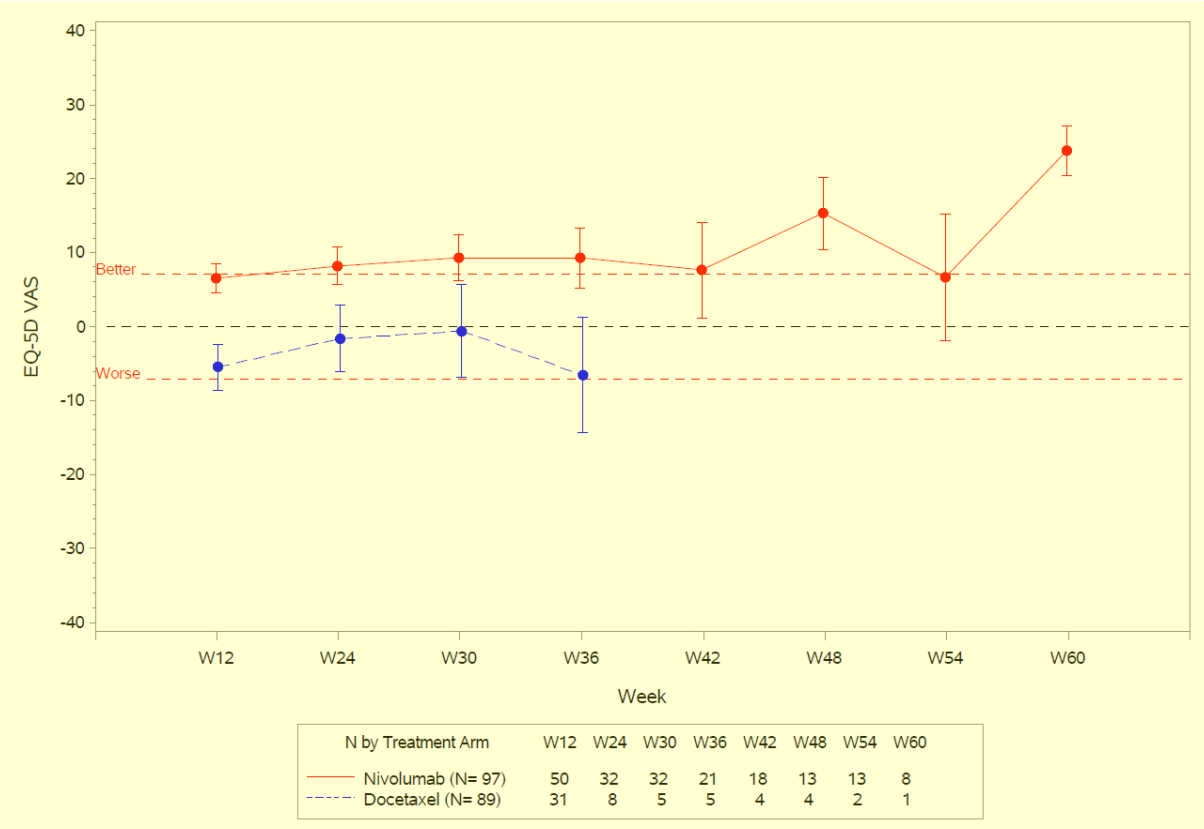
Similar trends were observed with the EQ-5D VAS ([redacted]), where significant improvement was observed with nivolumab at week 12 ([redacted]) and from week 20 ([redacted]) to week 36 ([redacted]), as well as at week 48 ([redacted]). The improvement through week 24 to 36, and week 48 was also considered clinically meaningful (greater than MID of 7). Again, with docetaxel, no significant changes from baseline were observed during treatment. At Follow-up visit 1, a statistically significant and clinically relevant deterioration was observed ([redacted]). Overall, the results of the EQ-5D analysis from CheckMate 017 shows that the HRQoL of patients treated with nivolumab improved from baseline during the first year of treatment, whilst that of patients treated with docetaxel remained unchanged relative to baseline scores.

Figure 24: CheckMate 017: EQ-5D utility index results



Abbreviations: EQ-5D = EuroQol 5 Dimensions; W = Week

Figure 25: CheckMate 017: EQ-5D VAS results



Abbreviations: EQ-5D VAS = EuroQol 5 Dimensions Visual Analogue Scale; W = Week

Health-related quality of life studies

The systematic literature review to identify HRQoL studies was performed as part of the systematic literature review described in Section 5.1 using the inclusion and exclusion criteria defined in Table 36 and the search strategy presented in Appendix 9.

A total of seven studies were identified that met the eligibility criteria for the review, however, none of the studies evaluated nivolumab and none were performed in a UK-based population. Primarily for this reason, HRQoL data from the CheckMate 017 study were used in this submission.

Adverse reactions

The economic model includes the quality of life impact of AEs of Grade 3 or higher severity, which occurred in ≥5% of patients in the CheckMate 017 trial. The disutility per episode for each of the included AEs is shown in Table 49, and the expected disutility per patient associated with the incidence of the included AEs was applied in the first cycle (i.e. without discounting).

Some patients may experience multiple AEs simultaneously. Published literature on the disutility of AEs does not provide evidence on the cumulative effect on patients experiencing more than one AE at a time, and in the absence of better information, the disutility of each adverse event is applied separately. This may introduce an element of double-counting. However, this approach to applying AE disutilities is routinely used in economic evaluations.

Table 55: Disutilities of adverse events

Adverse event	Disutility	Reference
Asthenia	-0.073	Assumption: same as fatigue
Dyspnoea	-0.050	(Doyle 2008)
Fatigue	-0.073	(Nafees 2008)
Febrile neutropenia	-0.090	(Nafees 2008)
Neutropenia	-0.090	(Nafees 2008)
Pneumonia	-0.008	(Marti 2013)

Health-related quality of life data used in cost-effectiveness analysis

The utility values used in the economic model are summarised in Table 56. The mean utility values derived from patients with advanced NSCLC based on the CheckMate 017 analysis (for the UK) are 0.719 (overall across all categories); 0.592 (progressed disease); and 0.75 (progression-free). These compare with a mean utility value of 0.86 derived from a representative sample of adults drawn from a national Health Survey of England in 2008 (Anokye 2012), which demonstrates that the HRQoL of patients with advanced NSCLC is lower than that of the general population.

Table 56: Summary of utility values used in the cost-effectiveness analysis

	Utility value: mean (SD or SE)	95% confidence interval	Reference in submission	Justification
Progression-free	0.750 (0.236)	0.734, 0.765	Section 5.4	Derived from EQ-5D data collected in CheckMate 017 (BMS data on file)
Progressed disease	0.592 (0.315)	0.550, 0.634	Section 5.4	
Death	0	-	Section 5.4	Assumption
Asthenia	-0.07346 (0.01849)	-	Section 5.4	Assumed to be same as fatigue based on medical opinion
Dyspnoea	-0.05	-	Section 5.4	Based on societal preferences for health states of patients with advanced NSCLC in England and Wales
Fatigue	-0.07346 (0.01849)	-	Section 5.4	Based on societal preferences for health states of patients with advanced NSCLC in England and Wales
Febrile neutropenia	-0.09002 (0.01633)	-	Section 5.4	Based on societal preferences for health states of patients with advanced NSCLC in England and Wales
Neutropenia	-0.08973 (0.01543)	-	Section 5.4	Based on societal preferences for health states of patients with advanced NSCLC in England and Wales
Pneumonia	-0.008	-	Section 5.4	Assumption that disutility is applicable to patients with advanced NSCLC

Abbreviations: NSCLC = Non-Small Cell Lung Cancer; SE: Standard Error; SD: Standard Deviation

5.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

A systematic literature review was carried out to identify studies reporting costs and healthcare resource use (Section 5.1) using the inclusion and exclusion criteria defined in Table 36 and the search strategy presented in Appendix 9. Two UK-based modelling studies contained resource use assumptions (Table 51), but these studies provided limited data and neither study was used to inform resource use in the model.

Published NICE technology appraisals in second-line NSCLC were also identified. An overview of the four relevant appraisals is provided in Table 37. Three of these were used to inform the resource use assumptions in the nivolumab model (Table 51): erlotinib (TA162), erlotinib and gefitinib multiple technology appraisal (rev TA162, TA175; [ID620]), and nintedanib (GID-TAG449; information taken from the draft appraisal consultation document).

Resource use data reported in the nintedanib draft appraisal consultation document (ID620, 2015b) provides the most recent information reflecting current clinical practice for the second-line treatment of NSCLC in England. The erlotinib technology appraisal (TA162) and the erlotinib and gefitinib multiple technology appraisal (rev TA162, TA175; [ID620]) were used to inform resource use not reported in the nintedanib consultation document. Resource use inputs were validated through one-on-one discussions with clinicians and health economists.

Table 57: Summary of cost and resource use studies identified within the systematic review

Study, year	Country	Population	Study type	Resource use and costs included
(Holmes 2004)	UK	Previously treated with platinum-based chemotherapy, taxane-naïve, with PS≤2	Cost-effectiveness analysis	• Drug costs • Drug administration costs • Co-drug costs • Toxicity treatment costs
(Lewis 2010)	UK	Previously treated stage IIIB – IV NSCLC with PS≤3	Cost-utility analysis	• Drug costs • Drug administration and health states • Drug administration per visit (docetaxel only) • Progression-free health state per month • Progression health-state per month • Adverse events
Erlotinib TA 162 (NICE 2012b)	England	Second-line patients with NSCLC	NICE STA	• Drug costs • Drug administration • Disease management costs • Progression-free costs and resource use • Post-progression costs and resource use • Adverse events
Nintedanib (in combination with docetaxel) GID-TAG449* (NICE 2015c)	England	Second-line patients with locally advanced, metastatic, or locally recurrent NSCLC	NICE STA	• Drug costs • Drug administration • Disease management costs • Progression-free costs and resource use • Post-progression costs and resource use • Adverse events
Erlotinib and gefitinib (MTA) (rev TA162, TA175) [ID620] (NICE 2015a)	England	Second-line patients with locally advanced or metastatic NSCLC	NICE MTA	• Drug costs • Drug administration • Disease management costs • Progression-free costs and resource use • Progression costs and resource use • Adverse events

Abbreviations: MTA = Multiple Technology Assessment; NSCLC = Non-Small Cell Lung Cancer; PS = Performance Status; STA = Single Technology Assessment; UK = United Kingdom

Intervention and comparators' costs and resource use

The costs of drug acquisition, administration, monitoring, AEs, and health states are included in this section. The price year for all costs is 2015.

Drug acquisition costs – initial treatment

Drug acquisition costs by pack/vial size and per dose for the initial treatments are presented in Table 58 and Table 59, respectively. The unit costs of all comparators and subsequent treatments were sourced from the British National Formulary 2015.

The dosage for nivolumab is calculated based on body weight in kilograms (kg). The dosage for docetaxel is calculated based on body surface area (BSA). Data on the typical weight distribution of patients with lung cancer were not readily available for the UK, so an indirect calculation was applied using the average BSA of patients with lung cancer receiving chemotherapy in the UK to derive the average body weight (formula below). Height data used in the calculation were sourced from the Health and Social Care Information Centre (Health and Social Care Information Centre 2014a). The average weight used to calculate nivolumab dose was 73kg.

$$BSA = Weight\ (kg)^{0.425} \times\ Height\ (cm)^{0.725} \times 0.007184$$

Source: (Sacco 2010)

Abbreviations: BSA = Body Surface Area; cm = centimetres; kg: kilograms

Although BSA was captured in the CheckMate 017 trial, because of regional variations, the systematic anti-therapy (SACT) (www.chemodataset.nhs.uk/home) dataset was thought to be more representative of patients with squamous NSCLC seen in UK clinical practice. The average BSA used to calculate docetaxel dose was 1.82m^2.

Table 58: Drug acquisition costs (initial treatments)

Drug	Tablet dose/vial concentration	Pack size/vial volume	Cost per vial/pack	Source
Nivolumab	10 mg/ml	4 ml	£439.00 (£10.98/mg)	UK list price
		10 ml	£1,097.00 (£10.98/mg)	
Docetaxel	10 mg/ml	2 ml	£138.33 (£6.92/mg)	BNF 2015
		14 ml	£900.00 (£6.43/mg)	

Abbreviations: BNF = British National Formulary; BSC = Best supportive care; mg = milligram; ml = millilitre; N/A = not applicable

Note: All BNF prices were retrieved in June 2015

Table 59: Drug acquisition cost per dose (initial treatments)

Drug	Total dose per administration	No. of vials / packs	Method of administration	Total drug cost per dose	Frequency of administration
Nivolumab	3 mg/kg * 73 kg = 219 mg	6 x 4 ml vials*	IV; no vial sharing (i.e. round up to nearest full vials)	£2634	Every 2 weeks
Docetaxel	75 mg/ m^2 * 1.82 m^2 = 137 mg	1 x 14ml vials*	IV; no vial sharing (i.e. round up to nearest full vials)	£900.00	Every 3 weeks

Abbreviations: BSC = Best Supportive Care; IV = Intravenous; kg = kilogram; m^2 = metres squared; mg = milligram; ml = millilitre; N/A = not applicable

*The 4 ml vial (nivolumab) and 14ml vial (docetaxel) are used in the base case because these are the smallest and cheapest vial sizes, respectively

Drug acquisition costs - subsequent treatment

The model includes costs of subsequent treatment for patients with PD (Table 52) based on the distribution of subsequent therapy observed in the CheckMate 017 trial. Drug acquisition costs for these subsequent treatments are shown in Table 54.

Table 60: Drug acquisition costs (subsequent treatments)

Drug	Tablet dose/vial concentration	Pack size/vial volume	Cost per vial/pack	Source
Cisplatin	1 mg/ml	50 ml	£24.50	BNF 2015
		100 ml	£50.22	
Carboplatin	10 mg/ml	5 ml	£20.00	BNF 2015
		45 ml	£160.00	
Gemcitabine	1000 mg/vial	1000 mg	£154.62	BNF 2015
	2000 mg/vial	2000 mg	£324.00	
Vinorelbine	10 mg/ml	1 ml	£29.00	BNF 2015
		5 ml	£139.00	
Docetaxel	10 mg/ml	2 ml	£138.33	BNF 2015
		14 ml	£900.00	
Erlotinib	150 mg	30 tablets	£1,631.53	BNF 2015

Abbreviations: BNF = British National Formulary; BSC = Best supportive care; mg = milligram; ml = millilitre

The cost of each subsequent treatment per dose and the frequency of administration are shown in Table 61. The treatment duration of subsequent therapy is [redacted] days, based on RWD collected in the CA209-116 observational study, which investigated the treatment patterns, resource use, and outcomes of patients with advanced NSCLC in Europe (Bristol-

Myers Squibb 2015b). An assumption was made that the pooled RWD collected from European countries was applicable to clinical practice in the UK.

Table 61: Drug acquisition cost per dose (subsequent treatments)

Drug	Total dose required per administration	No. of vials / packs	Method of administration	Total drug cost per dose	Frequency of administration
Cisplatin	100 mg/ m^2 * 1.82 m^2 = 182 mg	2 x 100 ml vials	IV; no vial sharing (i.e. round up to nearest full vials)	£100.44	Every 3 weeks
Carboplatin	400 mg/ m^2 * 1.82 m^2 = 728 mg	2 x 45 ml vials	IV; no vial sharing (i.e. round up to nearest full vials)	£320.00	Every 4 weeks
Gemcitabine	1000 mg/ m^2 * 1.82 m^2 = 1820 mg	2 x 1000 mg vials	IV; no vial sharing (i.e. round up to nearest full vials)	£309.24	Every 4 weeks (once per week for 3 weeks, followed by one week off-treatment)
Vinorelbine	30 mg/ m^2 * 1.82 m^2 = 55 mg	6 x 1 ml vials	IV; no vial sharing (i.e. round up to nearest full vials)	£174.00	Every week
Docetaxel	75 mg/ m^2 * 1.82 m^2 = 137 mg	1 x 14ml vials	IV; no vial sharing (i.e. round up to nearest full vials)	£900.00	Every 3 weeks
Erlotinib	150 mg	1/30 pack (30 x 150 mg)	Oral; vial sharing is N/A	£54.38	Daily

Abbreviations: BNF = British National Formulary; BSC = Best Supportive Care; IV = Intravenous; m^2 = metres squared; mg = milligram; ml = millilitre; N/A = not applicable

Treatment administration costs

The costs of treatment administration for nivolumab and docetaxel are shown in Table 62 as applied in the model. The administration costs for platinum-based therapy (cisplatin and carboplatin), gemcitabine, and vinorelbine are assumed to be the same as for docetaxel, which is considered to be a simple chemotherapy. There are no HRG or PbR codes specific to nivolumab; however, it is expected to be administered at a hospital outpatient setting (day care basis), and is assumed to be costed as a complex chemotherapy, which is consistent with the administration of ipilimumab as reported in TA319.

Table 62: Cost per administration

Treatment	Type of administration		Currency code	Cost per administration	Source
Nivolumab	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance	Outpatient setting	SB14Z	£269.94	NHS Reference Costs 2013-14
Docetaxel	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z	£167.34	NHS Reference Costs 2013-14

BSC = Best supportive care; N/A = not applicable; NHS = National Health Service

*All administration costs are assumed to be for first attendances in a cycle due to the length of time between administrations (for nivolumab and docetaxel, it is every 2 weeks and 3 weeks, respectively). All costs are inflated to June 2015 values

**Erlotinib is an oral therapy and therefore, has no associated administration costs. Patients receiving erlotinib attend 1 outpatient appointment per month (considered in the monitoring costs), where they are assumed to obtain repeat prescriptions

Monitoring costs

The cost of monitoring for a patient in the PF health state is shown in Table 63. The cost of an oncologist visit is assumed to include the costs of any blood analyses or metabolic tests required as part of treatment, based on ERG critiques from TA162

Table 63: Monitoring costs on treatment (per 4 weeks)

Drug	Monitoring cost	Unit cost	Currency code (NHS Reference costs)	Frequency per 4 weeks	Monitoring cost per 4 weeks*
Nivolumab or docetaxel	Outpatient visit (consultant-led)	£151.89	Medical oncology code 370, Consultant-led outpatient appointment	1	£151.89

Abbreviations: BSC = Best Supportive Care; N/A = Not Applicable; NHS = National Health Service

*All costs are inflated to June 2015 values

Disease management costs

Patients incur disease management costs for as long as they are alive. Unit costs are constant but the quantity or frequency of resource use per cycle varies by health state (PF or PD). The types of resources and frequency of use are derived from previous technology appraisals and validated by UK clinicians.

Table 64 shows the assumed resource use for disease management in the PF health state. Unit costs are shown in Table 66. The total cost per 4 weeks (4 cycles) in the PF health state is £313.55. This cost is adjusted in the model to reflect the weekly cycle length (£78.39).

Table 64: Resource use for progression-free health state

Resource	No. required per 4 weeks	% of patients requiring resource	Unit cost*	Cost per 4 weeks	Source (resource use)
Routine GP visit (at GP surgery)	0.92	100%	£47	£42.97	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE 2015a)
Palliative care (days)	2.00	100%	£86	£172.83	Nintedanib NICE submission (NICE 2015c). The values were updated following clinician validation
Radiotherapy (bone) – per fraction	0.31	100%	£128	£39.71	Nintedanib NICE submission (NICE 2015c). The values were adjusted following clinician validation
CT scan (thorax or abdominal/brain)	0.31	100%	£94	£29.22	Nintedanib NICE submission (NICE 2015c). The values were adjusted following clinician validation
X-ray	0.67	100%	£43	£28.81	Nintedanib NICE submission (NICE 2015c). The values were adjusted following clinician validation
Total cost per 4 weeks				£313.55	

Abbreviations: CT = Computerised Tomography; GP = General Practitioner; ID = In development; MTA = Multiple Technology Appraisal; NICE = National Institute for Health and Care Excellence; PD = Progressed Disease; 99Tc = Technetium-99m

*Sources of unit costs are in Table 66. All unit costs are inflated to June 2015 values

The resource use in the PD health state is shown in Table 65; the associated unit costs of each resource are shown in Table 66. The total cost per 4 weeks in the PD health state is £766.62. All disease management costs are adjusted in the model to reflect the weekly cycle length (£191.66).

Table 65: Resource use for the progressed disease health state

Resource	No. required per 4 weeks	% of patients requiring resource	Unit cost*	Cost per 4 weeks	Source
Routine GP visit (at surgery)	1.00	100%	£47	£46.71	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE 2015a)
Routine GP visit (at patient's home)	0.31	100%	£119	£37.02	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620](NICE 2015a). The values were adjusted following expert clinician validation
Palliative care (per day)	4.00	100%	£86	£345.67	Nintedanib NICE submission(NICE 2015c). The values were adjusted following expert clinician validation
Oxygen	1.33	100%	£14	£18.67	Nintedanib NICE submission (NICE 2015c). The values were adjusted following expert clinician validation clinician
Blood transfusion	0.46	100%	£156	£71.57	Nintedanib NICE submission(NICE 2015c). The values were adjusted following expert clinician validation
CT scan (thorax or abdominal/brain)	0.31	100%	£94	£29.22	Nintedanib NICE submission (NICE 2015c). The values were adjusted following expert clinician validation
Resource	No. required per 4 weeks	% of patients requiring resource	Unit cost*	Cost per 4 weeks	Source

X-ray	0.46	100%	£43	£19.78	Nintedanib NICE submission (NICE 2015c). The values were adjusted following expert clinician validation
Radiotherapy - per fraction	1.00	100%	£128	£128.11	Nintedanib NICE submission (NICE 2015c). The values were adjusted following expert clinician validation
Oncologist visit	0.46	100%	£152	£69.87	Based on expert clinical opinion
Total cost per 4 weeks				£766.62	

Abbreviations: CT = Computerised Tomography; GP = General Practitioner; ID = In development; MTA = Multiple Technology Appraisal; NICE = National Institute for Health and Care Excellence; PD = progressed disease; 99Tc = Technetium-99m

*Sources of unit costs are in Table 66. All cost were inflated to 2015 values

Table 66: Unit costs (PF and PD health states)*

Resource	Unit cost	Source
Routine GP visit (surgery)	£47	PSSRU 2014 (Curtis 2014) Section 10.8b, Per patient contact lasting 11.7 minutes (including direct care staff costs; with qualifications)
Routine GP visit (patient's home)	£119	PSSRU 2013 (Curtis 2013) Section 10.8b, Per out of surgery visit lasting 23.4 minutes (including direct care staff costs; with qualifications). Inflated to 2015 values (cost was not available in PSSRU 2014).
Palliative care (per day)	£86	NHS Reference costs 2013-2014 (Department of Health 2014) Community Health Services (code: N21AF), Specialist nursing, palliative/respite care, adult, face to face (national average unit cost)
Oxygen	£14	NHS Electronic Drug Tariff (National Health Service England and Wales 2013) Refer to "Part X - Home oxygen therapy service", section 8.11: Basic price for Oxygen BP, composite cylinder with integral headset" 2122 litres
Radiotherapy - per fraction	£128	NHS Reference costs 2013-2014 (Department of Health 2014) Deliver a fraction of complex treatment on a megavoltage machine (Outpatients) (currency code: SC23Z)
Blood transfusion	£156	NHS Reference costs 2013-2014 (Department of Health 2014) Blood and marrow transplantation (currency code: 308); non-consultant led outpatient attendance
CT scan (thorax or abdominal/brain)	£94	NHS Reference costs 2013-2014 (Department of Health 2014) Computerised Tomography Scan, one area, pre and post-contrast (currency code: RA10A)
X-ray	£43	NHS Reference costs 2013-2014 (Department of Health 2014) Diagnostic imaging (code: 812), Unit cost (weighted average of consultant-led and non-consultant led appointments)
Oncologist visit	£152	NHS Reference costs 2013-2014 (Department of Health 2014) Medical oncology code 370, Consultant-led outpatient appointment

Abbreviations: CT = Computerised Tomography; GP = General Practitioner; ID = In development; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD = Progressed Disease; PF = Progression-Free; PSSRU = Personal Social Services Research Unit; 99Tc = Technetium-99m

*All unit costs were inflated to June 2015 values

An end of life/terminal care cost is applied to patients who enter the death state as a one-off cost. The cost reflects treatment received in various care settings and is based on the erlotinib and gefitinib MTA. The end of life/terminal care cost is weighted by the percentage of patients treated in each setting. This cost is assumed to be the same for all treatments. Resource use in each care setting and the weightings applied are shown in Table 67. The overall weighted end of life cost is £3,628.70 (Table 67).

Table 67: Resource use for terminal care/end of life

Resource	Number required	Reference	% of patients in each care setting	Source

Hospitalisation admission (+ excess bed day)	1 (+ 0.84 excess bed days)	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE 2015a)	55.8%	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE 2015a)
Macmillan Nurse (home setting)	50.00	Marie Curie Cancer Care	27.3%	
Hospice care	1.00	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE 2015a)	16.9%	

Abbreviations: MTA = Multiple Technology Appraisal; TA = Technology appraisal

Table 68: Unit costs of terminal/end of life care

Resource	Unit cost	Reference	Weighted unit cost	Total cost of each care setting
Hospitalisation admission (+ excess bed day)	£4,217.12 (+ £273.54 for 0.84 excess bed days) = £4,490.66	NHS Reference Costs 2013-2014 (Department of Health 2014) Respiratory Neoplasms with CC Score 11+ (currency code: DZ17E), Non-elective inpatient stays - long stay	£2,353.15 (+ £152.64 for 0.84 excess bed days) = £2505.79	£2481.37
Macmillan Nurse (home setting)	£44.68 (assumed 2/3rd the cost of a community nurse)	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620] and PSSRU 2014 (NICE 2015a) (Curtis 2014)	£12.20	£609.84
Hospice care	£5,699.68 (25% increase on hospitalisation setting)	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE 2015a)	£573.49	£573.49
Total cost				£3,628.70

Abbreviations: ID = In development; MTA = Multiple Technology Appraisal; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; TA = Technology appraisal

*All unit costs are inflated to 2015 values

Adverse reaction unit costs and resource use

All Grade ≥3 AEs (regardless of causality) with a ≥5% incidence in the nivolumab or docetaxel arms of the CheckMate 017 trial are included in the base case analysis. The costs of treating AEs are per episode, and these costs were sourced from NHS Reference Costs guided by the currency codes used in recent NICE submissions in NSCLC (Table 69). Assumptions around the costs associated with the treatment of AEs were validated with clinical and economic experts.

The expected incidence of included AEs for each treatment arm was assumed to be captured in the CheckMate 017 trial data.

Table 69: Cost of adverse events

AEs from CheckMate 017	Cost per episode	Mean number of episodes per AE treatment course	Source
Asthenia	£3,015.13	1	NHS Reference costs 2013-2014
Dyspnoea	£0.00	1	Assumption based on Ipilimumab NICE STA submission for melanoma
Fatigue	£3,015.13	1	NHS Reference costs 2013-2014
Febrile neutropenia	£5,489.94	1	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE 2015a)
Neutropenia	£354.72	1	NHS Reference costs 2013-2014
Pneumonia	£1,822.85	1	NHS Reference costs 2013-2014

Abbreviations: AE = Adverse Event; ID = In development; MTA = Multiple Technology Appraisal; NHS = National Health Service; TA = Technology appraisal

*All costs are inflated to June 2015 values

Miscellaneous unit costs and resource use

None

5.6 Summary of base case de novo analysis inputs and assumptions

Summary of base case de novo analysis inputs

Details of all values used in the economic model are listed in Appendix 23. A summary of the key variables are presented in Table 70.

Table 70: Summary of variables applied in the economic model

Area	Variable	Value	Reference to section in submission
General Efficacy	Patient population	Patients with advanced NSCLC	Patient population in Section 5.2
	Time horizon	20 years	Section 5.2, Table 39
	Model cycle length	1 week	Section 5.2, Table 39
	Discount rate	3.5%	Section 5.2, Table 39
	Average body weight	73kg	Drug acquisition costs in Section 5.2
	Average BSA	1.82m^2	Drug acquisition costs in Section 5.2
	HR for OS	0.59	Section 4.7
Subsequent treatment	Patients moving to third line therapy following nivolumab	Platinum-doublet – [redacted]% Erlotinib – 2.63% Docetaxel -17.36% Gemcitabine – [redacted] % Vinorelbine -[redacted] % BSC – [redacted] %	Section 1.1, Table 60
	Patients moving to third line therapy following docetaxel	Platinum-doublet – [redacted] % Erlotinib – 4.69% Docetaxel - 2.93 % Gemcitabine – [redacted] % Vinorelbine -[redacted] % BSC – [redacted] %	Section 1.1, Table 60
	Average duration of subsequent treatment	[redacted] days	Subsequent therapy in Section 5.2
Costs	Cost of nivolumab per dose	£2634	Section 1.1, Table 59
	Cost of docetaxel per dose	£900.00	Section 1.1, Table 59
	Administration cost per dose (nivolumab)	£269.94	Section 1.1, Table 62
	Administration cost per dose (docetaxel)	£167.34	Section 1.1, Table 62

	Monitoring cost per 4 weeks	£151.89	Section 1.1, Table 63
	PFS cost per 4 weeks	£313.55	Section 1.1, Table 64
	PD cost per 4 weeks	£766.62	Section 1.1, Table 65
	EOL cost	£3,628.70	Section 1.1, Table 68
AEs	Frequency of AE with nivolumab	Asthenia – [redacted]% Fatigue – [redacted]% Dyspnoea - [redacted]% Pneumonia – [redacted]% Neutropenia – [redacted]% Febrile neutropenia – [redacted]%	Section 5.3, Table 51
	Frequency of AE with docetaxel	Asthenia – [redacted] % Fatigue – [redacted]% Dyspnoea - [redacted]% Pneumonia – [redacted]% Neutropenia – [redacted]% Febrile neutropenia – [redacted]%	
	Cost of asthenia	£3,015.13	Section 1.1, Table 69
	Cost of fatigue	£3,015.13	
	Cost of dyspnoea	£0	
	Cost of pneumonia	£1,822.85	
	Cost of neutropenia	£354.72	
	Cost of febrile neutropenia	£5,489.94	
Utility	PFS	0.750	Section 5.4, Table 54
	PD	0.592	
Disutility of AEs	Asthenia	-0.073	Section 1.1, Table 55
	Fatigue	-0.073	
	Dyspnoea	-0.050	
	Neutropenia	-0.089	
	Febrile neutropenia	-0.090	
	Pneumonia	-0.008	

Abbreviations: AE = Adverse Event; BSA = Body Surface Area; BSC = Best Supportive Care; CI = Confidence Interval; EOL = End of Life; NSCLC = Non-Small Cell Lung Cancer; OS = Overall Survival; PD = Progressed Disease; PFS = Progression-Free Survival

Assumptions

A list of the main parameters and assumptions used in the economic analysis is provided in Table 71.

Table 71: Key parameters in base case model

Parameter	Base case assumption	Justification
Comparator	Docetaxel	Based on UK clinical practice and consistent with CheckMate 017 trial data. Comparison with erlotinib presented as a sensitivity analysis
Time horizon	20 years	Lifetime equivalent consistent with NICE reference case
Survival: OS	Base case: log-logistic Sensitivity analysis: spline 2-knots hazards	Choice of extrapolation technique was based on statistical goodness-of-fit, clinical plausibility and validation with multiple trial data and RWE (NLCA and SEER)
Survival: PFS	Base case: spline 2 knots hazards Sensitivity analysis: nivolumab (spline 1 knot hazards) and docetaxel (log normal)	Choice of extrapolation technique was based on statistical goodness-of-fit, clinical plausibility and in-trial validation
End of life cost	Based on previous NICE TAs	Applied as a one-off costs for all patients who die to take into consideration the added expense of terminal care
HRQoL	Based on EQ-5D data collected in CheckMate 017. Utility values are allocated by health state and not differentiated by treatment arm	Consistent with NICE recommendations
Safety	Grade 3 or higher severity adverse events experienced by ≥5% of patients in CheckMate 017 are included in the analysis	Conservative approach given safety profile of nivolumab
Subsequent treatment	Treatment type is based on CheckMate 017 and duration of therapy is based on RWE reported in CA209-116 observational study	Applied as a one-off cost for all patients moving out of the progression-free health state to take into account any treatment costs following second-line therapy

Abbreviations: HRQoL = Health-Related Quality of Life; NICE = National Institute of Health and Care Excellence; NLCA = National Lung Cancer Audit; OS = Overall Survival; PFS = Progression-Free Survival; SEER = Surveillance; Epidemiology and End Results; RWE = Real World Evidence; TA = Technology Appraisal

5.7 Base case results

Base case incremental cost-effectiveness analysis results

Total costs, LYG, QALYs, and incremental cost per QALY for nivolumab versus docetaxel are shown in Table 72. The base case analysis is based on the log-logistic curve for OS and the spline 2-knots function for PFS. Life years are undiscounted. In the base case, nivolumab generates 0.76 incremental QALYs and 1.31 incremental life years compared with docetaxel and the nivolumab-treated cohort has higher total lifetime costs. The ICER is £85,950 per QALY gained.

Table 72: Base case results

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	86,599	2.26	1.30	65,355	1.31	0.76	85,950
Docetaxel	21,243	0.95	0.54				

Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; LYG = Life-Years Gained; QALYs = Quality-Adjusted Life Years

Clinical outcomes from the model

Table 73: Model predictions of median PFS and OS compared with CheckMate 017

Outcome	Nivolumab		Docetaxel	
	Checkmate 017	**Economic model**	**Checkmate 017**	**Economic model**
PFS, months (95% CI)	3.5 (2.1, 4.9)	3.7	2.8 (2.1, 3.5)	3.0
OS, months (95% CI)	9.2 (7.3, 13.3)	9.9	6.0 (5.1, 7.3)	6.2

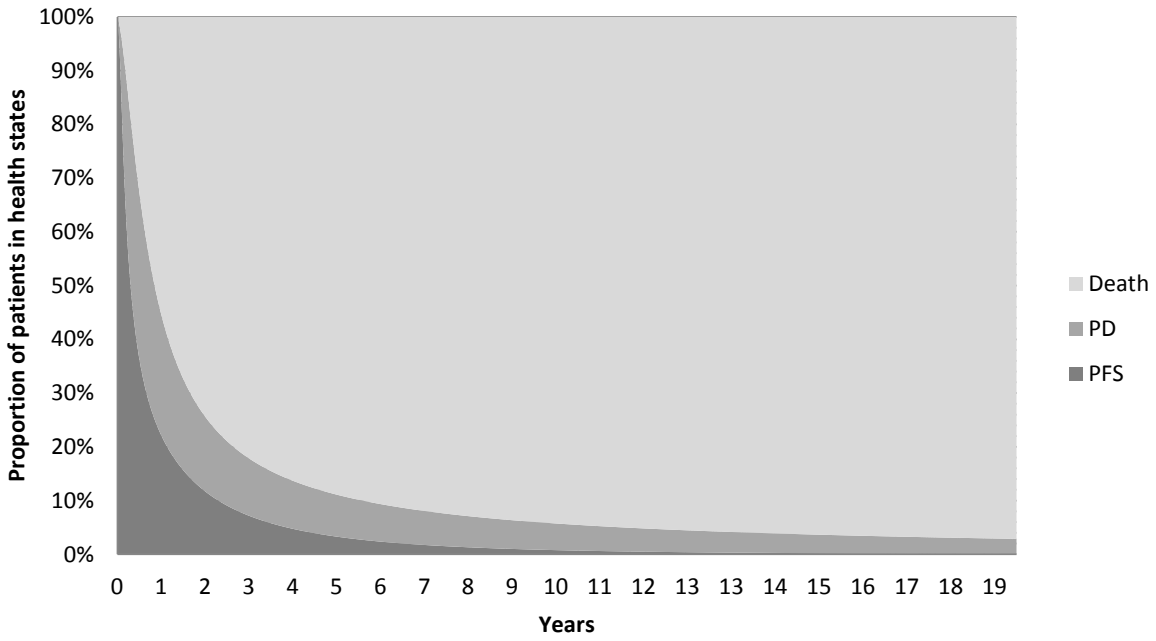
Abbreviations: CI = Confidence Interval; OS = Overall Survival; PFS = Progression-Free Survival

A comparison of PFS and OS observed in the CheckMate 017 trial and model extrapolation is shown in Table 73. The difference in median PFS is 0.2 months for both nivolumab and docetaxel. The difference in median OS is 0.7 months for nivolumab and 0.2 months for docetaxel. The economic model overestimates median PFS and OS compared with the trial, but this is not unexpected given the longer time horizon of the model. The median PFS and OS estimates from the model are within the 95% confidence intervals from CheckMate 017. No adjustment was made for crossover because no patients in the docetaxel arm had received nivolumab prior to the database lock.

The difference in median OS between nivolumab and docetaxel is 3.7 months based on the model (60%) and 3.2 months based on trial data (53%). The difference in median PFS is 0.7 months in the trial (25%) and also 0.7 months as predicted in the model (23%). These numbers suggest consistency across model and trial predicted values.

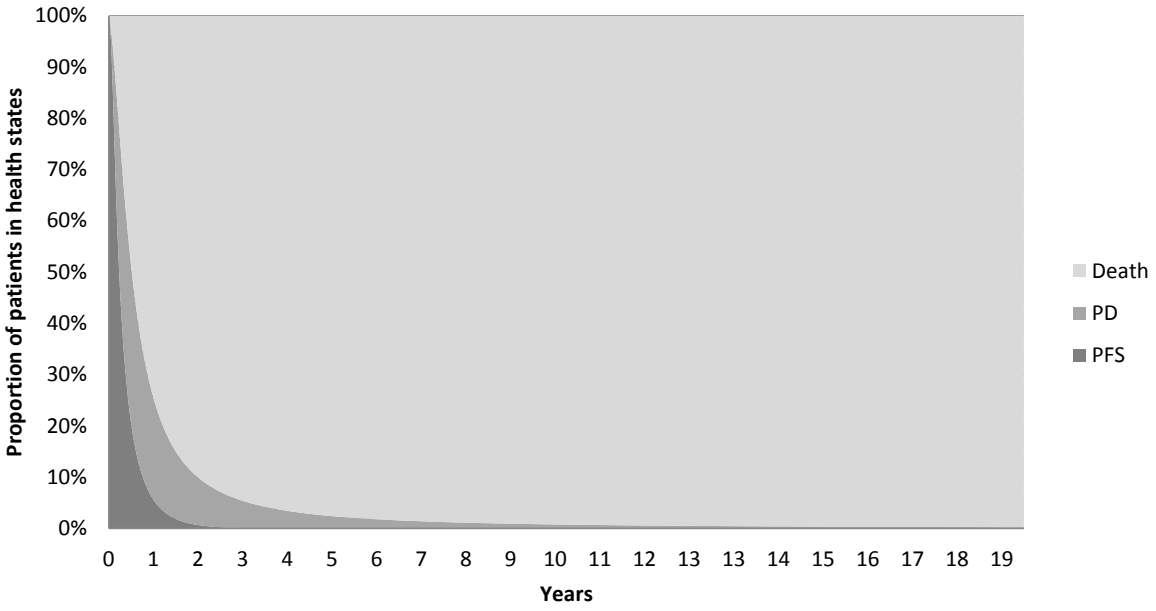
The distribution of patients between health states is shown for nivolumab and docetaxel in Figure 26 and Figure 27, respectively. These cohort traces are for the second-line indication using base case assumptions.

Figure 26: Cohort trace for nivolumab up to 20 years (base case analysis)



Abbreviations: PD = Progressed Disease; PFS = Progression-Free Survival

Figure 27: Cohort trace for docetaxel up to 20 years (base case analysis)



Abbreviations: PD = Progressed Disease; PFS = Progression-Free Survival

In the base case, 2.8% of patients in the nivolumab arm and 0.2% of patients in the docetaxel arm are alive at 20 years, and this suggests that the time horizon of the model is long enough to capture all of the significant differences in costs and utility between the two

treatments. Given that the age at study entry of patients in CheckMate 017 ranged between 39 years and 85 years of age, it is clinically plausible to expect that a small proportion of this cohort would be alive at 20 years of follow-up (the younger patients primarily). In addition, SEER data reports demonstrate that there is a trend for patients with advanced NSCLC who live to longer milestones from point of diagnosis to have increased 5-year conditional survival (Bristol-Myers Squibb 2010). Specifically, based on SEER data, the probability of surviving up to 12 years from point of diagnosis is 0.73%, however, a patient who survives up to this 12-year milestone then has a high 5-year survival probability of 56% - that is, the longer a patient lives, the longer they will continue to live, validating that this plateau effect in survival is seen in patients with advanced NSCLC in the real world.

Disaggregated results of the base case incremental cost-effectiveness analysis

Provide details of the disaggregated QALYs and costs by health state, and of resource use predicted by the model in the base case incremental cost effectiveness analysis by category of cost.

Expected QALYs for nivolumab and docetaxel disaggregated by health state are shown in Table 74. The main source of the benefits from nivolumab comes from extending the time in PF and PD health states, rather than from a reduction in the disutility of AEs, which is consistent with results from the CheckMate 017 study. In the CheckMate 017 study, the AE profile of nivolumab was considerably better than docetaxel (Section 4). This benefit is not fully captured in the economic model because of the limitation to include only Grade ≥3 AEs occurring in ≥5% of the trial population. Nivolumab provides patients with an absolute QALY gain of 48.9% and 45.1% compared to docetaxel in the PF and PD states, respectively. The QALY gain in the PD state is reasonable given that the treatment effect on OS is assumed to be applied over the full time horizon.

Expected costs disaggregated by health state and by type of cost are shown in Table 75. The higher expected costs of nivolumab are primarily driven by the costs of drug acquisition and by the longer period of treatment (i.e. disease management) because of the better survival outcomes associated with nivolumab. Figure 26 and Figure 27 illustrate the longer health state occupancy in patients treated with nivolumab.

Table 74: Summary of QALY gain per patient by health state

Health state	QALY intervention (nivolumab)	QALY comparator (docetaxel)	Incremental QALYs	% absolute incremental QALYs
PF	0.63	0.26	0.37	48.9%
PD	0.68	0.33	0.34	45.1%
AE disutility	-0.01	-0.05	0.05	6.1%
Total	1.30	0.54	0.76	100%

Abbreviations: AE = Adverse Event; PF = Progression-Free; PD = Progressed Disease; QALY = Quality-Adjusted Life Year

*No utility is assigned to the death state

Table 75: Summary of costs

Health state	Cost intervention (nivolumab)	Cost comparator (docetaxel)	Incremental costs	% absolute incremental costs
Disease management cost: PF	£3,425	£1,406	£2,019	3.1%
Disease management cost: PD*	£14,757	£9,164	£5,593	8.6%
Drug acquisition cost	£59,454	£6,636	£52,818	80.8%
Administration cost	£6,398	£1,486	£4,912	7.5%
Monitoring cost	£2,336	£1,248	£1,089	1.7%
AEs	£228	£1,304	-£1,076	-1.6%
Total treatment cost	£86,599	£21,243	£65,355	100%

Abbreviations: AE = Adverse Event; HS1 = Health State 1; HS2 = Health State 2; PF = Progression-Free; PD = Progressed Disease

*Progressed disease includes the costs of managing patients who have progressed and end of life / terminal care. No costs are assigned to the death state.

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

A second-order Monte Carlo simulation was run for 1000 iterations. The parameters included in the probabilistic sensitivity analysis (PSA) are shown in Table 76 to Table 90.

General inputs

Average body weight and BSA were included in the PSA assuming a normal distribution (Table 76). These parameters are used to calculate treatment dosage and drug acquisition costs.

Table 76: Average body weight and body surface area

Parameter	Mean deterministic	Distribution	Alpha	Beta
Average body weight	73kg	Gamma	100	0.73
BSA	1.82m^2	Gamma	100	0.0182

Abbreviations: BSA = Body Surface Area

Overall survival parameters

In the base case analysis, a log-logistic distribution was fitted to the docetaxel arm of CheckMate 017 and a treatment effect (hazard ratio) was applied to derive the survival curve for nivolumab. In the probabilistic analysis, uncertainty in OS is represented through the parameters of the survival function. For the OS survival function, a multivariate normal distribution with correlation between shape and scale parameters was applied (Table 77). For the relative treatment effects (hazard ratios), a lognormal distribution was applied. Lognormal distributions are considered appropriate given the clustering at the mean and the small yet non-zero likelihood of high relative risk measures (Table 78).

Table 77: Independent curve parameters (log-logistic fit to docetaxel) included in PSA

Parameter	Mean deterministic	Cholesky decomposition	
		OS alpha (shape) – docetaxel	OS beta (scale) – docetaxel
OS alpha (shape) – docetaxel	1.64	0.079	0
OS beta (scale) – docetaxel	6.04	-0.001	0.091

Abbreviations: OS = Overall Survival; PSA = Probabilistic Sensitivity Analysis

Table 78: Relative treatment effect (hazard ratio) for OS included in PSA

Parameter (vs. Docetaxel)	Mean deterministic	Distribution	Alpha	Beta
Nivolumab HR on OS	0.59	Log-normal	-0.52756051	0.099751345

Abbreviations: BSC = Best Supportive Care; HR = Hazard Ratio; OS = Overall Survival; PSA = Probabilistic Sensitivity Analysis

To explore uncertainty in the choice of survival function, a scenario analysis was separately undertaken where OS was modelled via a spline 2 knots hazards distribution (extrapolation details are given in Section 5.2). The probabilistic sensitivity analysis included survival parameters for this extrapolation technique, and these are presented in Table 79.

The deterministic mean and Cholesky decomposition parameters applicable to the spline-2 hazards function used to model the docetaxel arm for OS are outlined in Table 78.

Table 79: Dependent curves parameters (2-knot spline hazards) included in PSA

Parameter	Mean deterministic	Cholesky decomposition				
		Spline parameters – gamma 0	Spline parameters – gamma 1	Spline parameters – gamma 2	Spline parameters – gamma 3	Treatment coefficient
Spline parameters – gamma 0	-2.85	0.231	0	0	0	0
Spline parameters – gamma 1	1.39	-0.139	0.257	0	0	0
Spline parameters – gamma 2	-0.25	0.020	0.121	0.070	0	0
Spline parameters – gamma 3	0.43	-0.044	-0.142	-0.109	0.007	0
Treatment coefficient	-	-0.033	-0.018	0.038	0.079	0.108

Abbreviations: PSA = Probabilistic Sensitivity Analysis

Progression-free survival parameters

In the base case analysis, a dependent 2-knot spline hazard distribution was applied to both the docetaxel and nivolumab arms of CheckMate 017, adjusted for treatment effect at gamma 1. Uncertainty in PFS is represented through the parameters of the survival function. For the PSA, a multivariate normal distribution with correlation between shape and scale parameters was used as shown in Table 80.

Table 80: Dependent parametric curves (2-knot spline hazards; nivolumab and docetaxel) included in PSA

Parameter	Mean deterministic	Cholesky decomposition					
		Spline parameters – gamma 0	Spline parameters – gamma 1	Spline parameters – gamma 2	Spline parameters – gamma 3	Treatment coefficient	Gamma 1 nivolumab
Spline parameters – gamma 0	-1.91	0.191	0	0	0	0	0
Spline parameters – gamma 1	2.63 (docetaxel)/ 2.34 (nivolumab)	-0.023	0.402	0	0	0	0
Spline parameters – gamma 2	0.19	0.041	0.127	0.052	0	0	0
Spline parameters – gamma 3	-0.07	-0.047	-0.114	-0.067	0.006	0	0
Treatment coefficient	0.07	-0.143	0.035	0.091	-0.022	0.172	0
Gamma 1 nivolumab	-	0.056	-0.021	-0.035	0.055	-0.057	0.040

Abbreviations: PSA = Probabilistic Sensitivity Analysis

Scenario analysis of the PFS survival functions included using independent survival curves for the nivolumab and docetaxel arms. For docetaxel, the alternative survival curve was a lognormal distribution; the probabilistic parameters for this distribution are shown in Table 81. The alternative curve for the nivolumab arm is a 1-knot spline hazards distribution; the probabilistic parameters for this distribution are shown in Table 82.

Table 81: Independent parametric curves (log-normal for docetaxel) included in PSA

Parameter	Mean deterministic	Cholesky decomposition	
		Mu	Sigma
Mu	1.04	0.077	0
Sigma	0.87	0.002	0.065

Abbreviations: PSA = Probabilistic Sensitivity Analysis

Table 82: Independent parametric curves (1-knot spline hazards for nivolumab) included in PSA

Parameter	Mean deterministic	Cholesky decomposition		
		Gamma 0	Gamma 1	Gamma 3
Gamma 0	-1.90	0.193	0	0
Gamma 1	2.13	-0.185	0.243	0
Gamma 2	0.12	-0.012	0.024	0.004

Abbreviations: PSA = Probabilistic Sensitivity Analysis

Adverse event disutility

AE disutilities are included in the PSA and the parameters are shown in Table 83. A gamma distribution was used for disutilities because the values lie between minus infinity and zero.

Table 83: Adverse events disutilities included in PSA

Adverse event	Mean deterministic disutility (per event)	Distribution	Alpha	Beta
Asthenia	-0.073	Gamma	100	0.0007346
Dyspnoea	-0.050	Gamma	100	0.0005
Fatigue	-0.073	Gamma	100	0.0007346
Febrile neutropenia	-0.090	Gamma	100	0.0009002
Neutropenia	-0.090	Gamma	100	0.0008973
Pneumonia	-0.008	Gamma	100	0.00008

Abbreviations: AE = Adverse Event; PSA = Probabilistic Sensitivity Analysis

Adverse event incidence

The incidence of AEs (all-cause) is varied in the PSA for nivolumab and the comparators. A beta distribution is applied to the incidence data, because incidence lies in the range 0 to 1 (0% to 100%). The parameters used in the PSA are shown in Table 84 and Table 85.

Table 84: Incidence of AEs included in PSA - nivolumab

AE	Mean deterministic incidence	Distribution	Alpha	Beta
Asthenia	[redacted]	Beta	0	0
Dyspnoea	[redacted]	Beta	94.603	1675.826
Fatigue	[redacted]	Beta	97.687	4167.980
Febrile neutropenia	[redacted]	Beta	0	0
Neutropenia	[redacted]	Beta	99.229	12899.771
Pneumonia	[redacted]	Beta	93.061	1261.494

Abbreviations: AE = Adverse Event; PSA = Probabilistic Sensitivity Analysis

Table 85: Incidence of AEs included in PSA - docetaxel

AE	Mean deterministic incidence	Distribution	Alpha	Beta
Asthenia	[redacted]	Beta	92.953	1239.380
Dyspnoea	[redacted]	Beta	93.736	1417.764
Fatigue	[redacted]	Beta	91.388	980.340
Febrile neutropenia	[redacted]	Beta	89.822	801.486
Neutropenia	[redacted]	Beta	70.248	168.226
Pneumonia	[redacted]	Beta	93.736	1417.764

Abbreviations: AE = Adverse Event; PSA = Probabilistic Sensitivity Analysis

Costs and resource use

A gamma distribution is applied to all costs and resource use in the PSA, except for the end of life care resource use. The gamma distribution was chosen as it is a continuous probability distribution with positive shape (α) and scale (β) parameters. Gamma distributions are also bound by zero, therefore no negative values were included in the PSA. For the end of life care resource use, the beta distribution is applied as this type of resource use is restricted between zero and one. The parameters for the disease management, administration, monitoring, and adverse event costs are presented in Table 86 to Table 90.

Table 86: PF health state resource use and treatment costs included in PSA

Parameter	Mean deterministic	Distribution	Alpha	Beta
Resource use				
Routine GP visit (surgery)	0.92	Gamma	1.00E+02	9.20E-03
Routine GP visit (patient's home)	0	Gamma	0	0
Palliative care (per day)	2	Gamma	1.00E+02	2.00E-02
Oxygen	0	Gamma	0	0
Radiotherapy (bone) - per fraction	0.31	Gamma	1.00E+02	3.10E-03
Blood transfusion	0	Gamma	0	0
CT scan (thorax or abdominal / brain)	0.31	Gamma	1.00E+02	3.10E-03
X-ray	0.67	Gamma	1.00E+02	6.70E-03
Unit costs (£)				
Routine GP visit (surgery)	£46.71	Gamma	1.00E+02	4.67E-01
Routine GP visit (patient's home)	£119.43	Gamma	1.00E+02	1.19E+00
Palliative care (per day)	£86.42	Gamma	1.00E+02	8.64E-01
Oxygen	£14.04	Gamma	1.00E+02	1.40E-01
Radiotherapy (bone) - per fraction	£128.11	Gamma	1.00E+02	1.28E+00
Blood transfusion	£155.58	Gamma	1.00E+02	1.56E+00
CT scan (thorax or abdominal / brain)	£94.26	Gamma	1.00E+02	9.43E-01
X-ray	£43.01	Gamma	1.00E+02	4.30E-01

Abbreviations: CT = Computerised Tomography; GP = General Practitioner; PF = Progression-free; PSA = Probabilistic Sensitivity Analysis

Table 87: PD health state resource use and treatment costs included in PSA

Parameter	Mean deterministic	Distribution	Alpha	Beta
Resource use				
Routine GP visit (surgery)	1.00	Gamma	1.00E+02	1.00E-02
Routine GP visit (patient's home)	0.31	Gamma	1.00E+02	3.10E-03
Palliative care (per day)	4.00	Gamma	1.00E+02	4.00E-02
Radiotherapy (PD only) - per fraction	1.00	Gamma	1.00E+02	1.00E-02
Blood transfusion	0.46	Gamma	1.00E+02	4.60E-03
CT scan (thorax or abdominal / brain)	0.31	Gamma	1.00E+02	3.10E-03
X-ray	0.46	Gamma	1.00E+02	4.60E-03
Oxygen	1.33	Gamma	1.00E+02	1.33E-02
Oncologist visit	0.46	Gamma	1.00E+02	4.60E-03
Unit costs (£)				
Routine GP visit (surgery)	£46.71	Gamma	1.00E+02	4.67E-01
Routine GP visit (patient's home)	£119.43	Gamma	1.00E+02	1.19E+00
Palliative care (per day)	£86.42	Gamma	1.00E+02	8.64E-01
Radiotherapy (PD only) - per fraction	£128.11	Gamma	1.00E+02	1.28E+00
Blood transfusion	£155.58	Gamma	1.00E+02	1.56E+00
CT scan (thorax or abdominal / brain)	£94.26	Gamma	1.00E+02	9.43E-01
X-ray	£43.01	Gamma	1.00E+02	4.30E-01
Oxygen	£14.04	Gamma	1.00E+02	1.40E-01
Oncologist visit	£151.89	Gamma	1.00E+02	1.52E+00

Abbreviations: CT = Computerised Tomography; GP = General Practitioner; PD = Progressed Disease; PSA = Probabilistic Sensitivity Analysis

Table 88: End of life/terminal care resource use and treatment costs included in PSA

Parameter	Mean deterministic cost (£)	Distribution	Alpha	Beta
Resource use				
End of life costs (Hospitalisation)	1	Beta	-1.00E+00	0.00E+00
End of life costs (Hospitalisation - excess bed days)	0.84	Beta	1.52E+01	2.89E+00
Macmillan Nurse (home setting)	50	Beta	-4.95E+03	4.85E+03
Hospice care	1	Beta	-1.00E+00	0.00E+00
Costs				
End of life costs (Hospitalisation)	£2353.15	Gamma	1.00E+02	2.35E+01
End of life costs (Hospitalisation - excess bed days)	£152.64	Gamma	1.00E+02	1.53E+00
Macmillan Nurse (home setting)	£12.20	Gamma	1.00E+02	1.22E-01
Hospice care	£537.49	Gamma	1.00E+02	5.37E+00

Abbreviations: BSC = Best supportive care; CT = Computerised Tomography; GP = General Practitioner; PD = Progressed Disease; PSA = Probabilistic Sensitivity Analysis

Table 89: Administration and monitoring resource use and costs included in PSA

Parameter	Mean deterministic value	Distribution	Alpha	Beta
Administration resource use				
Nivolumab	1	Gamma	1.00E+02	1.00E-02
Docetaxel	1	Gamma	1.00E+02	1.00E-02
Erlotinib	0	Gamma	0	0
BSC	0	Gamma	0	0
Cisplatin	1	Gamma	1.00E+02	1.00E-02
Carboplatin	1	Gamma	1.00E+02	1.00E-02
Gemcitabine	1	Gamma	1.00E+02	1.00E-02
Vinorelbine	1	Gamma	1.00E+02	1.00E-02
Administration costs				
Nivolumab	£269.94	Gamma	1.00E+02	2.70E+00
Docetaxel	£167.34	Gamma	1.00E+02	1.67E+00
Erlotinib	0	Gamma	0	0
BSC	0	Gamma	0	0
Cisplatin	£167.34	Gamma	1.00E+02	1.67E+00
Carboplatin	£167.34	Gamma	1.00E+02	1.67E+00
Gemcitabine	£167.34	Gamma	1.00E+02	1.67E+00
Vinorelbine	£167.34	Gamma	1.00E+02	1.67E+00
Monitoring resource use				
Nivolumab	1	Gamma	1.00E+02	1.00E-02
Docetaxel	1	Gamma	1.00E+02	1.00E-02
Erlotinib	1	Gamma	1.00E+02	1.00E-02
BSC	1	Gamma	1.00E+02	1.00E-02
Cisplatin	1	Gamma	1.00E+02	1.00E-02
Carboplatin	1	Gamma	1.00E+02	1.00E-02
Gemcitabine	1	Gamma	1.00E+02	1.00E-02
Vinorelbine	1	Gamma	1.00E+02	1.00E-02
Monitoring costs				
Nivolumab	£151.89	Gamma	1.00E+02	1.52E+00
Docetaxel	£151.89	Gamma	1.00E+02	1.52E+00
Erlotinib	£151.89	Gamma	1.00E+02	1.52E+00
BSC	0	Gamma	0.00E+00	0.00E+00
Cisplatin	£151.89	Gamma	1.00E+02	1.52E+00
Carboplatin	£151.89	Gamma	1.00E+02	1.52E+00

Gemcitabine	£151.89	Gamma	1.00E+02	1.52E+00
Vinorelbine	£151.89	Gamma	1.00E+02	1.52E+00

Abbreviations: BSC = Best supportive care; PSA = Probabilistic Sensitivity Analysis

Table 90: AE costs included in PSA

AE	Mean deterministic cost	Distribution	Alpha	Beta
Fatigue	£3015	Gamma	1.00E+02	3.02E+01
Asthenia	£3015	Gamma	1.00E+02	3.02E+01
Dyspnoea	£0	Gamma	0	0
Pneumonia	£1823	Gamma	1.00E+02	1.82E+01
Neutropenia	£355	Gamma	1.00E+02	3.55E+00
Febrile neutropenia	£5490	Gamma	1.00E+02	5.49E+01

Abbreviations: AE = Adverse Event; PSA = Probabilistic Sensitivity Analysis

Results of the probabilistic sensitivity analysis on the base case model

Results of the PSA are shown in Table 91, which also shows results from the deterministic analysis for comparison. The probabilistic ICER is £89,343 per QALY gained compared with £85,950 per QALY gained in the deterministic analysis. The uncertainty in the ICER appears to be driven by the variation on treatment efficacy (HR on OS of nivolumab), resource utilisation, body weight and utility weights, given the high impact they have overall on the results of the model.

The cost-effectiveness scatterplot and cost-effectiveness acceptability curve are shown in Figure 28 and

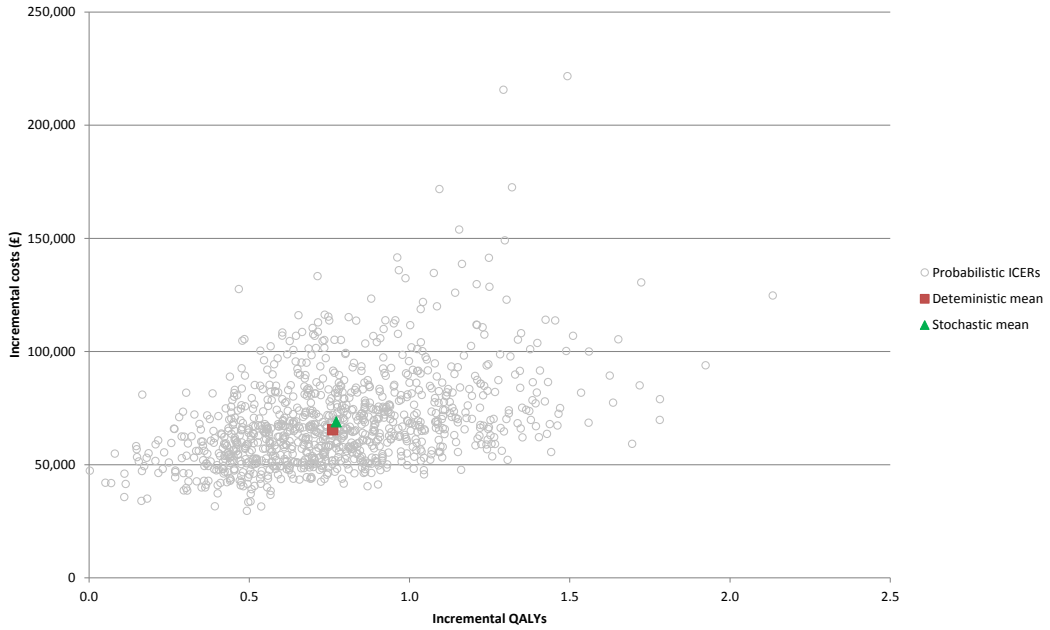
Figure 29, respectively. -

Table 91: PSA results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Nivolumab	91,677	1.35	68,938	0.77	89,343
Docetaxel	22,739	0.58			
Deterministic values			65,355	0.76	85,950

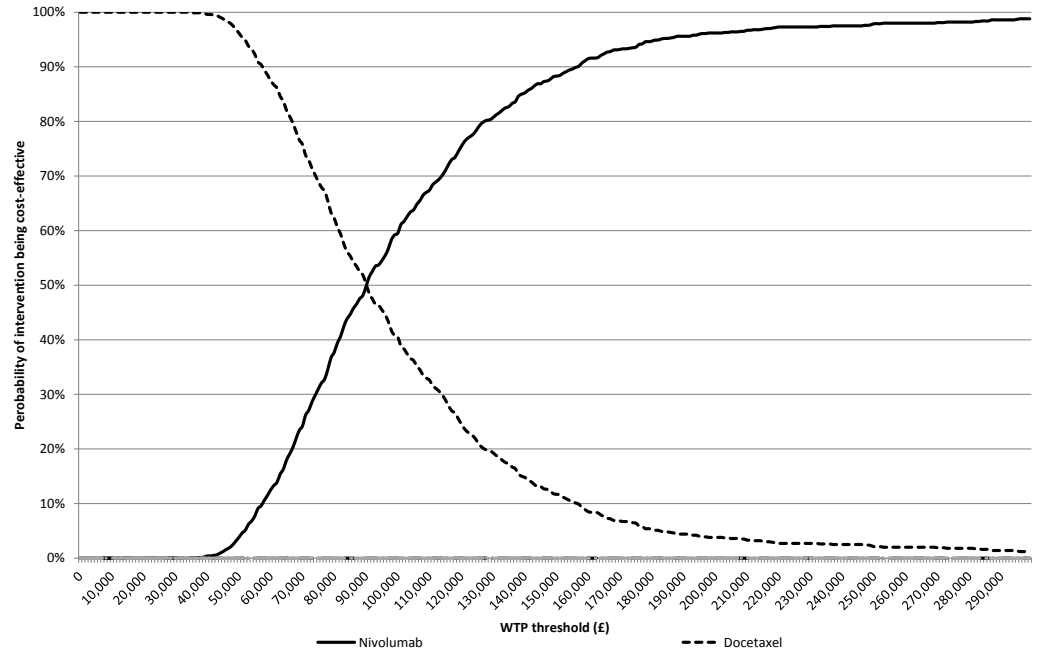
Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; PSA = Probabilistic Sensitivity Analysis; QALY = Quality-Adjusted Life Year

Figure 28: Scatter plot for cost-effectiveness of nivolumab vs docetaxel (1000 iterations)



Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; PSA = Probabilistic Sensitivity Analysis; QALY = Quality-Adjusted Life Year

Figure 29: Cost-effectiveness acceptability curve of nivolumab vs. docetaxel



Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; PSA = Probabilistic Sensitivity Analysis; QALY = Quality-Adjusted Life Year

Deterministic sensitivity analysis

A one-way sensitivity analysis was undertaken by varying cost, utility and OS base case parameter values by their confidence intervals or +/-20%, based on data availability (Table 92). The results of the analysis and a Tornado diagram are shown in Table 93 and Figure 30, respectively.

The Tornado diagram shows that the ICER was most sensitive to the hazard ratio applied to model overall survival with nivolumab. Additionally, the results were sensitive to average body weight, and the utility weights associated with the PF and PD health states. All other variables, including AE management, end of life care, and monitoring costs had minimal impact on the ICER.

Table 92: Deterministic sensitivity analysis parameters

Parameter	Mean deterministic	Lower value	Upper value
General			
Discount rate – costs	3.5%	0%	6.0%
Discount rate - outcomes	3.5%	0%	6.0%
Average body weight, kg	73	58.40	87.60
Body surface area, m^2	1.8	1.46	2.18
Costs			
Cost - PF state	£313.55	£250.84	£376.26
Cost - PD state	£766.62	£613.30	£919.94
Terminal cost	£3,628.70	£2,902.96	£4,354.44
Admin cost - nivolumab	£269.94	£215.95	£323.93
Admin cost - docetaxel	£167.34	£133.87	£200.81
Monitoring cost - nivolumab	£151.89	£121.52	£182.27
Monitoring cost – docetaxel	£151.89	£121.52	£182.27
Outcomes			
Utility weight, PFS	0.750	0.734	0.765
Utility weight, PD	0.592	0.550	0.634
Survival (upper/lower CIs)			
HR on OS - nivolumab	0.59	0.440	0.790

Abbreviations: CI = Confidence Interval; HR = Hazard Ratio; OS = Overall Survival; PD = Progressed Disease; PFS = Progression-Free Survival

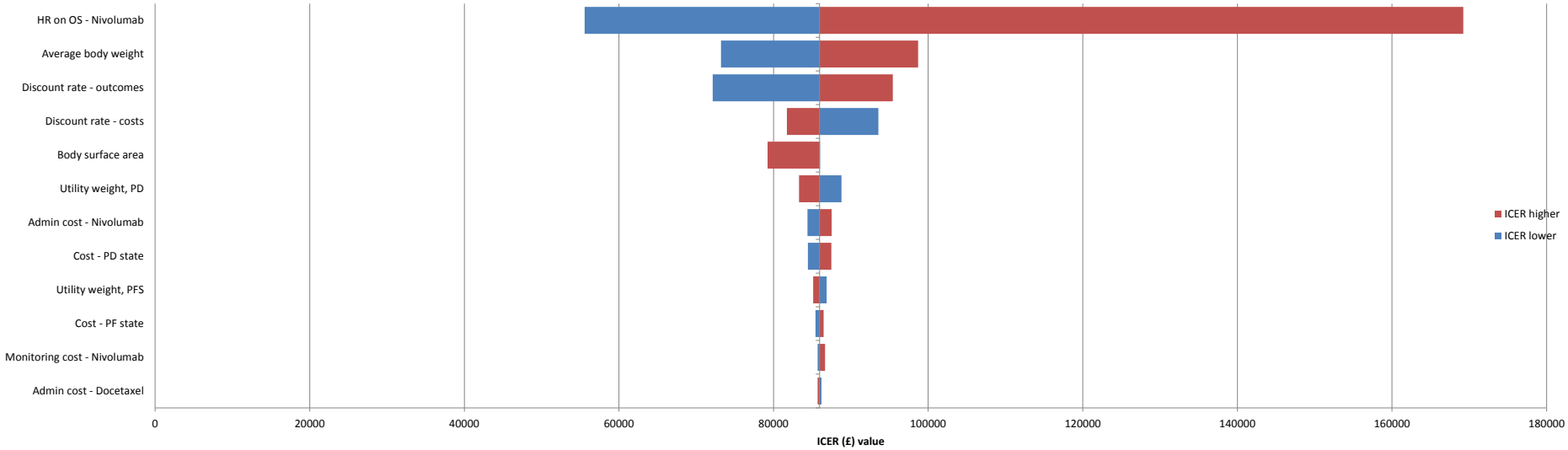
Table 93: Results of deterministic analysis vs docetaxel

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		**65,355**	**0.7604**	**85,950**
Discount rate - costs	Lower	71,139	0.7604	93,556
	Higher	62,141	0.7604	81,723
Discount rate - outcomes	Lower	65,355	0.9061	72,130
	Higher	65,355	0.6849	95,428
Average body weight	Lower	55,658	0.7604	73,197
	Higher	75,053	0.7604	98,704
BSA	Lower	65,400	0.7604	86,008
	Higher	60,248	0.7604	79,233
Costs				
Cost - PF state	Lower	64,952	0.7604	85,419
	Higher	65,759	0.7604	86,481
Cost - PD state	Lower	64,201	0.7604	84,433
	Higher	66,510	0.7604	87,468
Terminal cost	Lower	65,391	0.7604	85,997
	Higher	65,320	0.7604	85,904
Administration cost – nivolumab	Lower	64,163	0.7604	84,382
	Higher	66,548	0.7604	87,519
Administration cost – docetaxel	Lower	65,544	0.7604	86,199
	Higher	65,167	0.7604	85,702
Monitoring cost – nivolumab	Lower	65,159	0.7604	85,691
	Higher	65,890	0.7604	86,653
Monitoring cost - docetaxel	Lower	65,438	0.7604	86,059
	Higher	65,273	0.7604	85,842

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Outcomes				
Utility weight, PFS	Lower	65,355	0.7525	86,855
	Higher	65,355	0.7678	85,119
Utility weight, PD	Lower	65,355	0.7361	88,790
	Higher	65,355	0.7847	83,287
Survival				
HR on OS - nivolumab	Lower	75,118	1.3522	55,554
	Higher	58,495	0.3457	169,225

Abbreviations: BSA = Body Surface Area; CI = Confidence Interval; HR = Hazard Ratio; OS = Overall Survival; PD = Progressed Disease; PF = Progression-Free; PFS = Progression-Free Survival; QALY = Quality-Adjusted Life Year

Figure 30: Tornado diagram for nivolumab vs. docetaxel



Abbreviations: HR = Hazard Ratio; ICER = Incremental Cost-Effectiveness Ratio; OS = Overall Survival; PD = Progressed Disease; PF = Progression-Free; PFS = Progression-Free Survival

Scenario analysis

Summary of sensitivity analyses results

Survival analysis

Scenario analyses were undertaken on the survival modelling approaches applied for OS and PFS. Details of these scenarios are explained in more detail in Section 5.2.

Results are presented in Table 96 for the scenario where OS was modelled using a 2-knot spline-based approach for the docetaxel arm and applying a HR based on CheckMate 017 to derive the nivolumab survival curve. The increased ICER of £108,096 per QALY predicted from this approach is likely to be attributable to lower incremental QALYs accrued with nivolumab in this model compared with the base case OS model. However, as explained in Section 5.2, the spline-2 knots distribution was not considered clinically plausible based on validation against RWD. Scenario analysis was also considered for modelling PFS as described in Section 5.2. Because the proportional hazards assumption was not supported for PFS, the alternative PFS distributions considered were a log-normal curve for docetaxel and a spline 1 knot curve for nivolumab based on goodness-of-fit statistics (i.e. independent curves). Results of this analysis generate an ICER of £87,925 per QALY, which is comparable to the base case ICER (Table 99). This suggests that varying the survival distributions for PFS does not have a notable impact on the ICER.

Scenario 1: 2-knot spline distribution for OS

Table 94: Scenario 1 - Summary of QALY gain by health state

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.63	0.26	0.37	0.37	64.4%
PD	0.45	0.29	0.16	0.16	27.6%
AE disutility	-0.01	-0.05	0.05	0.05	8.0%
Total	1.07	0.49	0.58	0.58	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life Year

*No utility is assigned to the death state

Table 95: Scenario 1 - Summary of costs

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	3,425	1,406	2,019	2,019	3.2%
PD*	11,013	8,426	2,586	2,586	4.1%
Drug acquisition cost	59,453	6,636	52,817	52,817	84.7%
Administration cost	6,398	1,486	4,912	4,912	7.9%
Monitoring cost	2,336	1,248	1,088	1,088	1.7%
AEs	228	1,304	-1,076	-1,076	-1.7%
Total treatment cost	82,852	20,505	62,347	62,347	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free
*Progressed disease includes the costs of managing patients who have progressed and end of life/terminal care. No costs are assigned to the death state.

Table 96: Scenario 1 - Cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	82,852	1.07	62,347	0.58	108,096
Docetaxel	20,505	0.49			

Abbreviations: QALY = Quality-Adjusted Life Year

Scenario 2: Applying independent survival curves for PFS

Table 97: Scenario 2 - Summary of QALY gain by health state

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.65	0.26	0.39	0.39	51.0%
PD	0.66	0.33	0.33	0.33	42.9%
AE disutility	-0.01	-0.05	0.05	0.05	6.0%
Total	1.30	0.54	0.76	0.76	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life Year
*No utility is assigned to the death state

Table 98: Scenario 2 - Summary of costs

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	3,531	1,410	2,120	2,120	3.2%
PD*	14,498	9,153	5,344	5,344	8.0%
Drug acquisition cost	61,237	6,653	54,583	54,583	81.2%
Administration cost	6,581	1,489	5,092	5,092	7.6%
Monitoring cost	2,388	1,250	1,138	1,138	1.7%
AEs	228	1,304	-1,076	-1,076	-1.6%
Total treatment cost	88,462	21,260	67,202	67,202	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free
*Progressed disease includes the costs of managing patients who have progressed and end of life/terminal care. No costs are assigned to the death state.

Table 99: Scenario 2 - Cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	88,462	1.30	67,202	0.76	87,925
Docetaxel	21,260	0.54			

Abbreviations: QALY = Quality-Adjusted Life Year

Treatment discontinuation

The duration of treatment in the base case economic analysis assumes a treat-to-progression treatment regimen for nivolumab. This is consistent with CheckMate 017, in which patients received nivolumab until their tumour progressed (as defined by RECIST 1.1) or they experienced toxicities that required them to stop treatment. The OS and PFS and duration of treatment Kaplan Maier curves from CheckMate 017 are shown in Figure 8 and Figure 9, respectively. At 1 year, the OS rate was 42%, the PFS rate was 21%, and [redacted]% of patients remained on treatment with nivolumab.

In patients who experience a durable response, it may be feasible to stop nivolumab treatment before they progress and still maintain clinical benefit. Evidence to support this approach can be seen in study CheckMate 003, which had a 96-week stopping rule (Gettinger 2015). This is the only study of nivolumab in lung cancer to use anything other than a treat-to-progression regimen. The swimmers plot from CheckMate 003 is shown in Figure 31.

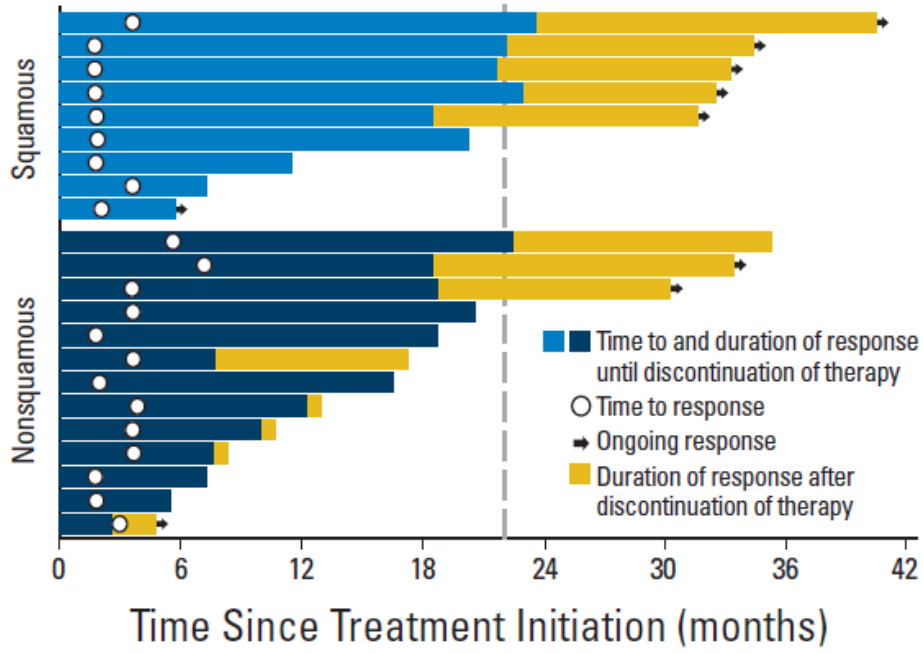
As can be seen from this plot (Figure 31), [redacted] responders stopped nivolumab at the pre-defined stopping point of 96 weeks. In each of these responders, there was a significant ongoing response beyond 96 weeks (indeed, at the last analysis, six of the seven responders had not progressed), demonstrating an ongoing clinical benefit despite

withdrawal of nivolumab, and supporting the hypothesis that stopping nivolumab treatment at a pre-defined time point may be feasible.

BMS are committed to addressing the question of optimal duration of treatment of nivolumab in lung cancer through planned studies. These include the Phase III CheckMate 153 safety CheckMate 153, in which responders are randomised at 1 year to either stop nivolumab or to continue nivolumab treatment until progression. Data from CheckMate 153 will be available in 2017.

Based on the projected availability of these data, and the evidence from study CheckMate 003, both 1-year and a 2-year stopping rules have been included in scenario analyses to investigate the impact of these on the cost-effectiveness of nivolumab.

Figure 31: Swimmers plot from CheckMate 003



Source: (Gettinger 2015)

Scenario 3: 1-year treatment stopping rule

Table 100: Scenario 3 - Summary of QALY gain by health state

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.63	0.26	0.37	0.37	48.9%
PD	0.68	0.33	0.34	0.34	45.1%
AE disutility	-0.01	-0.05	0.05	0.05	6.1%
Total	1.30	0.54	0.76	0.76	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life Year

*No utility is assigned to the death state

Table 101: Scenario 3 - Summary of costs

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	3,425	1,406	2,019	2,019	5.8%
PD*	14,757	9,164	5,593	5,593	16.2%
Drug acquisition cost	32,243	6,636	25,607	25,607	74.1%
Administration cost	3,610	1,486	2,124	2,124	6.1%
Monitoring cost	1,556	1,248	308	308	0.9%
AEs	228	1,304	-1,076	-1,076	-3.1%
Total treatment cost	55,818	21,243	34,575	34,575	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free
*Progressed disease includes the costs of managing patients who have progressed and end of life / terminal care. No costs are assigned to the death state.

Table 102: Scenario 3 - Cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	55,818	1.30	34,575	0.76	45,470
Docetaxel	21,243	0.54			

QALY = Quality-Adjusted Life Year

Scenario 4: 2-year treatment stopping rule

Table 103: Scenario 4 - Summary of QALY gain by health state

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.63	0.26	0.37	0.37	48.9%
PD	0.68	0.33	0.34	0.34	45.1%
AE disutility	-0.01	-0.05	0.05	0.05	6.1%
Total	1.30	0.54	0.76	0.76	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life Year
*No utility is assigned to the death state

Table 104: Scenario 4 - Summary of costs

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	3,425	1,406	2,019	2,019	4.4%
PD*	14,757	9,164	5,593	5,593	12.1%
Drug acquisition cost	42,631	6,636	35,995	35,995	77.7%
Administration cost	4,674	1,486	3,188	3,188	6.9%
Monitoring cost	1,853	1,248	606	606	1.3%
AEs	228	1,304	-1,076	-1,076	-2.3%
Total treatment cost	67,569	21,243	46,325	46,325	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free
*Progressed disease includes the costs of managing patients who have progressed and end of life / terminal care. No costs are assigned to the death state.

Table 105: Scenario 4 - Cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	67,569	1.30	46,325	0.76	60,923
Docetaxel	21,243	0.54			

Abbreviations: QALY = Quality-Adjusted Life Year

Vial optimisation

The base case economic analysis assumes there is full wastage, and that clinicians would not optimise the combination of vials to use based on a patient's weight. However, given that nivolumab is available in two vial sizes, it is likely that clinicians would attempt to minimise wastage by using the optimal combination of vials that would allow them to deliver the required dose of nivolumab for any patient. A scenario is therefore presented that considers such a vial optimisation approach.

As the average patient weight is 73kg, the dose of nivolumab required for a patient of this weight is 219mg (dose: 3 mg/kg). The optimal vial combination for this dose would be 1x vial of 100mg and 3x vials of the 40mg (220mg). The cost per dose for 220mg is therefore £2414 (3x £439 and 1x £1097). The summary of costs, QALYs gained and cost-effectiveness analysis for this scenario is presented in Table 106, Table 107 and Table 108, respectively.

Table 106: Scenario 5 - Summary of QALY gain by health state

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.63	0.26	0.37	0.37	48.9%
PD	0.68	0.33	0.34	0.34	45.1%
AE disutility	-0.01	-0.05	0.05	0.05	6.1%
Total	1.30	0.54	0.76	0.76	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life Year
*No utility is assigned to the death state

Table 107: Scenario 5 - Summary of costs

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	3,425	1,406	2,019	2,019	3.3%
PD*	14,757	9,164	5,593	5,593	9.2%
Drug acquisition cost	54,594	6,636	47,958	47,958	79.3%
Administration cost	6,398	1,486	4,912	4,912	8.1%
Monitoring cost	2,336	1,248	1,089	1,089	1.8%
AEs	228	1,304	-1,076	-1,076	-1.8%
Total treatment cost	81,739	21,243	60,496	60,496	100%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free
*Progressed disease includes the costs of managing patients who have progressed and end of life / terminal care. No costs are assigned to the death state.

Table 108: Scenario 5 - Cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	81,739	1.30	60,496	0.76	79,559
Docetaxel	21,243	0.54			

Abbreviations: QALY = Quality-Adjusted Life Year

5.9 Subgroup analysis

Patients were categorised by PD-L1 level expression status in CheckMate 017. However, a separate analysis of this patient subgroup has shown that PD-L1 expression is neither prognostic nor predictive of PFS and OS outcomes (Brahmer 2015a; Brahmer 2015b). On this basis no separate economic analysis was undertaken of the PD-L1 subgroup. No further subgroups were identified for analysis.

5.10 Validation

Validation of de novo cost-effectiveness analysis

Several sources were used to validate the survival models used in the base case analysis (Section 5.3). These include:

1. The Phase III CheckMate 017 KM data reported in the clinical study report for PFS – specifically in terms of the median PFS, 6-month PFS rate, and 12-month PFS rates for nivolumab and docetaxel (Bristol-Myers Squibb 2015a)
2. The Phase I safety study CheckMate 003 KM data reported at the Chicago Multidisciplinary Symposium in Thoracic Oncology (CMSTO) conference in 2014 which provides 3 years of PFS follow-up for patients receiving nivolumab for advanced squamous and non-squamous NSCLC across all three doses (1mg/kg, 3mg/kg, and 10mg/kg) (Gettinger 2015)
3. The Phase II single arm CheckMate 063 KM data reported at the CMSTO conference in 2014, which provides 6-month and 12-month PFS rates for patients receiving nivolumab for advanced squamous NSCLC at a 3mg/kg dose (Bristol-Myers Squibb 2014b)
4. The SEER database (data for up to 15 years)
5. The NLCA dataset (data for up to 5 years – relevant to UK clinical practice)

Table 109 shows the validation of the parametric survival models against CheckMate 017, CheckMate 063, and CheckMate 003 trials in terms of PFS. Table 110 shows the validation of the survival models for OS against CheckMate 017, CheckMate 063, and CheckMate 003. The data show that the survival patterns in the economic model are aligned well with the survival data available from all the nivolumab clinical trials.

In addition, external validation of these survival models for OS was explored using NLCA and SEER registry data and details of these validations are presented in Section 5.3. Comparison of epidemiological and survival data from NLCA and SEER registries suggested that populations in these two registries were comparable in terms of lung cancer incidence, mortality, stage distributions, and age of diagnosis (Table 43, Table 44, and Appendix 21). Conditional survival estimates from SEER and NLCA were closely matching those predicted by the long-term extrapolation techniques explored, which revealed that the economic model predicted OS estimates were clinically plausible (Table 111).

Table 109: In-trial validation of parametric survival models for PFS

Data source	Curve	Proportion alive (%)									Median PFS (months)	Mean PFS (months)
		6 months	1 year	2 years	3 years	4 years	5 years	10 years	15 years	20 years		
Single survival model adjusted for shape and scale: 2-knot spline hazard	Nivolumab PFS	36.9	22.0	11.4	6.9	4.5	3.1	0.7	0.2	0.1	3.7	10.7
	Docetaxel PFS	21.2	5.5	0.6	0.1	0.0	0.0	0.0	0.0	0.0	3.0	4.3
Independent survival model: docetaxel (log-normal), nivolumab (1-knot spline-based hazard)	Nivolumab PFS	36.4	21.8	11.7	7.3	4.9	3.5	0.9	0.3	0.1	3.7	11.1
	Docetaxel PFS	20.0	6.4	1.4	0.5	0.2	0.1	0.0	0.0	0.0	2.5	4.2
CheckMate 017	Nivolumab PFS	38.4	20.8	NA	NA	NA	NA	NA	NA	NA	3.5	NA
	Docetaxel PFS	21.7	6.4	NA	NA	NA	NA	NA	NA	NA	2.6	NA
CheckMate 003 (CMSTO 2014)	Nivolumab PFS	33	22	9	NA	NA	NA	NA	NA	NA	NA	NA
CheckMate 063 (CMSTO 2014)	Nivolumab PFS	26	20	NA	NA	NA	NA	NA	NA	NA	2.0	NA

Abbreviations: CMSTO = Chicago Multidisciplinary Symposium in Thoracic Oncology; KM = Kaplan-Meier; NA = Not Applicable; OS = Overall survival

Table 110: In-trial validation of parametric survival models for OS

Data source	Curve	Proportion alive				Median OS (months)	Mean OS (months)
		6 months	1 year	2 years	3 years		
Log-logistic	Nivolumab OS	68.0%	44.3%	25.1%	17.4%	9.9	27.2
	Docetaxel OS	52.0%	25.2%	9.6%	5.2%	6.2	11.5
Spline-2 knots	Nivolumab OS	67.3%	44.0%	25.9%	16.7%	9.7	20.5
	Docetaxel OS	51.0%	24.7%	10.1%	4.8%	6.0	10.3
CheckMate 017	Nivolumab OS	63.7%	42%	n/a	n/a	9.2	NA
	Docetaxel OS	50.4%	24%	n/a	n/a	6.0	NA
CheckMate 003	Nivolumab OS	n/a	42.0%	24.0%	18.0%	9.9	NA
CheckMate 063	Nivolumab OS	60%	41%	n/a	n/a	8.2	NA

Table 111: Comparison of conditional survival estimates predicted from OS parametric distributions vs. real world data

	Curve	**Conditional survival**				
OS parametric distributions	**Start-year**	**Yr 2**	**Yr 3**	**Yr 4**	**Yr 5**	**Yr 10**
	End-year	**Yr 3**	**Yr 4**	**Yr 5**	**Yr 10**	**Yr 15**
Spline – 2 knots	Nivolumab OS	64.5%	67.4%	69.4%	20.9%	26.4%
	Docetaxel OS	47.4%	51.1%	53.8%	7.0%	10.4%
Log-logistic	Nivolumab OS	69.4%	76.6%	81.0%	51.6%	67.7%
	Docetaxel OS	53.9%	63.6%	70.0%	32.6%	51.6%
RWD*	**Start-year**	**Yr 3**	**Yr 4**	**Yr 5**	**Yr 6**	**Yr 11**
	End-year	**Yr 4**	**Yr 5**	**Yr 6**	**Yr 11**	**Yr 16**
SEER stage IIIb/IV	Treatment not specified	69.3%	79.1%	81.3%	53.4%	57.0%
NLCA Stage IV	Treatment not specified	78.6%	90.9%	N/A	N/A	N/A

* Both SEER and NLCA capture overall mortality

Throughout the development of the economic model, external clinical and health economic experts were consulted, including:

1. Two EU advisory workshops attended by four health economists representing UK, Italy, Spain, and France. The primary purpose of this workshop was to help validate the key inputs in the economic model and determine the base case scenario for each country
2. One UK advisory workshop attended by four health economists and three clinicians reflecting practice in England, Wales and Scotland. Similar to the EU workshop, the primary purpose of this workshop was to help validate the key inputs within the economic model and determine the base case scenario for NICE
3. Ad-hoc consultation with a health economics advisory panel
4. Ad-hoc validation of model inputs with UK clinicians

A summary of the feedback is provided in Appendix 20.

5.11 Interpretation and conclusions of economic evidence

When interpreting and concluding your economic evidence, consider the following:

1. *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

   This is the first economic evaluation undertaken for nivolumab in a squamous NSCLC population. There is no published evidence for direct comparison.

2. *Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?*

   Yes, the economic evaluation considers patients with advanced squamous NSCLC in a second-line setting who have previously received platinum-doublet therapy. This population reflects patients enrolled in CheckMate 017 and is in line with the decision problem.

3. *How relevant (generalisable) is the analysis to clinical practice in England*?

The analysis is likely to be directly applicable to clinical practice in England:

- The patient population in CheckMate 017 and the economic analysis is reflective of patients with advanced NSCLC treated in the UK, and for this reason the clinical outcomes (PFS and OS) are likely to be applicable to the patient population in England
- The economic model structure is in line with other oncology models and previous NSCLC submissions to NICE
- The resource use in the analysis has been validated by UK clinicians
- Resource use and costs were sourced from UK-based publications (e.g. NHS Reference Costs and British National Formulary) and previous NICE TAs
- Extensive sensitivity analysis and validation of the model were undertaken
- In selecting the survival analysis methods for OS, NLCA UK registry data were used as a source of validation, as well as SEER registry data to ensure the clinical plausibility of the model and its applicability to UK clinical practice

4. *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

   The economic model is underpinned by patient-level data from the CheckMate 017 trial, which collected data on efficacy, treatment patterns, and quality of life. Survival extrapolation was essential to quantify the survival benefit beyond the trial period. A robust and comprehensive approach was followed during the survival extrapolation to ensure the methods were statistically sound, but also clinically plausible and reflective of real world clinical practice. In terms of resource utilisation, all inputs were validated and sourced from UK publications.

5. *What further analyses could be carried out to enhance the robustness or completeness of the results?*

   Longer follow-up of trial patients would generate more robust data for the long-term survival extrapolation. It is also important to be able to have more certainty around the optimal treatment duration for patients, beyond which clinical benefit would continue despite stopping treatment. The planned CheckMate 153 study is expected to generate data to support treatment discontinuation. Future analyses could make use of these additional datasets.

6 Assessment of factors relevant to the NHS and other parties

6.1 Number of people eligible for treatment in England.

It is estimated that approximately 853 patients will be eligible to receive nivolumab in the pre-treated setting (Table 112). The analysis is based on a closed cohort and therefore, the eligible population is 853 for each subsequent year.

Table 112: Eligible population for nivolumab

Population	Proportion of patients	Number of patients	Reference
Total NSCLC	N/A	27,300	(Health and Social Care Information Centre 2014b)
Patients with stage IIIb/IV NSCLC	N/A	19,138	(Health and Social Care Information Centre 2014b)
Squamous NSCLC	35.6%	6,822	(Powell 2013)
Patients who receive 1st line therapy	25.0%	1,706	(NICE 2010b)
Patients who failed 1st line therapy	50.0%	853	(Sculier 2009)

Abbreviations: NSCLC = Non-Small Cell Lung Cancer

6.2 Assumptions made about current treatment options and uptake of technologies

The budget impact model assumes that the OS of each patient for each treatment can be split into two treatment phases: active second-line treatment and BSC in second-line following active treatment. Assumptions around the mean amount of time a patient spends receiving active treatment (second-line) are based on clinical trial data used in the economic model. Specifically, the mean number of doses received by patients undergoing treatment with nivolumab and docetaxel are sourced from the CheckMate 017 trial; for erlotinib, the mean treatment duration is sourced from the manufacturer's submission to NICE (TA162) and is 4.11 months. BSC has no associated treatment costs. Details of these treatment durations for the intervention and comparators are presented in Table 113.

Table 113: Mean duration of treatment

Treatment	Mean duration of treatment (months)	Mean number of doses
Nivolumab	6.10	13.2
Erlotinib	4.11	125
Docetaxel	2.98	4.3
BSC	N/A	N/A

Abbreviations: BSC = Best Supportive Care

6.3 Assumptions made about market share in England

The current market share for systemic therapies relevant to the NICE decision problem in the second-line setting are presented in Table 114 and represents the 'scenario without nivolumab'. Based on internal projections, it is estimated that the uptake of nivolumab will reach 40% by year 3 following introduction (Table 115). Due to limited forecasts, the market share projections for years 4 to 5 are assumed to be the same as for year 3. For patients not treated with nivolumab in the 'scenario with nivolumab', the distribution of treatments is assumed to be equivalent to the distribution in the 'scenario without nivolumab' for years 1-5.

Table 114: Market share analysis - scenario without nivolumab

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Nivolumab	0%	0%	0%	0%	0%
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	100%	100%	100%	100%	100%

Abbreviations: BSC = Best Supportive Care

Table 115: Market share analysis - scenario with nivolumab

	Y1 (2016)	Y2 (2017)	Y3 (2018)*	Y4 (2019)*	Y5 (2020)*
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	100%	100%	100%	100%	100%

Abbreviations: BSC = Best Supportive Care

*Total percentage does not add to 100% due to rounding

6.4 Other significant costs associated with treatment

The costs in the budget impact analysis are those included in the cost-effectiveness analysis (Section 5.5). The drug acquisition costs are presented in Table 116. The mean duration of treatment for nivolumab, docetaxel, and the additional interventions were sourced from CheckMate 017 and published literature.

Table 116: Drug acquisition costs

Comparator	Cost of each treatment	Mean duration of treatment (months)	Total drug acquisition cost
Nivolumab	£439.00 (per 40mg vial)	6.10	£34,891
Docetaxel	£900.00 (per 140mg vial)	4.11	£3,884
Erlotinib	£54.38 (per 150mg tablet)	2.98	£6,793
BSC	N/A	N/A	N/A

Abbreviations: BSC = Best Supportive Care

6.5 Unit costs

All unit costs are those reported in the cost-effectiveness analysis. The costs included are drug acquisition costs, administration costs, monitoring costs, and AE management costs (Section 5.5).

6.6 Estimates of resource savings

There are no additional estimates of resource savings.

6.7 Estimated annual budget impact on the NHS in England

The budget impact analysis is for a closed cohort of patients based on the eligible population presented in Table 112. For the purposes of the analysis, it is assumed that nivolumab is introduced to the market in January 2016.

The budget impact analysis compares scenarios with and without nivolumab from years 1 to 5 after nivolumab introduction (Table 114 and Table 115). The results of this analysis show the net cumulative budget impact of introducing nivolumab from 2016 to 2020 is £46,581,975 (Table 117 and Table 118).

A limitation with this analysis is that it is based on a closed cohort, therefore there may be a small proportion of patients who are eligible for therapy not considered in these projections, and also, the uncertainty of sales projections limits the accuracy of the budget impact calculation.

Table 117: Scenario with nivolumab

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Patients on all comparators	819	546	512	512	512
Total drug acquisition cost on all comparators	£3,009,822	£2,006,548	£1,881,139	£1,881,139	£1,881,139
Total drug administration cost on all comparators	£398,695	£267,797	£249,184	£249,184	£249,184
Total drug monitoring cost on all comparators	£329,332	£219,555	£205,833	£205,833	£205,833
Total drug AE cost on all comparators	£751,963	£501,309	£469,977	£469,977	£469,977
Patients on Nivolumab	34	307	341	341	341
Total drug acquisition cost on nivolumab	£1,190,259	£10,712,331	£11,902,590	£11,902,590	£11,902,590
Total drug administration cost on nivolumab	£121,982	£1,097,835	£1,219,816	£1,219,816	£1,219,816
Total drug monitoring cost on nivolumab	£31,593	£284,333	£315,925	£315,925	£315,925
Total drug AE cost on nivolumab	£7,792	£70,126	£77,917	£77,917	£77,917
Total	**£5,841,437**	**£15,157,832**	**£16,322,381**	**£16,322,381**	**£16,322,381**

Abbreviations: AE = Adverse Event

Table 118: Scenario without nivolumab

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Patients on all comparators	853	853	853	853	853
Total drug acquisition cost on all comparators	£3,135,231	£3,135,231	£3,135,231	£3,135,231	£3,135,231
Total drug administration cost on all comparators	£415,307	£415,307	£415,307	£415,307	£415,307
Total drug monitoring cost on all comparators	£343,054	£343,054	£343,054	£343,054	£343,054
Total drug AE cost on all comparators	£783,295	£783,295	£783,295	£783,295	£783,295
Total	**£4,676,887**	**£4,676,887**	**£4,676,887**	**£4,676,887**	**£4,676,887**

Abbreviations: AE = Adverse Event

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Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811]

Dear [redacted]

The Evidence Review Group, Liverpool Reviews and Implementation Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on 17 August by Novartis Pharmaceuticals. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm**, **Thursday 24 September**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link: <<Insert NICE DOCS LINK>>.

If you have any further queries on the technical issues raised in this letter then please contact Ian Watson, Technical Lead (ian.watson@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on clinical effectiveness data

CheckMate 017

A1. **Priority request.** Please provide overall survival (OS) and progression-free survival (PFS) data for the latest data-cut ([redacted]).

In addition, please confirm if treatment crossover was permitted at the time of the latest data-cut ([redacted]) and, if so, how many patients crossed over from docetaxel to nivolumab.

A2. The submission states (on page 50) that hazard ratios for OS and PFS were estimated in a Cox proportional hazards model; however, page 126 states that the assumption of proportional hazards is not valid for the PFS data from CheckMate 017. Please provide further clarification of why the results obtained from the Cox proportional hazards model are presented, and whether alternative approaches were considered.

A3. The protocol for CheckMate 017 states: "If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints [ORR and PFS] will be used to preserve a study-wise type I error rate at 0.05."

a. Please confirm whether ORR and PFS were tested in the pre-specified hierarchical order.

b. Please clarify how the type 1 error rate of 0.05 was preserved; what level of testing was used for each of the 2 outcomes?

A4. Please clarify whether an 'adjusted-alpha' level was pre-specified for the analysis of OS.

A5. Figure 11 (page 67) and Brahmer et al. (2015) present forest plots of the treatment effect for nivolumab on OS and PFS in pre-defined subgroups. Please provide the p-values for tests for interaction for the subgroup analyses of OS and PFS.

A6. Figure 12 presents forest plot of OS and PFS according to PD-L1 expression level. Please provide a similar forest plot for ORR. Please also provide the p-values for tests for interaction for the analyses of OS, PFS and ORR according to PD-L1 expression.

A7. Please provide the number of patients treated with nivolumab or docetaxel who received concurrent palliative radiotherapy.

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A8. Page 53 of the submission states: “At the January 10, 2015 data assessment, no patients had crossed over during treatment from docetaxel to nivolumab or from nivolumab to docetaxel.” However, this page also states that 24% of patients in the nivolumab group received subsequent docetaxel. Please clarify why this was not considered ‘cross-over’.

A9. Please clarify from where data on subsequent therapy presented in Table 52 of the CS are derived. In addition, please provide data on subsequent therapy for the latest data-cut ([redacted]), if available.

A10. In figure 9 (page 61), the curves for PFS with nivolumab and docetaxel begin to diverge after approximately 3 months; in contrast, the curves for OS appear to diverge earlier. Can you provide an explanation for the similarity of the PFS curves in the first 3 months?

Indirect treatment comparisons

A11. **Priority question.** Appendix 7.1 of the submission states: “For all comparators in the analysis, information on treatment outcomes was only available at the study level. Therefore, the information available was averaged over the trial and treatment”. Please can you clarify the meaning of this statement, and how it applies to the indirect comparison (which is based on hazard ratios). What information is averaged, and how is this used in the analyses?

A12. **Priority question.** Please clarify how studies were selected to contribute to the indirect comparisons.

a. The submission (page 69–70) states that 12 studies met the inclusion criteria for the systematic review and included relevant comparators, but that only 3 studies contributed to the indirect comparison. Please confirm which studies were excluded and why.

b. The network diagrams (appendix 7.15) include studies that do not add any information to the networks and that are reported in appendix 7.10 to have been excluded (for example, the LUX-Lung 8, LUME-Lung 1, TITAN and NVALT-10 trials). Please confirm whether any data from these additional studies were included in the indirect comparisons.

c. Please clarify the reason for excluding the TAX 317 study.

d. Appendix 7.11 lists 29 studies included in the review that are not relevant to the decision problem, but does not explicitly state why these studies were excluded. Page 38 of the submission states: “29 studies included either non-squamous patients, or patients with mixed histology but with no sub-group data for the squamous population, and were therefore not considered relevant

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to the decision problem". Please confirm that this is the reason the studies listed in appendix 7.11 were excluded.

Other studies

A13. Page 106 of the submission states that [redacted]. Please provide a summary of these results.

Section B: Clarification on decision model parameters and cost-effectiveness data

B1. **Priority question.** Please provide the following Kaplan-Meier analyses (a, b and c below), to the following specification:

Population: ITT population including all patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off; i.e. *not* when last known to be alive (OS and post-progression survival [PPS]), and *not* at the date of last tumour assessment (PFS).

Trial data set: CheckMate 017, [redacted] data cut (if available, otherwise the most recent data).

a. Time to death from any cause (OS), time to disease progression or death based on investigator assessment (investigator-assessed PFS), and time from disease progression by investigator assessment to death from any cause (PPS), stratified by treatment arm (nivolumab vs docetaxel).

b. Time to treatment discontinuation, stratified by treatment arm (nivolumab vs docetaxel).

c. Time to death from any cause (OS), time to disease progression or death based on investigator assessment (investigator-assessed PFS), and time from disease progression by investigator assessment to death from any cause (PPS), for patients randomised to the nivolumab treatment arm *excluding* all patients who continued to receive nivolumab beyond investigator assessed disease progression.

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Please present analysis outputs using the following format:

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

B2. **Priority request.** Please provide results for EQ-5D utility scores (using the UK value set) in the CheckMate 017 trial ([redacted] data cut if available, otherwise the most recent data), showing the number of valid patient responses, and the mean and standard deviation of the EQ-5D values at each observation cycle stratified by treatment (nivolumab vs docetaxel) and health state (PFS vs PD).

B3. **Priority request.** Please repeat the analyses in question B2, for each of three subgroups defined by country of origin:

a. USA and Canada (27 sites with 86 patients)

b. Europe (51 sites with 155 patients)

c. Other (13 sites with 31 patients from Central & South America and Australia)

B4. Please provide additional details of the assumptions used in the scenario analyses using 1-year and 2-year treatment discontinuation rules.

a. What assumptions about clinical effectiveness (for example, survival, adverse events) were made? Please provide justifications for each assumption.

b. Was a stopping rule applied to the docetaxel arm?

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Section C: Textual clarifications, references and additional points

C1. The submission states that data from studies included in its systematic review were extracted and assessed for risk of bias by two independent reviewers. Please clarify whether a similar method was applied to study selection.

C2. The submission states that the use of erlotinib is declining. Please provide evidence to support this statement.

C3. Please provide the following references cited in the CSR for CheckMate 017:

a. Adverse Event Domain Requirements Specification. Bristol Myers Squibb Co. PRI. Version 2.1. April 23, 2012.

b. Non-Study Medication Domain Requirements Specification. Bristol Myers Squibb Co. PRI. Version 2.2 April 24, 2012

C4. Please confirm whether the results of the economic model (presented in sections 5.7 and 5.8 of the submission) include discounting for total costs, total life years gained and total QALYs.

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RE: BMS response to NICE / ERG questions for Single Technology Appraisal (Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811])

Section A: Clarification on clinical effectiveness data

CheckMate 017

It should be noted that the latest data set for the CheckMate 017 trial is based on a data-cut on 30 July 2015 and not [redacted]. Results from the data-cut taken on 30 July 2015 data set were presented at the World Lung Cancer Conference (6-9 September 2015) and are presented in this response (Reckamp 2015). All references to a data-cut on 19 June 2015 should be considered to be 30 July 2015.

A1. **Priority request.** Please provide overall survival (OS) and progression-free survival (PFS) data for the latest data-cut ([redacted]).

Results for CheckMate 017 trial were presented in the original NICE submission dossier (OS and PFS rate at 6 months and 12 months). These were results from database lock 15 December 2014. A further data-cut was taken on 30 July 2015. OS and PFS results are presented below (OS and PFS rate at 18 months) (Table 1 and Table 2).

Table 1: CheckMate 017 - OS results from all randomised patients in the trial (data cut July 2015)

OS	CheckMate 017	
	Nivolumab (N = 135)	Docetaxel (N = 137)
Events, n (%)	103 (76.3)	122 (89.1)
Stratified log-rank test p-value	P=0.0004	
HR for death (95% CI)	0.62 (0.48, 0.81)	
Median OS, months (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
OS rate at 6 months (95% CI)	63.7 (55.0, 71.2)*	50.4 (41.7, 58.4)*
OS rate at 12 months (95% CI)	42 (34, 50)	24 (17, 31)
OS rate at 18 months (%)	28	13

Source: (Bristol-Myers Squibb 2015; Brahmer 2015; Reckamp 2015)

Abbreviations: CI = Confidence Interval; HR = Hazard Ratio; OS = Overall Survival

*All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb 2015)

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Table 2: CheckMate 017 - Summary of PFS results from all randomised patients in the trial (data cut July 2015)

PFS	CheckMate 017	
	Nivolumab (N = 135)	Docetaxel (N = 137)
Events, n (%)	105 (77.8)	122 (89.1)
Stratified log-rank test p-value	<0.0008	
HR for progression or death (95% CI)	0.63 (0.48, 0.83)	
Median, months (95% CI)	3.5 (2.14, 5.06)	2.8 (2.14, 3.52)
PFS rate at 6 months (95% CI)	38.4 (30.0, 46.8)	21.9 (15.1, 29.5)
PFS rate at 12 months (95% CI)	21 (14, 28)	6 (3, 12)
PFS rate at 18 months (%)	17	2.7

Source: (Bristol-Myers Squibb 2015; Brahmer 2015; Reckamp 2015)

CI = Confidence Interval; HR = Hazard Ratio; PFS: Progression-free survival

In addition, please confirm if treatment crossover was permitted at the time of the latest data-cut (19th June 2015) and, if so, how many patients crossed over from docetaxel to nivolumab.

The latest data cut is 30 July 2015. Following the 15 December 2014 database lock and the Data Monitoring Committee's recommendation to lock the study based on superior OS in the nivolumab arm (10 January 2015), the protocol was amended to allow eligible patients originally randomized to docetaxel to receive nivolumab in an extension phase of the study. Prior to the most recent database lock on 30 July 2015 to support the 18-month survival analysis presented at WCLC 2015, [redacted] patients had initiated nivolumab in this extension phase.

A2. The submission states (on page 50) that hazard ratios for OS and PFS were estimated in a Cox proportional hazards model; however, page 126 states that the assumption of proportional hazards is not valid for the PFS data from CheckMate 017. Please provide further clarification of why the results obtained from the Cox proportional hazards model are presented, and whether alternative approaches were considered.

The Cox HR for OS and PFS that is presented on page 50 (the clinical section) is reported in the CSR and in publications for PFS. The economic model did not use the Cox HR reported for PFS in the clinical trial as there were non-proportional hazards for PFS based on visual assessment and statistical tests. PFS survival was modelled using a single curve fit to both the nivolumab and docetaxel arms with an adjustment for treatment effect. HR derived from this analysis was used in the model. Additionally, independent survival curves were also explored and presented as a sensitivity analysis.

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A3. The protocol for CheckMate 017 states: “If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints [ORR and PFS] will be used to preserve a study-wise type I error rate at 0.05.”

a. Please confirm whether ORR and PFS were tested in the pre-specified hierarchical order.

The secondary endpoints investigator-assessed ORR and PFS were tested hierarchically in the pre-specified order with ORR first followed by PFS

b. Please clarify how the type 1 error rate of 0.05 was preserved; what level of testing was used for each of the 2 outcomes?

Type 1 error rate of 0.05 was preserved by using a group sequential testing procedure applied to OS for interim and final analyses; and as superiority was demonstrated, a hierarchical testing approach was used for the key secondary endpoints following analysis of the primary endpoint of OS. The formal statistical testing for ORR took place only if OS was statistically significant, and the statistical testing for PFS took place only if both OS and ORR are statistically significant. A significance level of 0.05 was used for both ORR and PFS.

A4. Please clarify whether an ‘adjusted-alpha’ level was pre-specified for the analysis of OS.

A '1-adjusted-alpha level' was pre-specified for the analysis of OS

A5. Figure 11 (page 67) and Brahmer et al. (2015) present forest plots of the treatment effect for nivolumab on OS and PFS in pre-defined subgroups. Please provide the p-values for tests for interaction for the subgroup analyses of OS and PFS.

The hazard ratios from Figure 11 for OS have been presented in Table 3 along with the requested p-values for tests for interaction for the subgroups.

At the time of this response the p-values for tests for interaction for the subgroups for the PFS data were not available. BMS are fully committed to provide this information as soon as this analysis has been completed (anticipated by Oct 2nd 2015).

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Table 3: CheckMate: Treatment effect on OS in pre-defined subsets including p-values for test for interaction for the subgroup

	Hazard ratio (95% CI)	Test for interaction p- value
Overall	0.59 (0.44, 0.78)	
Prior paclitaxel vs. other prior treatment		[redacted]
Prior paclitaxel	0.51 (031, 0.83)	
Another Agent	0.63 (0.45, 0.90)	
Region		[redacted]
US/Canada	0.59 (0.36, 0.98)	
Europe	0.50 (0.34, 0.72)	
Rest of World	1.53 (0.65, 3.62)	
Age Categorisation		[redacted]
< 65 years	0.52 (0.35, 0.75)	
65 - 74 years	0.56 (0.34, 0.91)	
≥ 75 years	1.85 (1.76, 4.51)	
Gender		[redacted]
Male	0.57 (0.41, 0.78)	
Female	0.67 (0.36, 1.25)	
Race		
White	0.59 (0.44, 0.79)	
ECOG PS		[redacted]
0	0.48 (0.24, 0.99)	
1	0.54 (0.39, 0.74)	
Type of Prior Platinum Regimen		[redacted]
Cisplatin	0.67 (0.41, 1.10)	
Carboplatin	0.55 (0.93, 0.78)	
Time From Diagnosis to Randomisation		[redacted]
< 1 year	0.55 (0.39, 0.77)	
Other	0.73 (0.42, 1.36)	
Time from Completion of Most Recent Regimen to Randomisation		[redacted]
< 3 months	0.56 (0.37, 0.85)	
3-6 months	0.54 (0.31, 0.95)	
> 6 months	0.64 (0.37, 1.13)	
CNS Metastases		
No	0.60 (0.45, 0.80)	
Smoking Status		
Current/Former Smoker	0.59 (0.44, 0.80)	

NOTE: * indication of different effects; **proof of different effects

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Table 4: CheckMate: Treatment effect on PFS in pre-defined subsets including p-values for test for interaction for the subgroup

	Hazard ratio (95% CI)	Test for interaction p- value
Overall	0.63 (0.48, 0.82)	
Prior paclitaxel vs. other prior treatment		[redacted]
Prior paclitaxel	0.61 (0.39, 0.96)	
Another Agent	0.62 (0.44, 0.86)	
Region		[redacted]
US/Canada	0.68 (0.42, 1.09)	
Europe	0.57 (0.40, 0.81)	
Rest of World	0.82 (0.37, 1.83)	
Age Categorisation		[redacted]
< 65 years	0.62 (0.44, 0.89)	
65 - 74 years	0.51 (0.32, 0.82)	
≥ 75 years	1.76 (0.77, 4.05)	
Gender		[redacted]
Male	0.63 (0.46, 0.85)	
Female	0.71 (0.40, 1.26)	
Race		
White	0.62 (0.47, 0.82)	
ECOG PS		[redacted]
0	0.49 (0.27, 0.89)	
1	0.61 (0.27, 0.89)	
Type of Prior Platinum Regimen		[redacted]
Cisplatin	0.69 (0.43, 1.10)	
Carboplatin	0.62 (0.44, 0.86)	
Time From Diagnosis to Randomisation		[redacted]
< 1 year	0.62 (0.45, 0.86)	
Other	0.69 (0.43, 1.12)	
Time from Completion of Most Recent Regimen to Randomisation		[redacted]
< 3 months	0.53 (0.35, 0.79)	
3-6 months	0.59 (0.35, 1.00)	
> 6 months	0.83, (0.50, 1.37)	
Smoking Status		
Current/Former Smoker	0.63 (0.47, 0.83)	

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A6. Figure 12 presents forest plot of OS and PFS according to PD-L1 expression level. Please provide a similar forest plot for ORR. Please also provide the p-values for tests for interaction for the analyses of OS, PFS and ORR according to PD-L1 expression.

At the time of this response, a forest plot of ORR was not available. BMS are fully committed to provide this information as soon as this analysis has been completed (anticipated by Oct 2nd 2015).

The objective response rate by PD-L1 expression has been provided in Table 5. At the time of this response hazard ratios were available for OS and PFS and odds ratio were available for ORR.

Table 5: OS, PFS and ORR according to PD-L1 expression level

OS	**Hazard ratio (95% CI)**	**p- value**
≥1%	0.69 (0.45 – 1.05)	[redacted]
<1%	0.58 (0.37 – 0.92)	
≥5%	0.53 (0.31 – 0.89)	[redacted]
<5%	0.70 (0.47 – 1.02)	
≥10%	0.50 (0.28 – 0.89)	[redacted]
<10%	0.70 (0.48 – 1.01)	
PFS	**Hazard ratio (95% CI)**	**p-value**
≥1%	0.67 (0.44 – 1.01)	[redacted]
<1%	0.66 (0.43 – 1.00)	
≥5%	0.54 (0.32 – 0.90)	[redacted]
<5%	0.75 (0.52 – 1.08)	
≥10%	0.58 (0.33 – 1.02)	[redacted]
<10%	0.70 (0.49 – 0.99)	
ORR	**Odds ratio (95% CI)**	**p-value**
≥1%	[redacted]	[redacted]
<1%	[redacted]	
≥5%	[redacted]	[redacted]
<5%	[redacted]	
≥10%	[redacted]	[redacted]
<10%	[redacted]	

Source: (Bristol-Myers Squibb 2015; Brahmer 2015)

A7. Please provide the number of patients treated with nivolumab or docetaxel who received concurrent palliative radiotherapy.

Palliative radiotherapy to bone or CNS lesions were allowed per protocol. A total of six patients in the nivolumab arm and one patient in the docetaxel arm received concurrent palliative radiotherapy

A8. Page 53 of the submission states: “At the January 10, 2015 data assessment, no patients had crossed over during treatment from docetaxel to nivolumab or from nivolumab to docetaxel.” However, this page also states that 24% of patients in the

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nivolumab group received subsequent docetaxel. Please clarify why this was not considered 'cross-over'.

The standard of care for patients with squamous NSCLC who have failed first line therapy in the UK is docetaxel. Within CheckMate 017 patients who had failed first line therapy were randomised to either docetaxel (standard of care) or nivolumab. Patients who discontinued treatment with nivolumab received subsequent therapy. The [redacted] of patients who have subsequently received docetaxel in the study are those patients who have discontinued nivolumab therapy.

This is not considered crossover because patients went on to have another line of therapy in accordance with current treatment pathways and current standards of care.

A9. Please clarify from where data on subsequent therapy presented in Table 52 of the CS are derived. In addition, please provide data on subsequent therapy for the latest data-cut ([redacted]), if available.

Data used in the model are based on the CSR, however differ slightly from it as experimental therapies and immunotherapies were excluded. Only the top five most common systemic therapies were included, and the percentages of patients receiving any other treatment were redistributed among the top five treatments to ensure that the total proportion receiving subsequent therapy in either arm was aligned with the CSR.

Analysis of subsequent therapies from the 30 July 2015 data-cut is presented in Table 6.

Table 6: Subsequent Cancer Therapy (data cut 30 July 2015)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

*Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomisation date if subject never treated).

**Subjects who received protocol allowed palliative radiotherapy on-study reported on the Local Tumour Treatment CRF Module started on or after the first dosing date and before the off treatment date.

A10. In figure 9 (page 61), the curves for PFS with nivolumab and docetaxel begin to diverge after approximately 3 months; in contrast, the curves for OS appear to diverge earlier. Can you provide an explanation for the similarity of the PFS curves in the first 3 months?

The shape of the PFS curve is determined by both the actual data recorded within the trial and the by the timing of the data capture assessment of response. In the CheckMate 017 trial, the first clinical assessment of response for PFS took place at 9 weeks; therefore, the lack of divergence in PFS curves before this point is likely due to an absence of data between randomisation and the first clinical assessment at 9 weeks. At 3 months, approximately [redacted] of patients receiving nivolumab had not progressed compared to approximately [redacted] of patients in the docetaxel arm (n= [redacted] vs. n=[redacted], respectively). The assessment of survival, however, was not dependent on a predetermined schedule of assessment, and hence the differential survival benefit is demonstrated from the start of follow up.

Indirect treatment comparisons

A11. **Priority question.** Appendix 7.1 of the submission states: “For all comparators in the analysis, information on treatment outcomes was only available at the study level. Therefore, the information available was averaged over the trial and treatment”. Please can you clarify the meaning of this statement, and how it applies to the indirect comparison (which is based on hazard ratios). What information is averaged, and how is this used in the analyses?

The text above refers to a methodical approach for a MTC. However, considering the scarcity of evidence resulting in a star shaped network, only adjusted ITC was performed using Bucher et al. recommendations. No averaging was done as no Bayesian MTC was performed. Averaging is required to adjust the variability in baseline characteristics across studies in a univariate/multivariate meta-regression.

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A12. **Priority question.** Please clarify how studies were selected to contribute to the indirect comparisons.

a. The submission (page 69–70) states that 12 studies met the inclusion criteria for the systematic review and included relevant comparators, but that only 3 studies contributed to the indirect comparison. Please confirm which studies were excluded and why.

A list of studies excluded from the ITC were given in Appendix 7.10 (along with reason for exclusion). This table is reproduced here (Table 7). The were two main reasons for exclusion; either the study did not include treatments that allowed the formation of a network (linking nivolumab to erlotinib or BSC in the patient population) or the study did not report a full data set that would be suitable for inclusion in the analysis.

Table 7: List of excluded studies from the network meta-analysis

Trial ID (Acronym)	Treatment (N)	Reason for exclusion from analysis
Juan 2014	Docetaxel + Erlotinib	Not connected in networks
	Erlotinib	
NVALT-10 trial	Erlotinib	Not connected in networks
	Docetaxel + Erlotinib	
HORG trial	Erlotinib	No analysable data
	Pemetrexed	
JMID trial	Docetaxel	Not connected in networks
	Pemetrexed	
Li 2012	Docetaxel	No analysable data
	Pemetrexed	
TITAN trial	Docetaxel/Pemetrexed	Not connected in networks
	Erlotinib	
LUME-LUNG 1 trial	Docetaxel	Not connected in networks
	Docetaxel + Nintedanib	
NVALT-7 trial	Pemetrexed	Not connected in networks
	Carboplatin + Pemetrexed	
Kim 2015	Gefitinib	Not connected in networks
	Pemetrexed	
LUX-Lung 8 trial	Afatinib	Not connected in networks
	Erlotinib	
EMPHASIS trial	Erlotinib	No analysable data
	Docetaxel	

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b. The network diagrams (appendix 7.15) include studies that do not add any information to the networks and that are reported in appendix 7.10 to have been excluded (for example, the LUX-Lung 8, LUME-Lung 1, TITAN and NVALT-10 trials). Please confirm whether any data from these additional studies were included in the indirect comparisons.

As stated above the excluded studies (reported in Table 7) were excluded from the ITC as they did not report useable data or could not form a network to allow analysis. The studies excluded were not included in the indirect comparison.

c. Please clarify the reason for excluding the TAX 317 study.

The patient population assessed in TAX 317 was unclear to be of squamous, non-squamous, or mixed histology; therefore, this study was not considered in the analysis. Moreover data for docetaxel was available from Checkmate 017 study.

d. Appendix 7.11 lists 29 studies included in the review that are not relevant to the decision problem, but does not explicitly state why these studies were excluded. Page 38 of the submission states: "29 studies included either non-squamous patients, or patients with mixed histology but with no sub-group data for the squamous population, and were therefore not considered relevant to the decision problem". Please confirm that this is the reason the studies listed in appendix 7.11 were excluded.

Yes, the reason for the exclusion from the analysis was either that these studies included non-squamous patients or patients with mixed histology, with no subgroup data for squamous population.

Other studies

A13. Page 106 of the submission states that [redacted]. Please provide a summary of these results.

CheckMate 153 is an ongoing single arm study evaluating the long-term safety and tolerability of nivolumab in patient with advanced/metastatic NSCLC previous treated with systemic chemotherapy. This study included both squamous and non-squamous NSCLC patients.

Patients in this study were treated until disease progression or for a maximum of 1 year. Patients who remained progression free at 1 year were randomised to one of two cohorts. Cohort A continued to receive nivolumab until disease progression and Cohort B stopped receiving nivolumab at 1 year but could be re-treated with nivolumab upon disease progression.

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A total of 824 patients were treated with nivolumab; 65 patients (8%) had an ECOG PS 2. A subgroup analysis of squamous only NSCLC was not available. Results presented here are a pooled analysis of both squamous and non-squamous patients. As of 31 December 2014, 59% of patients remained on treatment. The most common reason for treatment discontinuation was progressive disease (24%) (Table 8). Across all patients, 93% experienced an adverse event; 38% had Grade 3 or 4 events and 5% had a Grade 3 or 4 Select AE (Table 9). Select AEs are presented by organ category and ECOG PS in Table 10. ECOG PS 2 patients experienced a higher rate of SAEs, but a similar incidence of treatment-related AEs or SAEs compared with ECOG PS 0–1 patients and no grade 5 treatment-related AE or SAE events. Six patients (0.8%) experienced drug-related pneumonitis (any grade).

The safety data from CheckMate 153 are consistent with results from other clinical trials of nivolumab in NSCLC and more specifically for patients with squamous NSCLC. No new safety signals were identified.

A subgroup analysis of safety data by ECOG PS status showed that the frequency of treatment-related SAEs and select AEs was similar between patients with ECOG PS 0-1 and ECOG PS 2.

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Table 8: CheckMate 153 - Summary of deaths and treatment discontinuations

Characteristics	Nivolumab 3 mg/kg N = 824
Patients treated, n	824
Patients still on treatment, n (%)	483 (59)
Patients off treatment, n (%)	341 (41)
Reason off treatment, n (%)	
Progressive disease	195 (24)
Death	56 (7)
Other	28 (3)
Patient request to discontinue study treatment	21 (3)
Patient withdrew consent	19 (2)
Patient no longer meets study criteria	9 (1)
Adverse event unrelated to study drug	6 (<1)
Study drug toxicity	5 (<1)
Maximum clinical benefit	1 (<1)
Not reported	1 (<1)
Total patients who died, n (%)	182 (22)
Disease-related	156 (19)
Other [a]	18 (2)
Unknown	8 (1)
Study drug toxicity	0

[a] other includes: respiratory failure due to multifactorial etiology; hypoxic respiratory failure; cardiac arrest, myocardial infarction, congestive heart failure; pulmonary embolism; cardiopulmonary failure; suicide; aspiration respiratory failure; intracranial hemorrhage; hypotension; disease progression; respiratory arrest, and pneumonia

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Table 9: CheckMate 153 - Summary of adverse events

	Nivolumab 3 mg/kg N=824		Nivolumab 3 mg/kg ECOG PS 0-1 (n = 742)		Nivolumab 3 mg/kg ECOG PS 2 (n = 65)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
All adverse events	762 (93)	311 (38)	683 (92)	268 (36)	62 (95)	33 (51)
All serious adverse events (SAEs)	309 (38)	223 (27)	257 (35)	185 (25)	42 (65)	29 (45)
All select adverse events	282 (34)	37 (5)	253 (34)	32 (4)	22 (34)	3 (5)
All treatment-related adverse events	439 (53)	59 (7)	403 (54)	52 (7)	27 (42)	4 (6)
All treatment-related SAEs	23 (3)	19 (2)	18 (2)	14 (2)	3 (5)	3 (5)
All treatment-related select AEs	199 (24)	20 (2)	181 (24)	16 (2)	14 (22)	2 (3)
All AEs leading to discontinuation	87 (11)	53 (6)	69 (9)	42 (6)	16 (25)	9 (14)
All treatment-related SAEs leading to discontinuation	14 (2)	12 (2)	11 (2)	9 (1)	2 (3)	2 (3)
All treatment-related select AEs leading to discontinuation	12 (2)	11 (1)	9 (1)	8 (1)	2 (3)	2 (3)

[a] G-bacteraemia, pleural effusion, pneumothorax, or tumour progression. This patient's death was classified as 'Other-Multifactorial' by the investigator.

Table 10: CheckMate 153 - Summary of treatment-related Select AEs by ECOG PS

	ECOG PS 0-1 Nivolumab 3 mg/kg, n = 742		ECOG PS 2 Nivolumab 3 mg/kg n = 65	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Skin disorders	**69 (9.3)**	**3 (0.4)**	**6 (9.2)**	**1 (1.5)**
Rash	14 (1.9)	0	1 (1.5)	0
GI disorders	50 (6.7)	3 (0.4)	4 (6.2)	0
Diarrhoea	48 (6.5)	2 (0.3)	4 (6.2)	0
Enterocolitis	1 (0.1)	1 (0.1)	0	0
Endocrine disorders	**37 (5.0)**	**2 (0.3)**	**1 (1.5)**	**0**
Hypothyroidism	28 (3.8)	1 (0.1)	0	0
Hyperthyroidism	8 (1.1)	1 (0.1)	0	0
Blood thyroid-stimulating hormone increased	0	0	1 (1.5)	0
Hepatic disorders	**26 (3.5)**	**4 (0.5)**	**2 (3.1)**	**1 (1.5)**
Autoimmune hepatitis	1 (0.1)	1 (0.1)	0	0
Hepatotoxicity	0	0	1 (1.5)	1 (1.5)
Infusion reaction	**8 (1.1)**	**2 (0.3)**	**1 (1.5)**	**0**
Hypersensitivity	2 (0.3)	0	0	0
Respiratory disorders	**6 (0.8)**	**2 (0.3)**	**0**	**0**
Pneumonitis	6 (0.8)	2 (0.3)	0	0
Renal disorders	**2 (0.3)**	**0**	**0**	**0**
Interstitial nephritis	0	0	0	0

Section B: Clarification on decision model parameters and cost-effectiveness data

B1. **Priority question.** Please provide the following Kaplan-Meier analyses (a, b and c below), to the following specification:

This analysis request is currently on-going and the results for this analysis were unavailable in time for the response due date. BMS are fully committed to provide this information as soon as this analysis has been completed (anticipated by Oct 2nd 2015).

Population: ITT population including all patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off; i.e. *not* when last known to be alive (OS and post-progression survival [PPS]), and *not* at the date of last tumour assessment (PFS).

Trial data set: CheckMate 017, [redacted] data cut (if available, otherwise the most recent data).

a. Time to death from any cause (OS), time to disease progression or death based on investigator assessment (investigator-assessed PFS), and time from disease progression by investigator assessment to death from any cause (PPS), stratified by treatment arm (nivolumab vs docetaxel).

All information presented in these figures are considered commercial in confidence

Figure 1: CheckMate 017 - Kaplan-Meier OS plot – all randomised patients in the trial (30 July 2015 data cut-off)

Figure 2: CheckMate 017 - Kaplan-Meier PFS plot – all randomised patients in the trial (30 July 2015 data cut-off)

[redacted]

[redacted]

Figure 3: CheckMate 017 - Kaplan-Meier PPS plot – all randomised patients in the trial (30 July 2015 data cut-off)

b. Time to treatment discontinuation, stratified by treatment arm (nivolumab vs docetaxel).

All information presented in these figures are considered commercial in confidence

Figure 4: CheckMate 017 - Kaplan-Meier time to treatment discontinuation plot – all randomised patients in the trial (30 July 2015 data cut-off)

c. Time to death from any cause (OS), time to disease progression or death based on investigator assessment (investigator-assessed PFS), and time from disease progression by investigator assessment to death from any cause (PPS), for patients randomised to the nivolumab treatment arm *excluding* all patients who continued to receive nivolumab beyond investigator assessed disease progression.

All information presented in these figures are considered commercial in confidence

Figure 5: CheckMate 017 - Kaplan-Meier OS plot – all randomised patients in the trial excluding patients who continued to receive nivolumab beyond investigator assessed disease progression (30 July 2015 data cut-off)

Figure 6: CheckMate 017 - Kaplan-Meier OS plot – all randomised patients in the trial excluding patients who continued to receive nivolumab beyond investigator assessed disease progression (30 July 2015 data cut-off)

Figure 7: CheckMate 017 - Kaplan-Meier Post-Progression Survival plot – all randomised patients in the trial excluding patients who continued to receive nivolumab beyond investigator assessed disease progression (30 July 2015 data cut-off)

Please present analysis outputs using the following format:

The following analysis was unavailable in the timeframe but will be forwarded as soon as it becomes available.

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

B1. **Priority request.** Please provide results for EQ-5D utility scores (using the UK value set) in the CheckMate 017 trial ([redacted] data cut if available, otherwise the most recent data), showing the number of valid patient responses, and the mean and standard deviation of the EQ-5D values at each observation cycle stratified by treatment (nivolumab vs docetaxel) and health state (PFS vs PD).

Please note that an analysis of the utility data from the 30 July 2015 data set was not possible within the timeframe of the response. Data presented in Table 11 are EQ-5D utility scores at each observation cycle stratified by treatment and health state.

Whilst better utility index scores for PD were observed in the docetaxel arm compared to nivolumab, this might be explained by the adverse events associated with docetaxel treatment. This toxicity may mask general health status thus when treatment is stopped health status is no longer impacted by toxicity. For subjects on docetaxel, toxicity is generally high. Once a subject progresses and comes off the drug, the toxicity is not then captured in their health status, resulting in higher scores for PD subjects on docetaxel when compared to nivolumab which has less toxicity.

Table 11: EQ-5D Utility Index by Tumour Response (PF/PD) in the overall sample (using UK value set)

	Nivolumab ([redacted])		Docetaxel ([redacted])	
	Progression-Free[1] ([redacted])	Progression of Disease (N=5)	Progression-Free[1] ([redacted])	Progression of Disease ([redacted])
Baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 3				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 4				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 6				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 8				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 9				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 12				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 15				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 16				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 18				
N			[redacted]	
Mean (SD)			[redacted]	
Week 20				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 21				

N			[redacted]	
Mean (SD)			[redacted]	
Week 24				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 30				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 36				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 42				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 54				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 60				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 66				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 72				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 78				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 84				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 96				
N	[redacted]			
Mean (SD)	[redacted]			
Follow-up 1				

N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 2				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 1				
N		[redacted]	[redacted]	[redacted]
Mean (SD)		[redacted]	[redacted]	[redacted]
Survival Follow-up 2				
N		[redacted]	[redacted]	
Mean (SD)		[redacted]	[redacted]	
Survival Follow-Up 4				
N			[redacted]	
Mean (SD)			[redacted]	
Survival Follow-Up 6				
N			[redacted]	
Mean (SD)			[redacted]	

B2. **Priority request.** Please repeat the analyses in question B2, for each of three subgroups defined by country of origin:

a. USA and Canada (27 sites with 86 patients)

b. Europe (51 sites with 155 patients)

c. Other (13 sites with 31 patients from Central & South America and Australia)

Please note that an analysis of the utility data from the 30 July 2015 data set was not possible within the timeframe of the responses. Data presented in Table 12, Table 13 and Table 14 are EQ-5D utility scores at each observation cycle stratified by treatment and health state sub-grouped by USA and Canada, Europe and Other, respectively.

The number of patients within each subgroup differ to the numbers provided above for each region. The reason for this is that the sample consists of patients not missing tumour response and EQ-5D data. As PD and PF category changes with time the N values provided in the header are based on the number of patients who had EQ-5D values and tumour response data available at baseline. Some patients who were missing either EQ-5D values or tumour response data at baseline may have been included at later timepoints if they had appropriate data.

Table 12: Subgroup analysis: EQ-5D Utility Index by Tumour Response (PF/PD) in the US/Canada sample

	Nivolumab [redacted]		Docetaxel [redacted]	
	Progression-Free[1] [redacted]	Progression of Disease [redacted]	Progression-Free[1] [redacted]	Progression of Disease [redacted]
Baseline				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 3				
N			[redacted]	
Mean (SD)			[redacted]	
Week 4				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 6				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 8				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 9				
N			[redacted]	
Mean (SD)			[redacted]	
Week 12				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 15				
N			[redacted]	
Mean (SD)			[redacted]	
Week 16				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 18				
N			[redacted]	
Mean (SD)			[redacted]	
Week 20				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		

Week 21				
N			[redacted]	
Mean (SD)			[redacted]	
Week 24				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 30				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 36				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 42				
N	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Week 48				
N	[redacted]			
Mean (SD)	[redacted]			
Week 54				
N	[redacted]			
Mean (SD)	[redacted]			
Week 60				
N	[redacted]			
Mean (SD)	[redacted]			
Week 66				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 72				
N	[redacted]			
Mean (SD)	[redacted]			
Week 78				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 84				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Follow-up 1				
N		[redacted]	[redacted]	[redacted]

Mean (SD)		[redacted]	[redacted]	[redacted]
Follow-up 2				
N		[redacted]	[redacted]	[redacted]
Mean (SD)		[redacted]	[redacted]	[redacted]
Survival Follow-up 1				
N		[redacted]	[redacted]	
Mean (SD)		[redacted]	[redacted]	
Survival Follow-up 2				
N		[redacted]	[redacted]	
Mean (SD)		[redacted]	[redacted]	
Survival Follow-Up 4				
N			[redacted]	
Mean (SD)			[redacted]	
Survival Follow-Up 6				
N			[redacted]	
Mean (SD)			[redacted]	

Note: The analysis sample includes all subjects with EQ-5D Utility Index scores and tumour response data.

[1] PF includes the tumour response categories of stable disease (SD), partial response (PR) and complete response (CR).

Table 13: Subgroup analysis: EQ-5D Utility Index by Tumour Response (PF/PD) in the Europe sample

	Nivolumab [redacted]		[redacted]	
	Progression-Free[1] [redacted]	Progression of Disease [redacted]	Progression-Free[1] [redacted]	Progression of Disease [redacted]
Baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 3				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 4				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 6				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 8				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 9				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 12				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 15				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 16				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 18				
N			[redacted]	
Mean (SD)			[redacted]	
Week 20				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 21				

N			[redacted]	
Mean (SD)			[redacted]	
Week 24				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 30				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 36				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 42				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 48				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 54				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 60				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 66				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 72				
N	[redacted]			
Mean (SD)	[redacted]			
Week 78				
N	[redacted]			
Mean (SD)	[redacted]			
Week 84				
N	[redacted]			
Mean (SD)	[redacted]			
Week 96				
N	[redacted]			
Mean (SD)	[redacted]			
Follow-up 1				

N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 2				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 1				
N		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]

Note: The analysis sample includes all subjects with EQ-5D Utility Index scores and tumour response data.

[1] PF includes the tumour response categories of stable disease (SD), partial response (PR) and complete response (CR).

Table 14: Subgroup analysis: EQ-5D Utility Index by Tumour Response (PF/PD) in the Rest of the World sample

	Nivolumab [redacted]		Docetaxel [redacted]	
	Progression-Free[1] [redacted]	Progression of Disease [redacted]	Progression-Free[1] [redacted]	Progression of Disease [redacted]
Baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 3				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 4				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 6				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 8				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 9				
N			[redacted]	
Mean (SD)			[redacted]	
Week 12				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 15				
N			[redacted]	[redacted]
Mean (SD)			[redacted]	[redacted]
Week 16				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 18				
N			[redacted]	
Mean (SD)			[redacted]	
Week 20				
N	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Week 21				
N			[redacted]	
Mean (SD)			[redacted]	
Week 24				
N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 30				

N	[redacted]	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 36				
N	[redacted]		[redacted]	[redacted]
Mean (SD)	[redacted]		[redacted]	[redacted]
Week 42				
N	[redacted]		[redacted]	[redacted]
Mean (SD)	[redacted]		[redacted]	[redacted]
Week 48				
N	[redacted]		[redacted]	[redacted]
Mean (SD)	[redacted]		[redacted]	[redacted]
Week 54				
N	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Week 60				
N			[redacted]	
Mean (SD)			[redacted]	
Week 66				
N	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Week 72				
N	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Week 78				
N			[redacted]	
Mean (SD)			[redacted]	
Week 84				
N			[redacted]	
Mean (SD)			[redacted]	
Follow-up 1				
N		[redacted]	[redacted]	[redacted]
Mean (SD)		[redacted]	[redacted]	[redacted]
Follow-up 2				
N		[redacted]		[redacted]
Mean (SD)		[redacted]		[redacted]
Survival Follow-up 1				
N				[redacted]
Mean (SD)				[redacted]

B5. Please provide additional details of the assumptions used in the scenario analyses using 1-year and 2-year treatment discontinuation rules.

a. What assumptions about clinical effectiveness (for example, survival, adverse events) were made? Please provide justifications for each assumption.

The scenario presented is a treatment discontinuation rule where treatment is discontinued only for nivolumab with no impact on clinical efficacy. It is assumed that clinical efficacy of nivolumab is retained for the full time horizon of the analysis, based on the survival estimates of OS and PFS used in the base-case analysis. No adjustments were made for adverse events and the costs of adverse event management in both arms remain unaffected when treatment discontinuation rules are applied.

In patients who experience a durable response, it may be feasible to stop nivolumab treatment before they progress and still maintain clinical benefit. Evidence to support this approach can be seen in study CheckMate 003, which had a 96-week stopping rule (Gettinger 2015). This is the only study of nivolumab in lung cancer to use anything other than a treat-to-progression regimen. In this study, [redacted] responders stopped nivolumab at the pre-defined stopping point of 96 weeks. In each of these responders, there was a significant ongoing response beyond 96 weeks (indeed, at the last analysis, six of the seven responders had not progressed), demonstrating an ongoing clinical benefit despite withdrawal of nivolumab, and supporting the hypothesis that stopping nivolumab treatment at a pre-defined time point may be feasible.

BMS are committed to addressing the question of optimal duration of treatment of nivolumab in lung cancer through planned studies. These include the Phase III CheckMate 153 safety CheckMate 153, in which responders are randomised at 1 year to either stop nivolumab or to continue nivolumab treatment until progression. Data from CheckMate 153 will be available in 2017.

Based on the projected availability of these data, and the evidence from study CheckMate 003, both 1-year and a 2-year stopping rules have been included in scenario analyses to investigate the impact of these on the cost-effectiveness of nivolumab.

b. Was a stopping rule applied to the docetaxel arm?

No, treatment stopping rules were not applied to the docetaxel arm.

Section C: Textual clarifications, references and additional points

C1. The submission states that data from studies included in its systematic review were extracted and assessed for risk of bias by two independent reviewers. Please clarify whether a similar method was applied to study selection.

Yes, a similar method was also applied for study selection, where two independent reviewers screened the studies with any discrepancies being resolved by a third independent reviewer.

C2. The submission states that the use of erlotinib is declining. Please provide evidence to support this statement.

To support our claim of declining use of erlotinib in the UK please see Figure 8. This graph shows docetaxel as the leading second line treatment in patients with NQ NSCLC since Q3 2014. Furthermore is shows a steady decline in the use of erlotinib

during this period. The source of these data is internal research from the Ipsos EU Oncology Monitor.

Figure 8: Top five second-line treatment regimens in the UK for SQ NSCLC Stage IIIb/IV

C3. Please provide the following references cited in the CSR for CheckMate 017:

a. Adverse Event Domain Requirements Specification. Bristol Myers Squibb Co. PRI. Version 2.1. April 23, 2012.

Reference has been provided

b. Non-Study Medication Domain Requirements Specification. Bristol Myers Squibb Co. PRI. Version 2.2 April 24, 2012

Reference has been provided

C4. Please confirm whether the results of the economic model (presented in sections 5.7 and 5.8 of the submission) include discounting for total costs, total life years gained and total QALYs.

Costs and QALYs are discounted at 3.5% and LYG are discounted at 0%.

References

Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, et al. (2015) Nivolumab Versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 373(2): 123-135.

Bristol-Myers Squibb. (2015) Nivolumab: Final Clinical Study Report for Study CA209017; An Open-label Randomized Phase III Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC) (DCN:930086504); Report dated 26 Feburary 2015.

Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, et al. (2015) Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 33(18): 2004-2012.

Reckamp KL, Spigel DR, Rizvi NA, Poddubskaya E, West HJ, et al. (2015) Phase 3, Global, Randomized Trial (CheckMate 017) of Nivolumab vs Docetaxel in Advanced Squamous (SQ) Cell Non-Small Cell Lung Cancer (NSCLC). 16th World Conference on Lung Cancer Denver, CO, USA.

Submission from **Roy Castle Lung Cancer Foundation,** for consideration by NICE, in their review of **Nivolumab** in the treatment of previously treated locally advanced or metastatic squamous cell Non Small Cell Lung Cancer [**ID811**].

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being only 7%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of squamous cell Non Small Cell Lung Cancer (NSCLC).

General Points

1. The current outlook for patients with relapsed squamous cell NSCLC is poor. In this scenario, improving quality of life and even small extensions in duration of life are of considerable significance to the individual and their family.

2. Active treatment options, after previous chemotherapy treatment, are limited in this patient group. Outcomes remain relatively poor from traditional second line chemotherapy, with many patients being unable to tolerate the side effects. There is, therefore, massive unmet need in this patient group.

3. The issue of "inverse weighting for duration of life" must be stressed. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this situation

4. Improvement in symptoms. Patients with relapsed squamous cell NSCLC are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief. The reality, however, is that few active options currently exist.

This Product

1. New and Innovative Therapy
   Nivolumab is the first Immunotherapy agent to be licenced for use in lung cancer patients. These agents work by harnessing the ability of the immune system to find and fight cancer. Nivolumab is a PD-1 (Programmed Death-1) Immune Checkpoint Inhibitor. This development represents a major milestone in the treatment of this disease.

2. Improvement in survival
   We do not have any information or trial data for this therapy, beyond that which is published and publicly available. However, we note, from the Phase III, CheckMate-017 Study, published in the New England Journal of Medicine, comparing Nivolumab with Docetaxel, that, in previously treated advanced squamous cell NSCLC patients, overall one year survival rate for Nivolumab was 42%, compared with 24% for Docetaxel. Also, that median overall survival for Nivolumab was observed at 9.2 months, compared with 6 months in the Docetaxel arm. Patients with relapsed advanced/metastatic squamous cell NSCLC are a group with significant unmet medical need. Thus, existing chemotherapy has provided these patients with a modest improvement in survival. Nivolumab, however, provides an additional option which can significantly extend survival.

3. Side effects
   Nivolumab is administered as a two weekly intravenous injection.

   We understand that where side effects occur, for the majority of patients, these are mild to moderate. The most common side effects associated with Nivolumab include fatigue, shortness of breath, decreased appetite, pain, cough, nausea and constipation. More serious side effects, though uncommon, can occur if the immune system attacks healthy tissues in the body, such as the lungs, colon, liver, kidneys or hormone producing glands. In the anecdotal patient experience reported to us, it appears well tolerated – in particular, when compared with current standard second line cytotoxic therapy for NSCLC.

4. As noted above, even relatively small benefits can be disproportionately large for patients.

   Our observations come from a combination of one-to-one discussion with lung cancer patients, published research and our patient information helpline.

In summary

Patients with advanced and metastatic lung cancer, which have relapsed after chemotherapy are in a particularly devastating situation. With the currently recommended options, the outlook for the majority is poor. It is for this reason that the availability of additional options is very important. Nivolumab represents a new and innovative therapy option, for this patient group.

[redacted], RCLCF.

July 2015.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Thoracic Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify) **Representative of BTS**

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The British Thoracic Society supports the introduction of this new technology.
We note that data presented at the American Society for Clinical Oncology (ASCO) suggested that Nivolumab increased overall survival (OS) from 8 to 19 months when compared to docetaxal in the second line setting.

We note that this cost of this technology is likely to be an issue.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], [redacted] submitting comments on behalf of:

Name of your organisation: NCRI/RCP/RCR/ACP

Comments coordinated by [redacted]

Are you (tick all that apply):

-

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

What is the expected place of the technology in current practice?

There a number of NICE approved systemic treatment options for patients requiring second line treatment having progressed after primary chemotherapy. These options are of limited effectiveness which will mean there is variation of practice across the UK particular as this area was not reviewed in the updated Management of Lung Cancer guideline 2011.

Clinical trial data indicates that Nivolumab is a more effective systemic treatment option than the currently available standards for patients with squamous lung cancer. Internationally it is expected that it will be offered as a treatment option, once licenced, and in due course is likely to replace docetaxel as an internationally recognised standard of care.

This treatment would need to be delivered through specialist Lung Cancer Oncology Clinics / chemotherapy units.

The advantages and disadvantages of the technology

Clinical trial conditions were consistent with those of standard NHS practice.

The complexity of treatment delivery will be similar to the current standard chemotherapy treatments.

The side effect profile is different to standard chemotherapy treatment and will require some (relatively minor) modifications for treatment assessment and follow up. There will be a training requirement so that staff becomes familiar with the management of the side effect profile. This is currently occurring as other drugs in this class have been introduced into standard clinical practice in other tumour sites.

Any additional sources of evidence

Nil to add

Implementation issues

See above

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

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To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] [redacted]

Name of your organisation:
Are you (tick all that apply): National Lung cancer Forum for Nurses

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect

current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix D – Clinical Expert statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Sanjay Popat

Name of your organisation: RCP/NCRI/BTOG
Are you (tick all that apply):

- √ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Appendix D – Clinical Expert statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Metastatic squamous NSCLC is currently treated by oncologists in hospitals usually with either docetaxel chemotherapy, erlotinib, within their licensed indications, or best supportive care. Both docetaxel and erlotinib have limited activity in relapsed NSCLC. Docetaxel has marked toxicities and required patients to be PS 0/1 to tolerate it. One hospital audit demonstrated 40% readmission rates after docetaxel use. Docetaxel is intravenous chemotherapy and is administered on the chemotherapy unit, whilst erlotinib is oral therapy that is usually prescribed in clinic and taken at home daily by the patient.

It is likely that nivolumab would be used in place of docetaxel or erlotinib in relapsed squamous NSCLC. Nivolumab is administered every two weeks intravenously. It is currently only administered in hospital after clinician review of the patient. The drug has had limited use in the UK prior to this submission through clinical trials, a manufacturer's named patient programme and through the EAMS programme.

Nivolumab would currently only be used within its licensed indication. Due to the recent EMA license no current EU guidelines currently recommend nivolumab within the licensed indication. However, in the US, where nivolumab was licensed earlier, the NCCN guidelines do recommend nivolumab use within the licensed indication.

Appendix D – Clinical Expert statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Nivolumab is associated with marked increased anti-cancer activity over docetaxel both in terms of responses, duration of responses and importantly, improving overall survival. This is supported by improvements in quality-of-life over docetaxel. The toxicity profile of nivolumab is generally much better than that of docetaxel. The toxicities with nivolumab are very different to that with docetaxel with a variety of immune-mediated toxicities identified including colitis, for which some education of treating oncologists would be required. This is already being performed by specialist societies, the manufacturer, and peers. Additional tests are not required for nivolumab usage, although the management of toxicities may require additional clinical expertise. Nivolumab is administered every 2 weeks intravenously compared with every 3 weeks intravenously for docetaxel and orally at home for erlotinib. Nivolumab will therefore require additional capacity in oncology day-units. Nivolumab is also given until time of progression, significant toxicity, or clinician/patient decision. Docetaxel is approved to be given similarly but in routine practice tends to be given for 4-6 cycles (3-4 months).

We have no current data on the activity of nivolumab in routine clinical practice compared to that from trials.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

The outcomes measured in the nivolumab trials (overall survival, progression free survival, response rates, toxicity, quality of life) are all appropriate.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Evidence for nivolumab activity will be presented at the major oncology congresses: ASCO, ESMO/ECCC, IASLC.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The infrastructure for delivery of nivolumab already exists.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

I am not aware of any equality-related issues

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Carol A Davies
Name of your nominating organisation: NLCFN
Do you know if your nominating organisation has submitted a statement?

☐ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☐ No

- a patient organisation employee or volunteer?
-

☐ Yes ✓ ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☐ ✓ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:
the course and/or outcome of the condition ✓
•
physical symptoms ✓
•
Pain ✓
•
• level of disability
• mental health
quality of life (such as lifestyle and work) ✓
•
other people (for example, family, friends and employers) ✓
•
• ease of use (for example, tablets rather than injection)
• where the treatment has to be used (for example, at home rather than in hospital)
• any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Increased overall survival & reduction in side effects than that of standard treatments

Please explain any advantages that you think this treatment has over other NHS treatments in England.

As above

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being

appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ✓
☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

No experience

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐✓
No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

☐ ✓

Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Survival benefit
- Less toxicities
- Suitable for use in some individuals who would not tolerate chemotherapy
-
-
-
-

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Roy Castle Lung Foundation and consequently I will not be submitting a personal statement.

Name: .....JESME FOX.....

Signed: .....*J Fox*.....

Date: .....19th October 2015.....

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated locally advanced or metastatic squamous non-small cell lung cancer [ID811]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/05

Completed 21 October 2015

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Nivolumab for previously treated locally advanced or metastatic squamous non-small cell lung cancer [ID811]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

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Correspondence to: Nigel Fleeman, Research Fellow, LR*i*G, University of Liverpool, Room 2.10, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 21 October 2015

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Declared competing interests of the authors: None.

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Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Fleeman N	Project lead, critical appraisal of clinical evidence, drafted clinical results section and supervised the final report
Bagust A	Critique of economic model and proposal of alternative interpretations of the evidence
Richardson M	Critical appraisal of the statistical evidence
Boland A	Critical appraisal of clinical and economic evidence
Beale S	Critical appraisal of the submission
Stainthorpe A	Critique of the economic model
Abdulla A	Summary and critical appraisal of economic evidence
Krishan A	Critical appraisal of the statistical evidence
Kotas E	Cross checking of the submission search strategy
McEntee J	Critical appraisal of the submission
Greystoke A	Clinical advice and critical appraisal of the submission

All authors read and commented on draft versions of the ERG report.

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
AIC	Akaike information criteria
ALK	anaplastic lymphoma kinase
ASBI	Average Symptom Burden Index
AST	aspartate transaminase
AUC	area under the curve
BIC	Bayesian information criteria
BMS	Bristol-Myers Squibbb
BSA	body surface area
BSC	best supportive care
CEAC	cost effectiveness acceptability curve
CI	confidence interval
CNS	central nervous system
CS	company's submission
CTCAE	Common Terminology Criteria for Adverse Events
CSR	clinical study report
DMC	Data Monitoring Committee
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EPAR	European Public Assessment Report
EMA	European Medicines Agency
EQ-5D	EuroQol-5 dimensions (questionnaire)
EQ-VAS	EuorQol – visual analogue scale
ERG	Evidence Review Group
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost effectiveness ratio
irAE	immune related adverse events
ITC	indirect treatment comparison
ITT	intention-to-treat
K-M	Kaplan-Meier
LCSS	Lung Cancer Symptom Scale
NCLA	National Lung Cancer Audit
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PF	progression-free
PFS	progression-free survival
PPS	post-progression survival
PS	performance status
PSA	probabilistic sensitivity analysis
Q2W	every 2 weeks
Q3W	every 3 weeks
QALY	quality adjusted life year

RCT	randomised controlled trial
RECIST	Response Evaluation in Solid Tumours
SACT	Systemic Anti-Cancer Therapy
SAEs	serious adverse events
SEER	Surveillance, Epidemiology and End Results Program
SmPC	summary of product characteristics
STA	single technology appraisal
TSAP	trial statistical analysis plan
TTD	time to treatment discontinuation
TTR	time to response

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by the company (Bristol-Myers Squibb [BMS]) in support of the use of nivolumab (current brand name: Nivolumab BMS; brand name expected to change at the end of 2015 to Opdivo®) for people with previously treated locally advanced or metastatic squamous non-small cell lung cancer (NSCLC). Nivolumab is an immuno-oncology therapy with a different mechanism of action to that of conventional anti-cancer therapies such as docetaxel (Nivolumab is a programmed death-1 [PD-1] inhibitor). The European Medicines Agency (EMA) granted nivolumab a marketing authorisation on 20 July 2015 for the treatment of patients with locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults. The company estimates that if recommended by NICE, around 850 patients would be eligible for treatment with nivolumab according to its marketing indication each year.

1.1 Critique of the decision problem in the company's submission

The patient populations identified in the NICE scope, in the company submission (CS) and in the licensed indication are similar: patients with previously treated locally advanced or metastatic squamous NSCLC. The company presents clinical evidence from the pivotal CheckMate 017 trial to support the use of nivolumab in this patient population. The ERG notes that the inclusion criteria used in CheckMate 017 prevented the following groups of patients from entering the trial: patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) >1, patients with autoimmune disease and patients using higher-dose corticosteroids (>10mg prednisone). There is, therefore, no clinical evidence to support treating these patients with nivolumab. Patients with ECOG PS >1 in particular, and patients using higher-dose corticosteroids may constitute some patients who would be seen in clinical practice in England.

The comparators specified in the NICE scope are docetaxel, erlotinib and best supportive care (BSC). The company considers that docetaxel is the most relevant comparator and used direct results from CheckMate 017 to provide clinical and cost effectiveness evidence of nivolumab versus docetaxel. The company carried out indirect treatment comparisons (ITCs) to compare nivolumab with erlotinib and nivolumab with BSC.

The ERG considers that all three comparators listed in the scope are relevant. However, based on expert clinical advice and market share estimates, the ERG considers that

docetaxel is the current standard of care in clinical practice in England and is therefore the most relevant comparator for this group of patients.

Clinical evidence is provided in the CS for all five outcomes specified in the NICE scope: overall survival (OS), progression-free survival (PFS), response rates (reported as overall response rates [ORR], duration of response [DoR] and time to response [TTR]), adverse events (AEs) and health related quality of life (HRQoL).

The ERG notes that the CheckMate 017 trial was stopped early for OS benefit in patients treated with nivolumab on the recommendation of the Data Monitoring Committee (DMC) at the time of the planned 12-month interim OS analysis (December 2014 data-cut); OS, PFS, ORR, DoR, TTR, AE and HRQoL data from the 12-month analyses are reported in the CS. During clarification, the company also provided PFS and OS data from the planned 18-month interim analysis ([redacted] data-cut); these data support the DMC's decision to stop the trial for benefit.

Health related quality of life data were collected during Checkmate 017 using the Lung Cancer Symptom Scale (LCSS), EuroQol 5-Dimensions utility index (EQ-5D) and visual analogue scale (EQ-VAS). These data are reported in the CS.

The company's base case cost effectiveness analysis, which is presented in the main body of the CS, compares nivolumab with docetaxel. The company also carried out a scenario analysis comparing nivolumab with erlotinib; the cost effectiveness results for this analysis are reported in the Appendices of the CS. The company did not carry out a cost effectiveness analysis of nivolumab versus BSC.

1.2 Summary of clinical effectiveness evidence submitted by the company

1.2.1 Direct evidence

The company carried out a broad search of the literature; only one randomised controlled trial (RCT) (CheckMate 017) included a comparison with nivolumab. In the CheckMate 017 trial, nivolumab 3mg/kg every two weeks (Q2W) was compared with docetaxel 75mg/m^2 every three weeks (Q3W) in patients with squamous NSCLC; 135 patients were randomised to nivolumab and 137 patients were randomised to docetaxel. All of the patients in the CheckMate 017 trial had received prior treatment with platinum doublet chemotherapy.

At the [redacted] data-cut, the OS data show a statistically significant treatment effect for nivolumab compared with docetaxel (HR=0.62; 95% CI 0.48 to 0.81, p=0.0004). The

difference in median OS between the trial arms also indicates an important treatment effect for nivolumab versus docetaxel (9.2 months vs 6 months). Similar findings were reported at the December 2014 data-cut. The OS rates (i.e. patients still alive) at 18 months were 28% for patients treated with nivolumab and 13% for patients treated with docetaxel.

PFS was measured by investigator assessment using the Response Evaluation Criteria in Solid Tumours (RECIST) (1.1). The data indicate a statistically significant effect for nivolumab compared with docetaxel (HR=0.63; 95% CI 0.48 to 0.83, p<0.0008); median PFS was however similar (3.5 vs 2.8 months respectively). Similar findings were reported at the December 2014 data-cut. Median PFS is skewed by the first radiological assessment occurring after 9 weeks. Hence the proportional hazards assumption does not hold for PFS. After 18 months, 17% of patients in the nivolumab arm were progression-free compared with 2.7% in the docetaxel arm.

Tumour response findings were only provided for the December 2014 data-cut. The ORR (20%) in the nivolumab arm was double the rate in the docetaxel arm (9%). Median DoR was not reached in either arm but both the minimum and maximum values of the range were higher in the nivolumab arm than in the docetaxel arm. Median TTR was similar for both treatments (around 2 months).

The majority of subgroup analyses results (including programmed death-ligand 1 [PD-L1] status) also appeared to favour nivolumab with the exception of patients over the age of 75 and patients grouped as 'Rest of the World' (i.e. Argentina, Australia, Chile, Mexico, and Peru) where the findings appeared to favour docetaxel. In both subgroups, confidence intervals were wide and crossed 1 due to small sample sizes (n=29 and n=31 respectively) therefore numbers of events were few. For PFS, similar findings were reported with docetaxel appearing to be most beneficial only for patients over the age of 75. [redacted] the results suggested that patients aged 75 years and over experience no treatment benefit from nivolumab over docetaxel (HR=1.85; 95% 0.76 to 4.51; p=0.0098). In subgroup analyses conducted by PD-L1 status, ORR was higher in patients treated with nivolumab than with docetaxel regardless of PD-L1 status. No other subgroup analyses were conducted for tumour response.

The AE rates from the CheckMate 017 trial indicate that treatment with nivolumab is associated with a more favourable safety profile than treatment with docetaxel. All drug-related AEs, including drug-related serious AEs and drug-related AEs leading to treatment discontinuation were less common in the nivolumab arm. The company also provided data

for ‘Select AEs’ (which are those caused by the immune system and are directly due to the immunologic mode of action of nivolumab) and the proportions of patients with Select AEs were shown to be similar in both arms of the CheckMate 017 trial. The EMA has stipulated that these AEs must continue to be monitored using post-marketing surveillance studies.

Statistically significant and clinically meaningful improvements in HRQoL were reported over time in the nivolumab arm but not the docetaxel arm: from Week 12 through Week 54 for LCSS ASBI, from Weeks 42 to 54 for EQ-5D utility index scores and from Weeks 24 to 36 and at Week 48 for EQ-VAS. In both the nivolumab and docetaxel arms, treatment discontinuation was observed to be associated with a worsening in HRQoL as measured by the LCSS ASBI scores at the two follow-up visits; [redacted] After treatment discontinuation, no statistically significant differences in EQ-5D utility index or EQ-VAS were reported in the nivolumab arm at 30 days or 100 days; for patients in the docetaxel arm, there was a statistically significant difference (worsening in HRQoL) from baseline using the EQ-VAS at 30 days but not at 100 days

1.2.2 Indirect evidence

There is no direct evidence comparing nivolumab with either erlotinib or with BSC. Hence, using 12-month efficacy data, the company performed two ITCs (one for PFS and one for OS) for each comparison using different study entry criteria for each comparison.

The company’s analysis of data from the CheckMate 017 and TAILOR (squamous subgroup) trials found that, compared with erlotinib, treatment with nivolumab statistically significantly improved PFS (HR=[redacted]; 95% CI [redacted], [redacted]) in patients who had received one prior therapy but that in terms of OS, the observed effect was not statistically significant (HR= [redacted]; 95% CI [redacted], [redacted]).

The company’s analysis of data from the CheckMate 017, TAILOR (squamous subgroup) and BR.21 (squamous subgroup) trials showed that, when compared with BSC, treatment with nivolumab statistically significantly improved OS (HR=[redacted]; 95% CI [redacted], [redacted]) in patients who had received one or more prior therapies. It was not possible to compare PFS in this patient population due to PFS results for squamous patients not being reported for BSC in the BR.21 trial.

The company advises that, due to heterogeneity across the included trials, the findings from the ITCs should be treated with caution.

1.3 Summary of the ERG's critique of the submitted clinical effectiveness evidence

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria (which was used for both the direct and indirect evidence) and is confident that the searching was carried out to an acceptable standard. The ERG is not aware of any additional studies that should have been included.

1.3.1 Direct evidence

The ERG considers the CheckMate 017 trial to be a well-conducted trial and agrees with the company that, in general, the baseline characteristics of the patients in the CheckMate 017 trial are similar to the characteristics of patients in England who would be considered for treatment with nivolumab or docetaxel. However, the ERG notes that a relatively large proportion of patients ([redacted]) discontinued docetaxel within the first week of starting treatment; this rate of discontinuation appears to be higher than would be expected in clinical practice. The ERG notes that the CheckMate 017 trial was stopped early due to the demonstrated net survival gain of nivolumab over docetaxel at the time of the 12-month interim analysis. Data are now available from the 18-month interim analysis and the ERG considers that these data support the DCM's decision to stop the trial early.

In the CheckMate 017 trial, the original RCT protocol stated that treatment with nivolumab and docetaxel would continue until disease progression. However, one fifth of patients carried on receiving nivolumab after disease progression (which was permitted in the nivolumab arm as per protocol when the investigator suspected the patient experienced a 'pseudo-progression') and one third of these patients (i.e. 6.7% of all patients treated with nivolumab) continued to benefit (in terms of tumour response) from treatment. The ERG is unsure how these 'non-conventional benefitters' (as the company describes such patients) would be identified and treated in routine clinical practice in England.

Response rates for HRQoL data collected were low. Furthermore, the company only planned to assess statistical significance for LCSS ASBI between randomisation and Week 12 (at which point in time, no statistically significant differences were reported). Hence aside from reasons relating to low response rates, findings which are reported to be statistically significant after this point in time should also be treated with caution for being post-hoc analyses.

1.3.2 Indirect evidence

The company carried out an ITC to allow treatment with nivolumab to be compared with treatment with erlotinib and BSC. The ERG agrees with the company that the results of the

ITCs should be interpreted with caution due to heterogeneity across the trials. In addition, the ERG is not confident that the results of the ITCs are credible as there are insufficient data available from the included studies to determine whether the assumption of proportional hazards, which underpins the reliability of results from any ITC, can be supported. This means that the clinical effectiveness of nivolumab versus erlotinib and the clinical effectiveness of nivolumab versus BSC remain unclear.

1.4 Summary of submitted cost effectiveness evidence

To compare the cost effectiveness of nivolumab 3mg/kg Q2W with docetaxel 75mg/m^2, the company developed a de novo cohort-based partitioned survival model. The model comprised three health states: pre-progression, post-progression and death. All patients entered the model in the pre-progression state. Variants of this model structure have been used in the modelling of metastatic oncology for a number of previous NICE STAs. The model was developed in Microsoft Excel using a 1-week cycle length and the time horizon was set to 20 years. As recommended by NICE, a discount rate of 3.5% was used for both costs and outcomes; outcomes were measured in quality adjusted life years (QALYs). The model perspective was that of the UK NHS. Survival was estimated based on data from the CheckMate 017 trial and published sources. Health state utility values were calculated from data collected during the CheckMate 017 trial. Resource use and costs were estimated based on information from the CheckMate 017 trial, published sources, and advice from clinical and economics experts. In the company's base case cost effectiveness analysis (nivolumab versus docetaxel), the full list prices of the drugs were used.

The company's results show that treatment with nivolumab is more expensive (+£65,355) and more effective (+0.76 QALYs) than docetaxel, and the incremental cost effectiveness ratio (ICER) is £85,950 per QALY gained. The company carried out a range of deterministic sensitivity analyses. The most influential parameter was the hazard ratio applied to modelled nivolumab OS; other influential parameters included average body weight, low discount rate and the utility weights associated with the PFS and progressive disease (PD) health states.

The company conducted a probabilistic sensitivity analysis (PSA). The ICER from the PSA is £89,343 per QALY gained with a 0% probability of being cost effective at a threshold of £30,000 per QALY gained and a 3.8% probability of being cost effective at a threshold of £50,000 per QALY gained.

The company carried out five scenario analyses comparing nivolumab with docetaxel and the resultant ICERs varied from £45,470 per QALY gained (1-year treatment stopping rule) to £108,096 per QALY gained (2-knot spline distribution for OS). The company also

presented results from an additional scenario analysis comparing nivolumab with erlotinib; nivolumab was found to be more expensive (+£69,698) and more effective (+0.81 QALYs) than erlotinib and this analysis yielded an ICER of £85,862 per QALY gained.

The company did not estimate the cost effectiveness of nivolumab versus BSC.

1.5 Summary of the ERG's critique of cost effectiveness evidence

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria and is confident that there are no studies that fully meet the company's inclusion criteria.

The assessment of the cost effectiveness of nivolumab versus docetaxel in this appraisal depends on data from a single Phase III clinical trial (CheckMate 017) with only 2 years follow-up. These limited data, supported by some data from published sources, have been used as the basis for projecting survival for an additional 18 years.

The decision model submitted by the company is structured conventionally. However, the code used to drive the model is very inefficient, meaning that there is considerable time delay between changing parameter values and the availability of model results. The ERG has identified three main areas of concern: (i) the manner in which PFS and OS have been projected, (ii) the cost of drugs and their administration and (iii) the magnitude of the utility values that have been employed as the basis for calculating HRQoL.

The ERG considers that the methods employed by the company to project PFS and OS are inappropriate and vastly overestimate the clinical effectiveness of treatment with nivolumab when compared with docetaxel. It is particularly noteworthy that in the company's base case analysis the majority (59%) of the estimated survival gain is attributable to the period after disease progression has been confirmed. This implies that additional benefit continues to accrue to patients whose disease has progressed on nivolumab despite no longer receiving the randomised treatment. The key issue in relation to the company's method of modelling PFS is that their assumption of time-invariant proportional hazards is violated, meaning that the company's use of hazard ratios to model PFS is invalid. In relation to modelling OS, the ERG has identified that the company's log-logistic method for projecting OS generates rapidly falling mortality rates which are implemented indefinitely. This implies that a few months of treatment with either nivolumab or docetaxel confers a life-long reduction in risk from *all* causes of death. This is clearly unrealistic.

In terms of treatment costs, the ERG has identified six issues:

1. Use of average trial body weight and body surface area values to calculate doses for nivolumab and docetaxel, rather than using distributions that are specific to UK patients with NSCLC
2. Use of average trial body weight and body surface area values to calculate doses for third-line treatments, rather than using distributions that are specific to UK patients with NSCLC
3. Use of an assumption that the administration of nivolumab would cost more than the administration of docetaxel
4. Unrestricted use of docetaxel (in the UK its use is restricted to four cycles)
5. Timing of receipt of chemotherapy drugs (which should be administered at the start of each cycle)
6. Basing drug cost estimates on time in the progression-free (PF) state, rather than using time to treatment discontinuation (TTD) data.

The ERG is also concerned about the utility values that the company has used in their model. These were calculated based on EQ-5D questionnaire data collected as part of the CheckMate 017 trial. However, over time, the number of responders rapidly declined and it is likely that those who continued to complete questionnaires were self-selecting and untypical of the initial cohort. In particular, the utility value used during the pre-progression phase (a point at which patients have already experienced one line of chemotherapy) seems unrealistic as it is very similar to the UK norm for individuals of a similar age to the baseline population.

1.6 Summary of company's case for end of life criteria being met

The company makes the following case for nivolumab to be considered under NICE's end of life criteria:

- Patients with advanced or metastatic squamous NSCLC have a life expectancy of less than 24 months
- Data from the CheckMate 017 trial demonstrate that nivolumab extends life by more than 3 months compared with docetaxel
- The patient population eligible for nivolumab treatment in England is expected to be small (n=853).

1.7 ERG commentary on end of life criteria

The ERG agrees with the company that nivolumab is a treatment that is indicated in patients with a short life expectancy and that the expected size of the patient population is small. The ERG also considers that nivolumab offers an extension to life of at least an additional 3 months compared to current NHS treatment; the ERG estimates a mean OS gain of more

than 6 months for patients treated with nivolumab compared with patients treated with docetaxel.

1.8 ERG commentary on the robustness of evidence submitted by the company

1.8.1 Strengths

Clinical evidence

- The key trial, CheckMate 017, is, in general, a well-conducted trial which measures efficacy in terms of PFS, OS, tumour response, AEs and HRQoL, all of which are important outcomes to clinicians and patients
- The ERG considers the comparator in the CheckMate 017 trial (docetaxel) to be the most appropriate comparator
- Clinical effectiveness and HRQoL data from patients with advanced or metastatic squamous NSCLC in CheckMate 017 add a great deal of reliable information to the limited clinical evidence available for this previously treated patient population
- There has been very little progress made in treating patients with squamous NSCLC since the approval of docetaxel for this patient population 10 years ago and nivolumab appears to demonstrate superior clinical effectiveness compared with docetaxel for this patient population.

Cost effectiveness evidence

- The company provided a detailed submission that fulfilled the requirements of NICE's scope for the base case analysis. The ERG's requests for further clinical information were met to a good standard
- Variants of this model structure have been used in the modelling of metastatic oncology for a number of previous NICE STAs
- The decision model submitted by the company is generally implemented to a good standard.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- There are some patients who may be seen in clinical practice who are not covered by the clinical effectiveness data in CheckMate 017 including patients with ECOG PS>1 in particular, and patients using higher-dose corticosteroids
- A relatively large proportion ([redacted]) of patients discontinued treatment with docetaxel within 1 week; this rate appears to be higher than expected when used in clinical practice
- The ERG notes that RECIST criteria were used to evaluate response in the CheckMate 017 trial which may not be the optimal method for capturing response with the use of an immuno-oncology therapy such as nivolumab
- Considering the limited number of patients aged 75 years and over in CheckMate 017, the relative efficacy of nivolumab with docetaxel is not known in this age group
- Given the small sample sizes (<20 patients completing either the LCSS or EQ-5D questionnaires) in the nivolumab arm after [redacted] and in the docetaxel arm after only

[redacted], the on-treatment HRQoL data should be treated with caution; response rates in relation to baseline at 30 days and 100 days follow-up were also relatively low ([redacted] and [redacted] respectively)

- Nivolumab is a PD-1 inhibitor which blocks the interaction of PD-1 with PD-L1. However, there is no evidence from the CheckMate 017 trial to suggest that treatment should be targeted based on PD-L1 status
- The ERG considers the results of the company's ITCs to be unreliable as, based on the OS and PFS data available, they appear to be based on flawed methodology.

Cost effectiveness evidence

- The company did not carry out a cost effectiveness analysis of nivolumab versus BSC
- Results from the company's model suggests that 59% of the estimated survival gain attributable to treatment with nivolumab, compared with docetaxel, occurs after disease progression has been confirmed. As only 28 patients in the CheckMate 017 trial received nivolumab post progression, this implies that benefit continues to accrue after treatment with nivolumab has ceased. The ERG considers therefore that the company's estimated post-progression survival gain is unlikely
- The method employed by the company to project PFS relies on the assumption of time-invariant proportional hazards; however, ERG analyses show that this assumption is clearly violated
- The company's projection of OS data suggests that receipt of either nivolumab or docetaxel confers a life-long reduction in mortality risk from all causes of death, this is clearly implausible
- The costs calculations undertaken by the company are inaccurate
- The utility data used in the company's model lack credibility.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The various changes implemented by the ERG for the comparison of nivolumab versus docetaxel yield a mixture of effects. When implemented individually, these revisions both increase and decrease the size of the ICER per QALY gained. However, the combined effect of all of the ERG changes yields an ICER of £132,989 per QALY gained.

In conclusion, the ERG considers that the company's base case result substantially underestimates the size of the most probable ICER per QALY gained for nivolumab versus docetaxel in previously treated patients with squamous NSCLC. The ERG was unable to compare the cost effectiveness of nivolumab versus erlotinib or nivolumab versus BSC for this patient population due to the limited clinical effectiveness data available.

2 BACKGROUND

2.1 Critique of the company's description of the underlying health problem

Key points from the description of the underlying health problem (lung cancer, and in particular squamous non-small cell lung cancer [NSCLC]) presented in the company submission (CS) are reproduced (as bulleted items) by the Evidence Review Group (ERG) in Box 1.

Box 1 Company's overview of the underlying health problem

Lung cancer

- Lung cancer is the second most common cancer in the UK and has the highest mortality of any cancer
- Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease and unresectable locally advanced disease; stages IIIA and IIIB) or to other parts of the body (metastatic disease; stage IV)
- Tumours that are staged IIIA and IIIB are termed 'locally advanced', whereas tumours that are stage IV are termed metastatic
- In 2011, lung cancer was the underlying cause for 30,148 deaths in England and Wales
- The median survival for all lung cancer in England and Wales was 232 days [7.6 months]
- Although lung cancer typically affects older patients (median age of diagnosis in England and Wales is 74 years), in 2013 more than one-third of patients diagnosed with lung cancer were aged between 50 and 70 years
- Approximately 54.4% of patients with lung cancer in 2013 were male

Non-small cell lung cancer (NSCLC)

- Approximately 84% of lung cancer cases in England and Wales fall within the NSCLC category
- In 2013, there were 27,300 patients with NSCLC in England; 19,138 patients (70%) had stage IIIB or IV lung cancer
- Median survival for all stage III patients with NSCLC was 293 days [9.6 months]
- Median survival for stage IV patients with NSCLC was only 100 days [3.3 months]
- Data from the UK suggest the 1-year relative survival rate (by stage at diagnosis) is 71%, 48%, 35%, and 14% for stage I, II, III, and IV disease, respectively
- In addition to high mortality, a large proportion of patients experience increasingly severe morbidity as they progress from localised to metastatic disease
- Approximately 90% of patients with advanced NSCLC experience two or more disease-related symptoms, such as cough, dyspnoea, pain, anorexia, or fatigue
- These symptoms, in turn, can cause psychological distress and may have a negative impact on a patient's health-related quality of life (HRQoL)

Squamous NSCLC

- NSCLC can be further divided into squamous NSCLC and non-squamous NSCLC, based on the cell type responsible for the tumour
- Approximately 36% of patients within England and Wales had squamous NSCLC in 2013
- Patients with squamous NSCLC rarely have EGFR or ALK mutations

ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer
Source: CS, Sections 3.1 and 3.3

The ERG considers that, in general, these key points appropriately summarise the issues. The ERG notes that patients with squamous disease rarely have epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations. Also, patients with

squamous disease tend to have different patient characteristics (e.g. they are more likely to be heavier smokers and tend to have more co-morbidities) than patients with non-squamous NSCLC disease.

2.2 Critique of company's overview of current service provision

The ERG has reproduced (as bulleted items) the key points from the company's description of current treatment options for patients with squamous NSCLC in Box 2. The ERG considers that these points provide an accurate overview of current service provision.

Box 2 Company's overview of current treatment options for patients with squamous NSCLC

Current treatment options

- For the majority of people with NSCLC with squamous histology, the aims of therapy are to prolong survival and improve HRQoL
- Treatment of patients with squamous NSCLC depends on a patient's ECOG PS and personal choice
- In England, patients with locally advanced, unresectable (stage IIIB) or metastatic (stage IV) squamous NSCLC are typically treated with platinum-based doublet chemotherapy in the first-line, unless they are otherwise unfit for chemotherapy
- NICE clinical guideline 121 (CG121) recommends platinum-based doublet chemotherapy (cisplatin or carboplatin in combination with gemcitabine, vinorelbine, or a taxane) as a first-line treatment option for people with previously untreated stage III or IV NSCLC and good ECOG PS

Issues relating to current clinical practice

- In the UK, patients with squamous NSCLC are often diagnosed late in the progression of their disease; the median age of diagnosis in the UK is 74 years
- Due to their age and/or co-morbidities, most patients in the UK are unlikely to receive systemic treatment
- Furthermore, first-line therapy in this patient population is a platinum-based combination therapy, which is associated with high toxicity and may not be suitable for many patients
- Consequently, the mortality rate in these patients is high and the OS rate is low following first-line therapy, with a short duration of survival
- Long-term survival, with a concomitant good HRQoL, is not currently deemed achievable with current treatments in this patient population
- In second-line patients, docetaxel has been the standard of care with no new treatments in this patient population for the last decade in the UK
- Erlotinib has been recommended for use in the second-line setting for squamous NSCLC patients, but this recommendation is currently under review by NICE
- There is currently no recommended treatment for patients who fail second-line therapy; therefore, third-line treatment varies for patients with locally advanced or metastatic squamous NSCLC in UK clinical practice
- BSC, such as analgesics, antiemetics, and palliative interventions, are a part of the care package offered to all patients with squamous NSCLC, regardless of eligibility for systemic anti-cancer therapies and line of treatment
- BSC [alone] is used in the case where patients are not eligible or do not wish to undergo systemic therapy

HRQoL=health related quality of life; NSCLC=non-small cell lung cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; BSC=best supportive care
Source: CS, Sections 3.2 and 3.5

In addition, as noted in the European Public Assessment Report (EPAR),[1] despite the emergence of new treatments for NSCLC in the last 15 years, most of the available agents do not benefit patients with squamous NSCLC. This is because these treatments are either not efficacious for squamous disease (e.g. bevacizumab and pemetrexed) or because activity is limited to tumours with specific mutations and gene alterations that are rarely found in squamous NSCLC tumours (e.g. EGFR or ALK inhibitor).

Nivolumab received a positive opinion from the EMA on 21 May 2015 and marketing authorisation was granted on 20 July 2015. It is indicated for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults.[2]

Nivolumab is a human, monoclonal immunoglobulin G4 antibody (IgG4 HuMAb) that acts as a programmed death-1 (PD-1) inhibitor; nivolumab blocks the interaction of PD-1 with programmed death-ligands 1 and 2 (PD-L1 and PD-L2).[3,4] The typical immune response to foreign antigens or cells in the body is the activation of T-cells that can destroy these antigens or cells; the PD-1 receptor is a negative regulator of T-cell activity. Engagement of PD-1 with its ligands (PD-L1 and PD-L2) results in the inhibition of T-cell activation and T-cell death. PD-1 has also been shown to control the inhibition of T-cell response in human malignancies.[5-7] Hence, nivolumab stimulates the patient's own immune system to directly fight cancer cells, resulting in destruction of the tumour. Nivolumab's mechanism of action differs from that of conventional anti-cancer therapies which generally act through cytotoxicity and destroy all rapidly dividing and fast growing cell types. Their mode of action means that non-cancerous cells, such as hair follicles and gut mucosa, are often targeted alongside cancer cells, resulting in undesirable side effects such as hair loss and diarrhoea.

In the CS (CS, Figure 5), the company proposes nivolumab as a second- or even third-line treatment option for patients with squamous NSCLC. However, the ERG notes that the clinical evidence presented by the company, from the pivotal CheckMate 017 trial,[8] is limited to second-line treatment only and that the company only provides an estimate of the potential number of patients eligible for nivolumab as a second-line treatment. In England, the company estimates the number to be 853 (Table 1); the ERG agrees that this is a reasonable estimate.

Table 1 Company's estimated number of patients eligible to receive nivolumab in England

Population	Proportion of patients	Number of patients	Reference
Total NSCLC	N/A	27,300	Health and Social Care Information Centre 2014b[9]
Patients with stage IIIb/IV NSCLC	N/A	19,138	Health and Social Care Information Centre 2014b[9]
Squamous NSCLC	35.6%	6,822	Powell *et al* 2013[10]
Patients who receive 1st line therapy	25.0%	1,706	NICE 2010b[11]
Patients who failed 1st line therapy	50.0%	853	Sculier and Moro-Sibilot 2009[12]

NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer
Source: CS, Table 112

3 ERG'S CRITIQUE OF THE COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2 provides a summarised comparison of the final scope issued by NICE and the decision problem addressed by the company in the CS. Each parameter is discussed in more detail in the text (see Section 3.1 to Section 3.7).

Table 2 ERG's comparison of the NICE scope and the company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the CS
Population	People with previously treated locally advanced or metastatic (stage IIIB or IV) squamous NSCLC	As per scope The company appears to have interpreted 'previously treated' to mean 'previously treated with platinum doublet-based chemotherapy' (as per CheckMate 017)
Intervention	Nivolumab	As per scope
Comparator(s)	Docetaxel Erlotinib* Best supportive care (BSC)	Base case economic analysis is nivolumab versus docetaxel. This is the only comparison for which direct randomised controlled trial evidence is available Effectiveness data to compare nivolumab with erlotinib and BSC are provided by indirect treatment comparisons; cost effectiveness analysis of nivolumab versus erlotinib is provided as an appendix (Appendix 20) to the company submission An economic analysis of nivolumab versus BSC was not possible due to a paucity of data
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rates • Adverse events • HRQoL	As per scope Response rates are presented as overall response rate (complete response + partial response), and also duration of response and time to response
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any patient access schemes for the comparator technologies should be taken into account	As per scope The economic model has a time horizon of 20 years Only an NHS perspective was employed
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on biological markers	As per scope

* Subject to an ongoing review of NICE TA162
Source: Company submission, adapted from Table 1

3.1 Population

Nivolumab is licensed for the treatment of patients with locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults.[2] The NICE scope[13] specifies that the patient population is people with previously treated locally advanced or metastatic (Stage IIIB or IV) squamous NSCLC, i.e. with no reference to the type of previous treatment received. In the CS, the population is referred to as having received platinum-based doublet chemotherapy.

As noted by the company, alongside patients with stage IIIB NSCLC, patients with stage IIIA NSCLC may also have locally advanced cancer, albeit resectable disease (i.e. may be treated with surgery). However, the NICE scope specifies only patients with Stage IIIB or IV locally advanced NSCLC are to be considered in this single technology appraisal (STA). Patients in the pivotal CheckMate 017 trial did have Stage IIIB or IV NSCLC.

The ERG notes that in the CheckMate 017 trial, patients are excluded from the study if they have Eastern Co-operative Oncology Group (ECOG) performance status (PS) >1, had autoimmune disease or were using higher-dose corticosteroids (>10mg prednisone). There is, therefore, no clinical evidence to support treating such patients with nivolumab. Patients with ECOG PS >1, in particular, and patients using higher-dose corticosteroids may constitute some patients who would be seen in clinical practice in England.

3.2 Intervention

The NICE scope specified that the intervention is nivolumab. Nivolumab's brand name is 'Nivolumab BMS' but the company anticipates that the brand name will change to Opdivo® towards the end of 2015. Nivolumab is administered via intravenous infusion at 3mg/kg over 60 minutes every 2 weeks. The intervention referenced in the company's decision problem is identical to that specified in the NICE scope.

3.3 Comparators

The NICE scope specifies that the relevant comparators to nivolumab are docetaxel, erlotinib and best supportive care (BSC). The comparators referenced in the company's decision problem are identical to those specified in the NICE scope. The ERG agrees that based on current clinical practice, these are all valid comparators.

The company argues that the most relevant comparator to nivolumab in UK clinical practice is docetaxel and provides clinical and cost effectiveness evidence for this comparison. The company presents (indirect) clinical evidence for the comparison of nivolumab versus erlotinib; however, only the cost effectiveness results of a scenario analysis for this

comparison are reported in Appendix 20 of the CS. The company presents (indirect) clinical evidence for the comparison of nivolumab versus BSC; however, the company does not compare the cost effectiveness of nivolumab with BSC.

The company claims that the second-line use of erlotinib relative to docetaxel is declining. During the clarification process the ERG requested evidence from the company regarding the relative size of the market share of erlotinib and docetaxel. In response, the company provided data on second-line treatment of patients with squamous NSCLC from its internal research carried out by Ipsos EU Oncology Monitor.[14] [redacted] Figure 1 [redacted]

Furthermore, the data show a sharp and steady decline in the use of erlotinib. [redacted]

Figure 1 Top five second-line treatment regimens in the UK for squamous NSCLC Stage IIIb/IV

Source: Company response to ERG's clarification letter (Figure 1)

The rationale as to why the company considers docetaxel to be the most appropriate comparator is summarised in Table 3, alongside the ERG's own view.

Table 3 Reasons why docetaxel is considered to be the most appropriate comparator to nivolumab

Company's argument	ERG observation
Market share data shows that, in patients who have been previously treated for squamous NSCLC in UK clinical practice, docetaxel use is higher than that of erlotinib and appears to be increasing whilst use of erlotinib appears to be decreasing. [redacted]	The ERG's clinical expert states that, to the best of his knowledge, docetaxel is the current standard of care in England. The ERG concurs that docetaxel is likely to be standard clinical practice in England.
Erlotinib has limited efficacy in patients with squamous NSCLC as this patient population is predominantly without an EGFR mutation.	The ERG concurs that patients with squamous NSCLC are predominantly without an EGFR mutation; one source has estimated this to be between 96% and 97% of all patients with squamous NSCLC.[15] Furthermore, the ERG also agrees that the efficacy of erlotinib may be considered to be limited. The recent LUX-Lung 8 trial[16] has reported a response rate of only 2.8% for patients receiving erlotinib as second-line treatment for advanced or metastatic squamous NSCLC.
Erlotinib use is currently being reviewed as part of a NICE multiple technology appraisal (MTA) and that the draft Appraisal Committee Document (ACD) states that it is not recommended,[17] which is likely to further limit the use of erlotinib in patients with squamous NSCLC who have been previously treated with chemotherapy.	The ERG notes that in this ongoing MTA, the Appraisal Committee's preliminary decision regarding the use of erlotinib does not specifically mention patients with squamous NSCLC. The ACD does, however, only recommend erlotinib as a second-line treatment in cases where patients either have EGFR mutation-positive NSCLC or the treating clinician considers that the tumour is very likely to be EGFR mutation-positive. The ACD proposed guidance explicitly states erlotinib is not recommended as a second-line treatment for patients who are EGFR mutation-negative. Thus, given patients with squamous NSCLC are predominantly without an EGFR mutation, this does imply erlotinib would not be recommended for patients with squamous NSCLC.
BSC is a part of the care package offered to all patients with squamous NSCLC, regardless of eligibility for systemic anti-cancer therapies and line of treatment.	The ERG agrees that BSC is a part of the care package offered to all squamous NSCLC patients, regardless of eligibility for systemic anti-cancer therapies and line of treatment. However, the ERG is also aware that patients may not want to receive docetaxel or erlotinib, in which case the only option would be BSC.
There is no direct RCT evidence to support the use of nivolumab vs erlotinib or nivolumab vs BSC in patients with squamous NSCLC who have been previously treated. The results of the ITCs performed by the company are limited due to a paucity of evidence and high levels of heterogeneity.	The ERG agrees with the company that there is only limited RCT evidence available to compare nivolumab with docetaxel, erlotinib or BSC in previously treated patients with squamous NSCLC. All of the available evidence for erlotinib (in particular) and BSC is limited to small subgroup analyses from two RCTs. In addition, the ERG considers that the ITCs carried out by the company are inherently flawed because it is impossible to confirm that the proportional hazards assumption which underpins the method has not been violated.

BSC=best supportive care; EGFR=epidermal growth factor receptor; ICER=incremental cost effectiveness ratio; ITC=indirect treatment comparison; NSCLC=non-small cell lung cancer; QALY=quality adjusted life year; RCT=randomised controlled trial
* This draft guidance is from August 2014. The ERG notes that a NICE Appraisal Committee meeting to discuss this MTA was scheduled for 22 September 2015; no new information has yet become available from this meeting

In summary, the ERG concurs with the company's view that docetaxel is the most relevant comparator to nivolumab; the expert clinical advice provided to the ERG has confirmed that docetaxel is the current standard of care for patients with squamous NSCLC in England. In addition, the ERG considers that the market share data provided by the company show that

docetaxel has the larger share of the market, compared to erlotinib, for the treatment of patients with squamous NSCLC who have been previously treated.

3.4 Outcomes

Clinical evidence is reported in the CS for all five outcomes specified in the scope: overall survival (OS), progression-free survival (PFS), response rates, adverse events (AEs) and health related quality of life (HRQoL). Response rates are reported as overall response rate (ORR) along with the supporting outcomes of duration of response (DoR) and time to response (TTR).

The ERG notes that the OS data presented in the CS from the CheckMate 017 trial are immature as the trial was stopped early for benefit on the recommendation of the Data Monitoring Committee (DMC). Initially, the ERG was concerned that a lack of mature OS data would mean that the true impact of nivolumab on OS may never be fully known. This concern was based on the knowledge that there is published evidence to suggest that some cancer trials that had been stopped early for benefit were shown not to reach the expected survival gain estimated at the time of stopping. [18-21] However, the 18-month efficacy data that are now available ([redacted] data-cut), and which are almost fully mature, appear to support the DMC's decision to stop the trial early (based on the December 2014 data-cut).

3.5 Economic analysis

As specified in the final NICE scope, the cost effectiveness of treatments are expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes are assessed over a 20-year time horizon (equivalent to a lifetime horizon) and costs are considered from an NHS perspective.

3.6 Subgroups

The NICE scope specifies that if the evidence allows, consideration should be given to subgroups based on biological markers. A range of subgroup analyses (including analyses by PD-L1 status) were carried out by the company to assess clinical effectiveness. No subgroup analyses were carried out to assess cost effectiveness since there is a lack of evidence from the CheckMate 017 trial to suggest that there is a differing treatment effect for any particular subgroup to that of the overall trial population (see Section 4.2.5 of the ERG report).

3.7 Other considerations

As noted in Section 3.6 of the CS, the company does not foresee any equality issues.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

A description of the searches used to identify trials relevant to the decision problem for the comparison of nivolumab, docetaxel, erlotinib and BSC are provided in the CS (Section 4.1 [systematic review] and Section 4.10 [indirect treatment comparison, ITC]). The search strategies are reported in full (CS, Appendices 2 and 10) and are an updated version of the search strategies described in a protocol for a previous MTA report.[22] To ensure consistency between the MTA review and the company's update, the search strategy included a broad NSCLC patient population (both squamous and non-squamous NSCLC). The company searched Medline, Medline In-Process, Embase and The Cochrane Library. The company also searched the conference proceedings of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the World Conference on Lung Cancer (WCLC) for the last 3 years.

Overall, the searches for clinical effectiveness evidence are very comprehensive, with wide-ranging use of search terms, correct use of Medical Subject Headings (MeSH) and free text terms included. The RCT filter is of good quality and the search strategy is well constructed. The date of the searches and the full date span are included in the CS; the searches are well reported and reproducible. However, the ERG notes that searches in Medline and Embase were limited to English language only, which may have resulted in the omission of potentially useful papers in other languages. Despite this, the ERG considers that searching was carried out to an acceptable standard.

In addition to RCT evidence, the company has also provided supporting evidence from two non-randomised studies (CheckMate 003[23] and CheckMate 063[24]). No details as to how these studies were identified are reported in the CS.

4.1.2 Eligibility criteria

As confirmed by the company during the clarification process, two reviewers independently assessed all of the citations for potential inclusion through two stages. Detailed eligibility criteria are presented in the CS (Table 7). The ERG considers these criteria to be consistent with the NICE scope and company's decision problem. The ERG notes that although the company's search aimed to identify RCTs which included patients with squamous and non-squamous histology, ultimately, studies were only included in the review if they either included only patients with squamous NSCLC or if the study included a relevant subgroup

analysis describing patients with squamous NSCLC. The ERG concurs that this approach was appropriate.

4.1.3 Methodological quality and risk of bias

A descriptive critical appraisal of all of the trials included in the systematic review and in the ITCs was conducted by the company using the minimum criteria recommended by NICE for the quality assessment of company submissions[25] (based on Centre for Reviews and Dissemination's guidance[26]) and by also assigning a Jadad score[27] and allocation concealment grade; it is not clear from which checklist or tool the allocation grade originates but it appears it may be similar to that which was used previously by the Cochrane Collaboration (Grade A: adequate; Grade B: uncertain; Grade C: inadequate; Grade D: no allocation concealment attempted). In all cases, two analysts separately conducted risk of bias assessments with any discrepancies reconciled by a third, independent, analyst.

The company also assessed the methodological quality of the non-randomised studies that were provided as supportive evidence using the Down and Black's checklist for non-randomised studies.[28] This checklist is cited in Appendix H of the manual for developing NICE guidelines.[29,30]

4.1.4 Evidence synthesis

Fourteen RCTs were included in the company's review but only one (CheckMate 017) assessed the clinical effectiveness of nivolumab (versus docetaxel). The trial characteristics and findings of the CheckMate 017 trial were appropriately presented narratively in the CS. Evidence from the other 13 RCTs included in the systematic review was reported in tables in the CS (CS, Appendices 7.12 to 7.14). The supporting evidence from the two non-randomised studies (CheckMate 003 and CheckMate 063) were presented narratively in Section 4.11 and in Appendix 16 of the CS. For information, the two non-randomised studies, CheckMate 063 and CheckMate 003, are described in the Appendices to this ERG report (Section 11.5).

To compare nivolumab with erlotinib and BSC, the other comparators specified in the NICE scope, the company conducted ITCs using evidence derived from the CheckMate 017, TAILOR and BR21 trials. The ERG's critique of the company's ITCs is presented in Section 4.3.5.

Nivolumab AE data are available from one RCT (Checkmate 017) and two non-randomised studies (CheckMate 003 and CheckMate 063), however, the two non-randomised studies include slightly different patient populations (see Section 4.3.5 of this report). The company

did not pool any AE data. The ERG notes that a pooled analysis of AE data from CheckMate 017 and one of the non-randomised studies (CheckMate 063) is described in the EPAR for nivolumab.[1] For completeness, the ERG has included some information from the pooled analysis in the Appendices to this ERG report (Section 11.6).

4.2 Critique, analysis and interpretation of trials of the technology

4.2.1 Identified studies in systematic review

Fourteen RCTs[8,31-43] were included in the company's systematic review. However, only one study (CheckMate 017) included nivolumab as an intervention and was therefore directly relevant to the decision problem. A brief summary of the characteristics of all the trials are provided by the ERG in the Appendices to this ERG report (Section 11.1). The ERG is not aware of any additional studies that should have been included.

4.2.2 Statistical approach adopted for the conduct and analysis of studies included in the systematic review

Only the CheckMate 017 trial compared nivolumab with a relevant comparator (docetaxel) and therefore no meta-analysis was conducted. A full description and critique of this trial is presented in this Section of the ERG report. Information relevant to the statistical approach taken by the company has been taken from the clinical study report (CSR[44]) (including the trial statistical analysis plan [TSAP]) and the trial protocol), and from the CS.

Trial population

For the analysis of all primary and secondary outcomes, the intention-to-treat (ITT) population was used. All patients were analysed according to the treatment arm to which they were initially randomised, regardless of which treatment they actually received. The safety population was analysed using a modified ITT population.

Outline of analyses

In the CS, the company states that a 12-month interim OS analysis was scheduled to take place once 196 deaths had been reported and that recruitment would be ongoing throughout the interim analysis. As a consequence of this interim review (December 2014 data-cut), the independent DMC declared that the trial had reached its primary endpoint, and hence recommended that the trial be stopped (January 2015). The comparative element to the CheckMate 017 trial was then halted and the protocol was amended to allow any eligible patients (n=6) who were originally randomised to docetaxel to receive nivolumab in an extension phase of the study.

During the clarification period, the company provided 18-month PFS and OS data to the ERG ([redacted] data-cut).

The ERG was initially concerned that CheckMate 017 had been stopped early for benefit as previous technology appraisals have highlighted the fact that early closure of cancer trials can lead to exaggerated treatment effects that are not borne out in the longer term.[18-21] However, having had access to 18-month PFS and OS data from the CheckMate 017 trial ([redacted] data-cut), the ERG considers that, on this occasion, stopping the trial early does not appear to have biased the efficacy results in any way since the OS data are now virtually mature and consistent with the findings from 12-months (December 2014 data-cut).

Efficacy outcomes

The definitions, and methods of analysis, for the primary and secondary efficacy outcomes from the CheckMate 017 trial are listed in Table 4. The ERG is satisfied that all outcomes were pre-specified in the TSAP and that all outcomes were fully reported in the CSR.

Table 4 Analysis strategy for key efficacy endpoints

Endpoint	Definition	Statistical method
Primary outcome		
OS	Defined as the time between the date of randomisation and the date of death	Stratified log-rank test Cox model using randomised group as a single covariate K-M method used for OS curve estimation in each treatment arm
Secondary outcomes		
ORR	Defined as the number of patients whose best confirmed objective response is either a confirmed CR or confirmed PR, as determined by the investigator, divided by the number of randomised patients	Stratified Clopper-Pearson method
PFS	Defined as the time from randomisation to the date of the first documented tumour progression as determined by the investigator using RECIST version 1.1 criteria, or death due to any cause	Stratified log-rank test Cox model using randomised group as a single covariate K-M method used for PFS curve estimation in each treatment arm

CR=complete response; K-M=Kaplan-Meier; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; RECIST= Response Evaluation Criteria in Solid Tumors
Source: CS, adapted from Table 11

Stratification

The stratified log-rank test and stratified Cox model used two randomisation stratification factors: prior treatment (with paclitaxel-based doublet versus other doublet), and region (US/Canada versus Europe versus Rest of the World).

Censoring methods

For the primary outcome (OS), subjects without documentation of death were censored on the last date the subject was known to be alive.

For PFS, subjects who did not progress or die were censored on the date of their last evaluable tumour assessment. Subjects who did not have any on study tumour assessments and did not die were censored on the date they were randomised. Subjects who started any subsequent anti-cancer therapy without a prior reported progression were censored at the last evaluable tumour assessment prior to initiation of the subsequent anti-cancer therapy.

Subgroup analyses

The company performed subgroup analyses for the pre-trial PD-L1 expression level for the outcomes OS, PFS and ORR. Pre-specified expression level cut-off values of 1%, 5% and 10% were used for the patients. Subgroup analyses, for OS and PFS, were also performed for a range of baseline characteristics (see Table 5 for details).

ERG assessment of statistical approach

A summary of the checks made by the ERG regarding the statistical approach adopted by the company to analyse data from the CheckMate 017 trial is provided in Table 5.

Proportional hazards

The analyses carried out by the company to generate PFS and OS hazard ratios were conducted using Cox proportional hazards modelling. The validity of this method relies on the hazards of the two comparative drugs being proportional. To test the assumption of proportional hazards, visual inspection of the log-cumulative hazards, log-cumulative odds, and standardised normal curve plots were carried out by the company; in addition, the Schoenfeld residuals method was performed. However, the results of the testing carried out by the company (see page 126 of CS) and the ERG (see Appendices to this ERG report, Section 11.9 for details) indicates that the assumption of proportional hazards is only valid for the OS data and is violated for the PFS data. The ERG is disappointed that the company has presented hazard ratio results for PFS data when the assumption of proportional hazards has been violated and has not provided any rationale to explain why alternative approaches were not considered.

Table 5 ERG assessment of statistical approach used to analyse CheckMate 017 data

Component	Statistical approach	ERG comments
Sample size calculation	Provided in the CS (pages 51-52)	The ERG considers that the methods used to calculate the sample size are correct
Protocol amendments	Provided in the CSR (Section 4.5)	The ERG notes that the changes detailed in the protocol amendments including an extension of OS analyses to 5 years were unlikely to have been driven by the results of the trial and are therefore not a cause for concern. All protocol amendments were carried out prior to the analysis being conducted
Missing data approach	Provided in the CS (pages 51-52)	The ERG is satisfied that the company took a suitable approach to handling missing data
Pre-specified subgroup analyses for the primary outcome	OS, ORR, or PFS based on pre-trial PD-L1 expression level For OS and PFS only: • Age • Gender (male vs female) • Race (White vs African American vs Asian vs Other) • Region (US/Canada vs Europe vs Rest of World) • Baseline ECOG PS (0 vs 1) • Prior paclitaxel vs other prior treatment • Type of prior pre-treatment regimen (cisplatin vs carboplatin) • Time from diagnosis to randomisation (< 1 year (yes vs other)) • Time from completion of most recent regimen to randomisation (< 3 months vs 3-6 months vs >6 months) • Presence or absence of CNS metastases (yes vs no) • Smoking status (yes vs other (no or unknown))	The ERG is satisfied that the results of all subgroup analyses are provided in the CSR
Adverse events	Safety was assessed through summaries of deaths, SAEs, AEs leading to discontinuation, overall AEs, Select AEs, and laboratory abnormalities	The ERG is satisfied that the results of all the AE data analyses are provided in the CSR
Health related quality of life	• Disease-related Symptom Improvement Rate by Week 12 as measured by LCSS between randomisation and week 12) • Overall health status using the EQ-5D Index and Visual Analogue Scale	The ERG is satisfied that the methodology used to analyse HRQoL data is appropriate

AE=Adverse Event; CNS=Central Nervous System; CS=company submission; CSR=clinical study report; ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol-5 Dimensions; ERG=Evidence Review Group; HRQoL=health related quality of life; LCSS=Lung Cancer Symptom Scale; ORR=overall response rate; OS=overall survival; PD-L1=programmed cell death 1 ligand; PFS=progression-free survival; PS=performance status RECIST=Response Evaluation Criteria in Solid Tumours; SAE=Serious Adverse Event; US=United States
Source: CS, CSR and ERG comment

4.2.3 Characteristics of the studies included in the systematic review

Direct evidence was only available for a comparison of nivolumab with docetaxel. This evidence was derived solely from the CheckMate 017 trial. As well as being published as a paper[8] with a full appendix in a peer reviewed journal, data from the CheckMate 017 trial were also provided by the company in the CSR.[44] The key characteristics of the CheckMate 017 trial are summarised in the Appendices to this ERG report (Section 11.3, Table 43).

CheckMate 017 is a Phase III open-label RCT of nivolumab versus docetaxel in adult (≥18 years) patients with advanced or metastatic squamous cell NSCLC after failure of prior platinum doublet-based chemotherapy. It was conducted internationally at 95 sites in 21 countries (including four sites in the UK) and the investigators randomised 272 patients in a 1:1 ratio. Randomisation was stratified according to prior treatment with paclitaxel-based doublet versus other doublet and region (US/Canada vs Europe vs Rest of the World). The primary endpoint of the CheckMate 017 trial was OS. Secondary endpoints included PFS (investigator assessed), confirmed investigator assessed ORR, DoR, TTR, AEs and HRQoL.

Given that regional differences may exist in clinical practice regarding clinician and patient preferences for first-line doublet therapy (e.g. in the UK, a gemcitabine-based doublet tends to be preferred) and, given that paclitaxel is a taxane like docetaxel, the ERG considers stratification by prior doublet therapy and region to be sensible. The company states the endpoints used to assess the efficacy and safety profile of nivolumab in the CheckMate 017 trial are consistent with other studies exploring the use of other anti-cancer agents in this patient population. Once again, the ERG concurs with the company's view.

The company states that an open-label study design was selected because the management of patients with similar AEs was different between treatment arms due to the different mechanisms of action of docetaxel and nivolumab. Different dose modification rules (no dose reductions for nivolumab vs allowance for dose reductions for docetaxel) and different drug-drug interaction profiles would have added complexity to any blinding strategy. In addition, the ERG notes that side-effects such as hair loss are common with docetaxel. Hence the ERG concurs with the company's reasoning for conducting an open-label study.

The median age of all randomised patients in the CheckMate 017 trial was 63 years. The patients in the trial were more likely to be white (93%), male (76%) and have Stage IV disease at baseline (80%). Nearly half (48.2%) of patients were from the European Union.[1] [redacted] patients were from the UK (CSR, Table S.2.1). At baseline, there were some notable (≥5%) differences in patient characteristics between treatment arms (Table 6). Overall, the

ERG does not consider that these differences are likely to lead to major bias and/or favour one arm over another.

Table 6 Baseline characteristics more common in one arm than another (CheckMate 017)

Trial characteristic	More common (≥5%) in nivolumab arm (nivolumab vs docetaxel)	More common (≥5%) in docetaxel arm (nivolumab vs docetaxel)
Age	Age <65 years (59% vs 53%)	Age ≥75 years (8% vs 13%)
Sex	Male (82% vs 71%)	Female (18% vs 29%)
Race		White (90% vs 95%)
ECOG PS	ECOG PS 1 (79% vs 73%)	ECOG PS 0 (20% vs 27%)
Prior surgery		Had prior surgery (51% vs 56%)
Previous treatment	Previously treated with an experimental drug (7% vs 2%) Previously treated with etoposide (13% vs 8%) Most recent platinum therapy was cisplatin (40% vs 26%)	 Previously treated with gemcitabine (44% vs 52%) Most recent platinum therapy was carboplatin (60% vs 74%)
Previous best response to therapy	Previous best response to disease was a complete or partial response (36% vs 31%)	Previous best response to disease was stable disease (24% vs 34%)

Source: adapted from CS, Table 13 and from appendix to published paper, Table S1

Palliative radiotherapy to bone or central nervous system (CNS) lesions was allowed per protocol in the CheckMate 017 trial. Clinical advice received by the ERG is that radiotherapy within clinical trials of immune therapies is not atypical and preclinical data suggest that radiotherapy may even improve efficacy of drug treatments (although the ERG is unaware of any published clinical evidence to support this). A total of six patients in the nivolumab arm and one patient in the docetaxel arm received concurrent palliative radiotherapy. In addition, it is stated in the CSR (page 94) that: [redacted]

Overall, aside from the caveat that, in general, patients who participate in RCTs tend to be slightly younger and fitter than patients seen in clinical practice, the ERG considers that the patient population in the CheckMate 017 trial is likely to be similar to patients treated in routine clinical practice in England for the following reasons:

- eligibility criteria for entry into this trial appear to be reasonable (see Appendices to ERG report, Section 11.1)
- drug dose for docetaxel in the trial is the same as the drug dose used in England
- clinical opinion received by the ERG is that baseline characteristics of included patients are similar to those who would be considered for treatment with nivolumab or docetaxel in England.

4.2.4 Assessment of risk of bias of the studies included in the systematic review

The ERG is generally satisfied with the assessments of risk of bias presented in the CS (see Table 7). The ERG is confident that stopping the trial early did not bias results since the OS data from this latter data-cut ([redacted]) are now virtually mature and consistent with the findings from 12-months (December 2014 data-cut). Furthermore, while CheckMate 017 was not a double-blind trial but concurs that blinding patients and health professionals would have been difficult for a number of reasons highlighted in Section 4.2.3; it may, however, have also been possible to have conducted an independent blinded assessment of ORR and PFS. However, the ERG also notes that of patients who received their allocated study drug (131 out of 135 patients in the nivolumab arm and 129 out of 137 patients in the docetaxel arm) a relatively large proportion discontinued docetaxel within the first week of starting treatment: [redacted] compared with [redacted] who withdrew treatment with nivolumab within the first week (if the four patients in the nivolumab arm and eight in the docetaxel arm who withdrew without ever receiving the study drug, the proportions rise to [redacted] and [redacted] respectively). The rate of early discontinuation in the docetaxel arm may be higher than would be expected in clinical practice and could therefore have introduced some bias from drop-outs

Table 7 Company's assessment of risk of bias for CheckMate 017 with ERG comments

Risk of bias criteria	CheckMate 017	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Agree
Were there any unexpected imbalances in drop-outs between groups?	No	Partially agree*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree
Did the analysis include an intention-to-treat analysis? Was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree

* A relatively large proportion of patients [redacted] discontinued docetaxel within the first week of starting treatment: Appendix 2.3 of the CSR reports [redacted] patients discontinued at the first cycle and the time to treatment discontinuation analysis of the Kaplan-Meier data supplied by the company during the clarification response also shows [redacted] patients out of 129 discontinued docetaxel treatment on day 1 ([redacted]); in the nivolumab arm, Appendix 2.3 of the CSR reports [redacted] patients discontinued at the first cycle and the time to treatment discontinuation analysis of the Kaplan-Meier data supplied by the company during the clarification response also shows [redacted] patients out of 131 discontinued nivolumab treatment on day 1 ([redacted]). In addition, Figure 7 of the CS shows that more patients in the docetaxel arm withdrew without ever receiving the study drug than in the nivolumab arm (eight and four respectively); six (75%) did so because they withdrew consent in the docetaxel arm compared with one (25%) for the same reason in the nivolumab arm
Source: CS, adapted from Table 14

4.2.5 Results from the studies included in the systematic review

Fourteen trials[8,31-43] were included in the company's systematic review. Excluding the CheckMate 017 trial, 11 trials[31-37,39,40,42,43] included one of the comparators specified in the NICE scope and data from these trials are summarised in the Appendices to this ERG report (Section 11.1,Table 41). In patients with squamous NSCLC, these findings can be interpreted to suggest that:

- erlotinib improves OS compared with placebo (BSC) (BR.21 trial[32])
- erlotinib is more efficacious than pemetrexed in terms of time to tumour response (HORG trial[37]) but possibly no more efficacious than pemetrexed in terms of OS (TITAN trial[36] which compared erlotinib with either pemetrexed or docetaxel)
- erlotinib is no more efficacious than docetaxel in terms of PFS (TAILOR trial[31]) and OS (TAILOR), data from the TITAN trial could also be argued to show no OS benefit for erlotinib over docetaxel (this trial compared erlotinib with either pemetrexed or docetaxel)
- nintedanib + docetaxel improves PFS but not OS when compared with docetaxel (LUME-Lung 1 trial[40]); the ERG notes that currently, nintedanib + docetaxel is only licensed for treatment of NSCLC patients with adenocarcinoma histology.

The remainder of this section focusses on the results from comparison of nivolumab with docetaxel from the CheckMate 017 trial.

The CheckMate 017 trial met its primary objective earlier than planned, demonstrating a statistically significant and clinically meaningful improvement in OS for patients in the nivolumab arm compared with patients in the docetaxel arm during a pre-planned interim analysis after 12 months (December 2014 data-cut). The study also demonstrated the consistent, statistically significant superiority of nivolumab over docetaxel across the secondary endpoints. The OS, PFS and response rate data from the 12-month interim analyses are summarised in Table 8. During the clarification process, the ERG requested OS and PFS data from a more recent data-cut, if available. The company provided OS and PFS data from the planned 18-month interim analysis ([redacted] data-cut); these data were presented at the World Lung Cancer Conference (September 2015)[45] and are summarised alongside the 12-months data in Table 8.

Table 8 Summary of efficacy findings from the CheckMate 017 trial

Endpoint	December 2014 data-cut		[redacted] data-cut	
	Nivolumab (n=135)	Docetaxel (n=137)	Nivolumab (n=135)	Docetaxel (n=137)
OS				
Events, n (%)	86 (63.7)	113 (82.5)	103 (76.3)	122 (89.1)
Stratified log-rank test p-value	p<0.001		p=0.0004	
HR for death (95% CI)	0.59 (0.44 to 0.79)		0.62 (0.48 to 0.81)	
Median OS, months (95% CI)	9.2 (7.3 to 13.3)	6.0 (5.1 to 7.3)	9.2 (7.33 to 12.62)	6.0 (5.29 to 7.39)
OS rate at 6 months (95% CI)	63.7 (55.0 to 71.2)	50.4 (41.7 to 58.4)	[redacted]	[redacted]
OS rate at 12 months (95% CI)	42 (34 to 50)	24 (17 to 31)	42 (34 to 50)	24 (17 to 31)
OS rate at 18 months (%)	NA	NA	28	13
PFS				
Events, n (%)	105 (77.8)	122 (89.1)	105 (77.8)	122 (89.1)
Stratified log-rank test p-value	p<0.001		p<0.0008	
HR for progression or death (95% CI)	0.62 (0.47 to 0.81)		0.63 (0.48 to 0.83)	
Median, months (95% CI)	3.5 (2.1 to 4.9)	2.8 (2.1 to 3.5)	3.5 (2.14 to 5.06)	2.8 (2.14 to 3.52)
PFS rate at 6 months (95% CI)	38.4 (30.0 to 46.8)	21.9 (15.1 to 29.5)	[redacted]	[redacted]
PFS rate at 12 months (95% CI)	21 (14 to 28)	6 (3 to 12)	21 (14 to 28)	6 (3 to 12)
PFS rate at 18 months (%)	NA	NA	17	2.7
Tumour response				
ORR, % of patients (95% CI)	20 (14 to 28)	9 (5 to 15)	Not reported*	Not reported*
Odds ratio estimate (95% CI)	2.6 (1.3 to 5.5)		NA*	
p value	p=0.008		NA*	
Median DOR, months (95% CI)	NtR [redacted]	8.41 [redacted]	Not reported*	Not reported*
Range, months: minimum to maximum	2.9 to 20.5+	+1.4 to 15.2+	Not reported*	Not reported*
Median TTR, months	2.2	2.1	Not reported*	Not reported*
Range, months: minimum to maximum	1.6 to 11.8	1.8 to 9.5	Not reported*	Not reported*

DOR=duration of response; HR=hazard ratio; NA=not applicable; NtR=not reached; ORR=overallresponse rate; OS=overall survival; PFS=progression-free survival; TTR=time to response
*Updated data were not requested by the ERG; these findings are expected by the ERG to be almost identical to those reported at the December 2014 data-cut since all patients can be considered to be a responder or a non-responder by the time of the first data-cut; however, it is possible that it would now be able to calculate the median DOR in the nivolumab arm
Source: CS, adapted from Tables 15 to 17 and company response to ERG's clarification letter (Table 1 and Table 2)

Overall survival

At the time of the December 2014 data-cut, the risk of death in the nivolumab arm was 41% lower than in the docetaxel arm. Median OS was improved by 3.2 months, with 42% of patients still alive at 12 months in the nivolumab arm, an increase of 18% compared with patients in the docetaxel arm. At the time of the [redacted] data-cut, the risk of death was very similar (38% lower in the nivolumab arm than that in the docetaxel arm) and median OS was still improved in the nivolumab arm by 3.2 months. The difference in survival rates between arms at 18 months (15%) was similar to the difference in survival rates between arms at 12 months (18%).

At the time of the December 2014 data-cut, the majority of results from subgroup analyses (including PD-L1 status) also appeared to favour nivolumab with the exception of patients aged 75 years and over and patients grouped as 'Rest of the World' (i.e. Argentina, Australia, Chile, Mexico, and Peru) where the findings appeared to favour docetaxel. For both subgroups, confidence intervals were wide and crossed 1 due to small sample sizes (n=29 and n=31 respectively) and therefore numbers of events were few. [redacted] a subgroup analysis conducted for age which suggested that patients aged 75 years and over experience no treatment benefit from nivolumab over docetaxel (HR=1.85; 95% 0.76 to 4.51). The company conducted three subgroup analyses for age, categorising patients as (i) <65 and ≥65 (ii) <75 and ≥75 and (iii) <65, ≥65 and <75 and ≥75. [redacted]

In Section 4.2.3, the ERG stated that it considered the patient population in the CheckMate 017 trial to be similar to patients treated in clinical practice in England. Additional evidence to support this assertion may be drawn from comparing the OS estimate in patients treated with docetaxel in the CheckMate 017 trial with estimates typically observed in clinical practice or reported in other trials. Clinical opinion received by the ERG is that patients treated with docetaxel typically have similar, possibly even worse, OS than patients included in the CheckMate 017 trial. Docetaxel OS data are available from the patients with squamous NSCLC in the EMPHASIS trial;[34] however EMPHASIS only reported findings based on serum protein status (poor or good) as defined by the VeriStrat test and not for all patients treated with docetaxel. In that trial OS ranged from 4.8 months (poor classification) to 7.8 months (good classification) for patients treated with docetaxel. These OS data compare well with the OS estimate of 6.0 months (95% CI 5.3 to 7.4) observed at the time of the [redacted] data-cut in the CheckMate 017 trial. The ERG is not aware of any other trial

evidence that has reported median OS for patients who have squamous NSCLC and been treated with second-line docetaxel.

It should be noted that although treatment crossover was not originally permitted in the CheckMate 017 trial, patients did receive subsequent lines of therapy following disease progression. At the time of the December 2014 data-cut, 49 (36%) patients in the nivolumab arm and 41 (24%) patients in the docetaxel arm received subsequent chemotherapy and five (4%) patients treated with nivolumab and eight (6%) patients treated with docetaxel received subsequent erlotinib. Of those receiving chemotherapy, most (39 [95%]) of the patients in the nivolumab arm received a subsequent taxane but only seven (17%) of those in the docetaxel arm received subsequent taxane therapy. Although 32 (24%) patients treated with nivolumab received subsequent docetaxel this is not considered crossover because the therapy received was in accordance with current treatment pathways and current standards of care. Following the analysis of OS at the December 2014 data-cut, the protocol was modified to allow patients initially treated with docetaxel to crossover to receive nivolumab; at the time of the most recent data-cut ([redacted]), only [redacted] patients had initiated nivolumab in this extension phase. Sensitivity analyses taking subsequent treatment into consideration were not reported in the CS but were reported in the EPAR.[1] The ERG is unaware as to the company's methods for adjusting for subsequent treatment (since these are not pre-specified in the protocol) but the results suggest a consistent effect in favour of nivolumab (HR=0.50, 95% CI: 0.35 to 0.71).

Progression-free survival

At the time of the December 2014 data-cut, median PFS for patients in the nivolumab arm was improved by 0.7 months compared with patients in the docetaxel arm. Median PFS is skewed by the first radiological assessment occurring after 9 weeks. Hence the risk of progression was 38% lower for patients treated with nivolumab than for patients treated with docetaxel. At 12 months, 21% of patients in the nivolumab arm were progression-free compared with 6% of patients in the docetaxel arm. As shown in Figure 9 of the CS, the Kaplan-Meier (K-M) curves for PFS for nivolumab and docetaxel start to separate at approximately 3 months and, over time, this separation continues to increase and is sustained.

Similar PFS findings were reported at the time of the [redacted] data-cut. The difference in median PFS was still 0.7 months and the risk of progression was 37% lower for patients treated with nivolumab than for patients treated with docetaxel. The difference in PFS rates between arms was 14.3%, similar to the difference between arms at 12 months (15%).

At the time of the December 2014 data-cut, the majority of subgroup results (including PD-L1 status) also appeared to favour nivolumab with the exception of patients over the age of 75. [redacted]

The ERG notes that both the company (see page 126 of CS) and the ERG (see Appendices to this ERG report, Section 11.9 for details) consider that the assumption of proportional hazards is violated for the PFS data in CheckMate 017. Therefore the ERG considers that the hazard ratio generated by the PFS data from the CheckMate 017 trial should be interpreted with caution.

Tumour response

The ORR (20%) in the nivolumab arm was double the rate in the docetaxel arm (9%). The only patient with a complete response in the CheckMate 017 trial was in the nivolumab arm and all other patients who experienced a response were partial responders. Median DoR was not reached in either arm but both the minimum and maximum values of the range were higher in the nivolumab arm than in the docetaxel arm. Median TTR was similar for both treatments (around 2 months).

The only subgroup analysis conducted for response was ORR across PD-L1 expression level subgroups (1%, 5%, 10%). The ORR observed in nivolumab-treated patients was numerically higher in PD-L1 high expressors, than in low expressors, but responses were also seen in PD-L1 low expressors. In all subgroups, the ORR was higher in patients treated with nivolumab than with docetaxel.

‘Non-conventional benefitters’

In the CheckMate 017 trial, patients in the nivolumab arm were permitted to continue to receive treatment with nivolumab if the clinician assessed the treatment to be having a beneficial effect, in spite of evidence of progression as defined by Response Evaluation Criteria in Solid Tumours (RECIST) criteria (Version 1.1), as per a trial protocol. This action was permitted because, as highlighted in the CS, immuno-oncology therapies such as nivolumab can, in some instances, have the initial effect of making the tumour appear bigger, which is thought to be due to the proliferation of activated T-cells infiltrating the tumour to destroy it. This is commonly referred to as an ‘unconventional immune-related response’ and can result in ‘pseudo-progression’ where patients who ultimately achieve a positive clinical outcome may appear to have tumours that have enlarged when assessed in the early stages of treatment. However, if patients continued to show evidence of progression at their next follow-up (around 6 weeks later) patients were considered to have progressed. In total, 28 (20.7%) patients continued to receive treatment for a further (approximately) [redacted] following progression. Of these, around a third (nine or 6.7% of all patients treated with nivolumab) were considered to derive clinical benefit from treatment beyond progression; these patients are referred to as ‘non-conventional benefitters’ in the CS. In the CheckMate 017 trial, a non-conventional benefitter was defined as a patient who had one of the following:

- appearance of a new lesion followed by decrease from baseline of at least 10% in sum of target lesions (five patients)
- initial increase from nadir ≥20% in sum of target lesions followed by reduction from baseline of at least 30% (one patient)
- initial increase from nadir ≥20% in sum of target lesions followed by at least two tumour assessments showing no further progression defined as 10% additional increase in sum of target lesions and new lesions (three patients).

Health related quality of life

In the CheckMate 017 trial, the effect of nivolumab treatment on patients' HRQoL was measured according to the Lung Cancer Symptom Scale (LCSS) Average Symptom Burden Index (ASBI) score (which is the mean score computed from the six symptom-specific questions of the LCSS) and EuroQol 5-Dimensions utility index (EQ-5D) and the EuroQol Visual Analogue Scale (EQ-VAS) at each assessment point. As described in Table 53 of the CS, assessments for both LCSS and EQ-5D/EQ-VAS were performed at every other cycle in the nivolumab arm (i.e. at 4 weeks, 8 weeks, 12 weeks, etc) or at every cycle in the docetaxel arm (i.e. 3 weeks, 6 weeks, 12 weeks, etc) for the first 24 weeks on study, then every 6 weeks thereafter in both arms for the remainder of the study. The scores were also assessed twice at 30 days and at 100 days following the last dose administered to patients.

Response rates for LCSS ASBI are not reported in the CS. Rates are presented in the CSR (Table S.10.1) and are reported to be [redacted] for nivolumab and [redacted] for docetaxel at baseline. However at [redacted] in the docetaxel arm and at [redacted] in the nivolumab arm, the number of available patients (i.e. all those eligible to complete a questionnaire) fell to 20 or less (n=[redacted]) and n=[redacted] respectively) although the actual number who did respond fell below 20 at [redacted] (n=[redacted]) and at [redacted] (n=[redacted]) respectively (CSR, Table S.10.1). Therefore, in addition to the two post-treatment follow-ups the company has only summarised on treatment findings up to [redacted] for nivolumab and up to [redacted] for docetaxel. Response rates at each follow-up assessment reported in the CSR (Table S.10.1) were [redacted] (n=[redacted] at 30 days) and [redacted] (n=[redacted] at 100 days) in the nivolumab arm and [redacted] (n=[redacted] at 30 days) and [redacted] (n=[redacted] at 100 days) at each follow-up assessment in the docetaxel arm. In terms of a response rate from baseline, the response rates across both arms were relatively low ([redacted] at 30 days and [redacted] at 100 days). In summary, the LCSS ASBI findings were as follows:

- statistically significant and clinically meaningful improvements from baseline were reported over time (from Week 12 through Week 54) in the nivolumab arm; in the docetaxel arm, scores remained relatively stable with no significant change from baseline through Week 18
- in both the nivolumab and docetaxel arms, treatment discontinuation was observed to be associated with a worsening in HRQoL as measured by the LCSS ASBI scores at the two follow-up visits; [redacted]

The company only planned to assess statistical significance for disease-related symptom improvement rate by Week 12 as measured by LCSS ASBI between randomisation and week 12 [redacted]. Hence aside from reasons relating to low response rates, findings which are reported to be

statistically significant after this point in time should also be treated with caution for being post-hoc analyses.

The EQ-5D (utility index and EQ-VAS) completion rates were almost identical to those for LCSS. Hence, again by [redacted] in the docetaxel arm and [redacted] in the nivolumab arm, the number of patients responding fell to 20 or less (n=[redacted] and n=[redacted] respectively; CSR, Table S.10.5 to Table S.10.10). Similarly, in terms of a response rate from baseline, the response rates across both arm were relatively low ([redacted] at 30 days and [redacted] at 100 days respectively). No adjustments were made for missing data when scoring the EQ-5D utility index. In summary, the EQ-5D/EQ-VAS findings were as follows:

- EQ-5D utility index scores were statistically significantly higher with nivolumab from baseline at Week 16 to Week 30 and at Week 42 to 54, with the improvements at Weeks 42 to 54 also being clinically meaningful; in the docetaxel arm, EQ-5D scores remained relatively stable with no significant change from baseline through Week 18
- EQ-VAS scores were statistically significantly higher with nivolumab from baseline at Week 12, Week 20 to 36 and Week 48, with the improvements at Weeks 24 to 36 and at Week 48 also being clinically meaningful; in the docetaxel arm, EQ-5D scores remained relatively stable with no significant change from baseline through Week 18
- after treatment discontinuation, there were no statistically significant differences from baseline at 30 days or 100 days using the EQ-5D utility index in either the nivolumab or docetaxel arms
- after treatment discontinuation, no statistically significant differences in EQ-VAS were reported in the nivolumab arm at 30 days or 100 days; for patients in the docetaxel arm, there was a statistically significant difference (worsening in HRQoL) from baseline using the EQ-VAS at 30 days but not at 100 days.

Given the low response rates, the ERG believe the EQ-5D/VAS findings should be treated with caution.

Adverse events

Comparative safety data from the CheckMate 017 trial demonstrated that nivolumab has a more favourable safety profile than docetaxel (Table 9). There were no deaths as a result of drug-related AEs for patients treated with nivolumab, compared with three (2%) of patients treated with docetaxel. All drug-related AEs, including drug-related serious AEs (SAEs), and drug-related AEs leading to treatment discontinuation, were less common in the nivolumab arm. The most frequently reported (≥1%) drug-related AE leading to discontinuation in the nivolumab arm was pneumonitis (2%). In the docetaxel arm, the most frequently reported (≥1%) treatment-related AEs leading to discontinuation were peripheral neuropathy (3%) and fatigue (2%).

Table 9 Summary of safety profiles in the CheckMate 017 trial

Type of AE	Proportion of patients with each type of AE (%)	
	Nivolumab (n=131)	Docetaxel (n=129)
All cause and any Grade AE	97	97
All cause Grade 3 to 5 AE*	51	73
All cause and any Grade SAE	47	54
All cause Grade 3 to 5 SAE*	39	46
All cause AE leading to discontinuation	11	20
All cause Grade 3 to 5 AE leading to discontinuation†	[redacted]	[redacted]
Drug-related AE	58	86
Drug-related Grade 3 to 5 AE†	[redacted]	[redacted]
Drug-related SAEs	7	24
Drug-related AE leading to discontinuation	3	10
Drug-related Grade 3 to 5 AE leading to discontinuation†	[redacted]	[redacted]
Death from drug-related AE	0	2

AE=adverse event; SAE=serious adverse event
Source: CS, adapted from pages 87 to 89 (including Table 27) except * taken from EPAR,[1] page 96 and † taken from CSR, Table 8.1-1

The toxic effect rates normally reported for traditional chemotherapies were lower for patients in the nivolumab arm than patients in the docetaxel arm (for a summary of types of AEs, see Appendices to this ERG report, Section 11.4, Table 44). The only drug-related AE that occurred in more patients in the nivolumab arm, than in the docetaxel arm, was pneumonitis (5% vs 0%). The majority of drug-related AEs in the nivolumab arm were reported to be Grade 1 or Grade 2, with only 7% Grade 3 to 4 (and [redacted] Grade 3 to 5) in severity compared with 55% Grade 3 to 4 (and [redacted] Grade 3 to 5) in the docetaxel arm.

In the CheckMate 017 trial, data were also collected for Select AEs (Table 10). The company defines Select AEs as a category of immune-related adverse events (irAEs) with immune-related aetiology that require more frequent monitoring or intervention with immune suppression. Select AEs are primarily caused by the inflammatory mechanism of the

immune system, are directly due to the immunologic mode of action of nivolumab and are based on the types of AEs observed across all nivolumab studies (where they are also sometimes referred to as AEs of special interest [AESIs]). The company notes that there are treatment algorithms for each Select AE category to guide management of these types of AE.[2] Typically treatment requires systemic corticosteroids.

Overall, the proportions of Select AEs were similar in both arms (Table 10); the incidence and severity of drug-related Select AEs are reported in Table 11. Skin and gastrointestinal AEs were the most common Select AEs with nivolumab (9% and 8% respectively). However, the ERG notes the same proportion of skin AEs was reported for patients treated with docetaxel and nivolumab (9%) but the proportion of gastrointestinal AEs with use of docetaxel (20%) was more than double that reported with use of nivolumab (8%). The majority of Select AEs were of low severity. There were only three Grade 3 drug-related Select AEs reported with treatment with nivolumab: a case of tubulointerstitial nephritis, a case of colitis and a case of pneumonitis. No Grade 4 or Grade 5 Select AEs were reported in the nivolumab arm.

Table 10 Summary of Select AEs in CheckMate 017

Type of Select AE	Proportion of patients (%)	
	Nivolumab (n=131)	Docetaxel (n=129)
All cause Select AE	[redacted]	[redacted]
Drug-related Select AE	[redacted]	[redacted]
Median time to onset of drug-related Select AEs, weeks	0.3 to 17.6	1.0 to 17.6
Median time to resolution of drug-related Select AEs, weeks	0.3 to 0.5	0.7 to 5.6

Source: CS, adapted from Table 27 and page 92

In summary, the ERG agrees with the company that the overall safety profiles of both nivolumab and docetaxel were consistent with expectations based on prior data with respect to the type, frequency, and severity of AEs. Further information on AEs from previous nivolumab studies is reported in the Appendices to this ERG report (Section 11.5.3) and the results of a pooled analysis of AEs from the EPAR[1] are also summarised in the Appendices to this ERG report (Section 11.6).

Table 11 Summary of drug-related Select adverse events in CheckMate 017

Type of AE	Patients with each type of AE, n (%)			
	Nivolumab (n=131)		Docetaxel (n=129)	
	All Grade	Grade 3 to 5	All Grade	Grade 3 to 5
Endocrine	5 (4)	0	0	0
• Hypothyroidism	5 (4)	0	0	0
Gastrointestinal	11 (8)	1 (1)	26 (20)	3 (2)
• Diarrhoea	10 (8)	0	26 (20)	3 (2)
• Colitis	1 (1)	1 (1)	0	0
Hepatic	2 (2)	0	2 (2)	1 (1)
• Alanine aminotransferase increased	2 (2)	0	1 (1)	1 (1)
• Aspartate aminotransferase increased	2 (2)	0	1 (1)	1 (1)
• Blood bilirubin increased	0	0	1 (1)	0
Pulmonary	7 (5)	1 (1)	0	1 (1) †
• Pneumonitis	6 (5)	1 (1)	0	0
• Lung infiltration	1 (1)	0	0	0
• Interstitial lung disease	0	0	0	1 (1) †
Renal	4 (3)	1 (1)	3 (2)	0
• Blood creatinine increased	4 (3)	0	2 (2)	0
• Tubulointerstitial nephritis	1 (1)	1 (1)	0	0
• Renal failure acute	0	0	1 (1)	0
Skin	12 (9)	0	11 (9)	2 (2)
• Rash	5 (4)	0	8 (6)	2 (2)
• Pruritus	3 (2)	0	0	0
• Erythema	1 (1)	0	2 (2)	0
• Rash maculopapular	1 (1)	0	0	0
• Skin exfoliation	1 (1)	0	2 (2)	0
• Urticaria	1 (1)	0	0	0
• Palmar-Plantar erythrodysaesthesia syndrome	0	0	1 (1)	0
Hypersensitivity/infusion reaction	1 (1)	0	3 (2)	1 (1)
• Infusion-related reaction	1 (1)	0	1 (1)	0
• Hypersensitivity	0	0	2 (2)	1 (1)

AE=adverse event
NOTE: a patient may be recorded as having more than one adverse event within a category
† Grade 5 AE; there were no Grade 5 AEs (i.e. deaths) in the nivolumab arm
Source: adapted from CS, Table 29

4.3 Critique of the indirect treatment comparisons

The company carried out two ICTs. The first compared nivolumab with erlotinib (in patients who had received only one previous line of therapy) and the second compared nivolumab with BSC (in patients who had received one or more previous lines of therapy). ITCs were required because there were no data available from head to head trials to enable any of the comparisons to be made directly. Different patient populations were utilised due to differences in trial populations, as described in this Section.

4.3.1 Included studies in the indirect treatment comparisons and statistical approach employed

Using broad criteria, 14 trials[8,31-43] were eligible for inclusion in the company's original systematic review of clinical effectiveness data. Of these, data from three were included in the ITCs: CheckMate 017, TAILOR[31] and BR.21.[32] The other eleven studies[33-43] identified by the company did not add any information to the comparisons between the relevant comparators. The ERG did not identify any additional studies that met the company's eligibility criteria for inclusion in the ITCs.

The ERG notes that in BR.21, erlotinib was compared with placebo; the company assumes that in this study all of the patients who were randomised to placebo continued to receive palliative BSC. Therefore, the company reasons that it is appropriate to assume that the clinical effectiveness data from the placebo arm of BR.21 can be used to describe patients receiving BSC. The ERG is satisfied that this is a valid assumption and from hereafter refers to the comparison in BR.21 as erlotinib versus BSC. BSC is a part of the care package offered to all patients with squamous NSCLC, regardless of eligibility for systemic anti-cancer therapies and line of treatment. Therefore the ERG notes that all patients also treated with nivolumab and erlotinib can be considered to receive BSC

The company performed the ITCs using the Bucher method, as described in Appendix 7.1 of the CS. The Bucher method can be used to obtain indirect estimates of treatment effect when there are no closed loops in the network of evidence. As is evident from Figure 2, there were no closed loops in the available network of evidence and hence the ERG is satisfied that the modelling approach chosen by the company was appropriate.

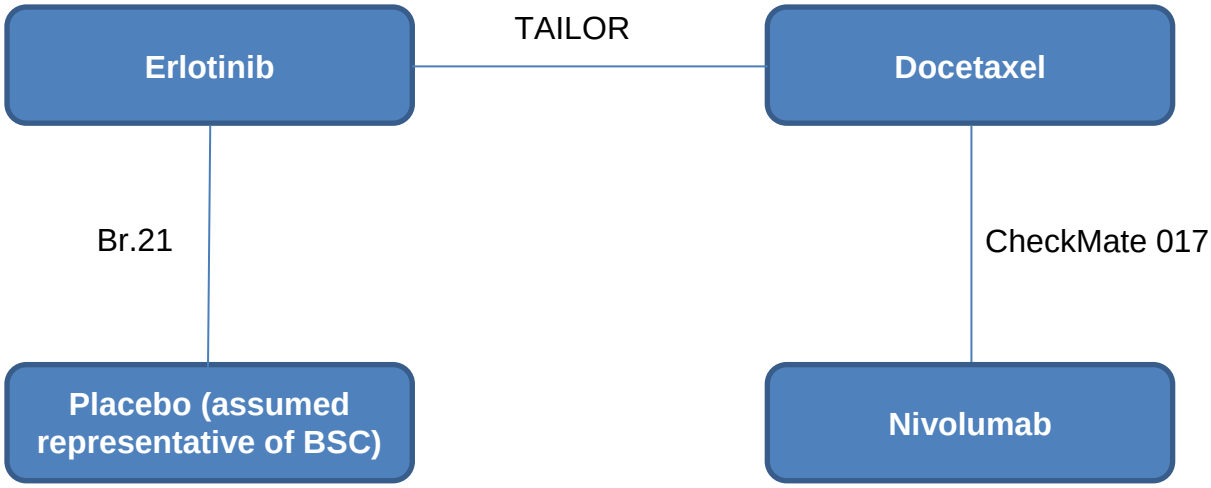


Figure 2 Network diagram for ITCs

BSC=best supportive care
Source: CS, adapted from Appendix 7.15 (Figures 5, 10 and 11)

The patient population described in the company's decision problem is previously treated patients with locally advanced or metastatic squamous NSCLC. For the comparison of nivolumab versus erlotinib, data were available from patients in the CheckMate 017 and TAILOR trials who had been treated with only one prior therapy (the ERG notes that in the TAILOR trial, in 7% of all patients, treatment was prior adjuvant treatment rather than first-line treatment for advanced NSCLC). However, for the comparison of nivolumab versus BSC, data were available from the CheckMate 017 and TAILOR trials in which all patients had received only one previous line of chemotherapy and from the BR.21 trial in which patients had received one or more lines of chemotherapy. Therefore, some patients in the BR.21 study received study treatment as third-line treatment.

It is important to note that both the TAILOR and BR.21 trials were performed in populations that included both squamous and non-squamous patients. Therefore, the data used to inform the ITCs were taken from the results of subgroup analyses of squamous patients in these trials. The outcomes of interest for the ITCs were OS and PFS. However, PFS data were not available from the subgroup analysis of BR.21; therefore, the comparison between nivolumab and BSC was conducted using OS data only.

The populations, comparators and outcomes used to inform the ITCs from each study are summarised in Table 12. The characteristics of trials included in the ITCs are summarised in Table 13.

Table 12 Key characteristics of RCTs included in the ITCs

Trial name	Intervention	Comparator	Population used in ITC	Outcomes used in the ITC
CheckMate 017	Nivolumab	Docetaxel	Whole population (squamous patients), n=272	OS and PFS
TAILOR	Erlotinib	Docetaxel	Squamous patients subgroup, n=54	OS and PFS
BR.21	Erlotinib	Placebo (assumed to be representative of BSC)	Squamous patients subgroup (2^{nd} or later line therapy), n=233	OS

BSC=best supportive care; OS=overall survival; PFS=progression-free survival

Table 13 Further details about the RCTs included in the ITCs

Trial	Design	Location	Intervention/ comparators (n)	Duration	Patient population
CheckMate 017	Randomised, multicentre international, open-label, active-controlled Phase III study	21 countries worldwide	Nivolumab (135) Docetaxel (137)	Duration of the study from start of randomisation to final analysis: approximately 38 months (14 months of accrual + 24 months of follow-up) Minimum follow-up: 10.6 months	Age >18 years Histologically- or cytologically-documented squamous cell NSCLC (stage IIIB/IV) Recurrent or PD following multimodal therapy Recurrence or progression during or after 1 prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease Measurable disease by CT or MRI per RECIST 1.1 criteria ECOG PS ≤1
TAILOR	Randomised, multicentre, open-label, active-controlled Phase III study	105 sites in Italy	Erlotinib (109) Docetaxel (110) Note: squamous NSCLC is a subgroup analysis: erlotinib (31) docetaxel (23)	Median follow-up: 33 months	Age ≥18 years Histological or cytological confirmation of NSCLC Locally advanced or metastatic NSCLC in second-line treatment Wild-type EGFR Recurrence or progression after platinum-based chemotherapy No previous treatment with taxanes or anti-EGFR drugs ECOG PS ≤2 Adequate vital function
BR.21	Randomised, multicentre international, double-blind, placebo-controlled Phase III study	15 countries worldwide	Erlotinib (488) BSC (243) Note: squamous NSCLC is a subgroup analysis: erlotinib (144) BSC (78)	Not reported	Age ≥18 years Stage IIIB or IV NSCLC ECOG PS 0 to 3 1 or 2 prior chemotherapy Ineligible for further chemotherapy Adequate haematologic and biochemical values

CT=computerised tomography; ECOG=European Cooperative Oncology Group; EGFR=epidermal growth factor receptor; MRI=magnetic resonance imaging; NSCLC=non-small cell lung cancer; PD=progressive disease; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumors
Source: CS, Table 18

4.3.2 Participant characteristics of included studies in the indirect treatment comparisons

Baseline characteristics of the patients recruited to RCTs that were included in the ITCs are reported in Table 14. The ERG notes that the baseline characteristics are provided for the whole trial populations for the TAILOR and BR.21 trials, rather than for the subgroups of squamous patients who are included in the ITCs; for BR.21 the data are reported in a trial report by Shepherd *et al* [46] that was published in 2005 whereas data for patients with squamous NSCLC were only available from a later retrospective analysis by Clark *et al* [32] that was published in 2008. Therefore, it is difficult to assess whether the trial populations included in the ITCs are comparable, and consequently whether performing ITCs is suitable for this network of evidence.

Due to differences in eligibility criteria, the proportions of patients with different types of ECOG PS varied considerably between the included trials. Patients included in BR.21 were generally less fit (higher ECOG PS) than patients in the TAILOR and CheckMate 017 trials. In the BR.21 trial a considerable proportion of patients had ECOG PS 2 (25.8% in the erlotinib arm and 23% in the BSC arm) or ECOG PS 3 (8.6% in both arms), whereas all patients in the TAILOR and CheckMate 017 trials had ECOG PS 0 or 1. Moreover, patients in the TAILOR trial appeared to be fitter (lower ECOG PS) than in either of the other two trials: 48% had ECOG PS 0 in both the docetaxel and erlotinib arms, compared with between 13% and 14% in the BR.21 trial (erlotinib and BSC arms respectively) and 20% and 27% (nivolumab and docetaxel arms respectively) in the CheckMate 017 trial.

The trials also differed with regards to the smoking status of the patient populations; the CheckMate 017 trial included more current or former smokers (90% in the nivolumab arm and 94% in the docetaxel arm) than the BR.21 trial (73% in the erlotinib arm vs 77% in the placebo arm), and the TAILOR trial (73% in the docetaxel arm vs 83% in the erlotinib arm). Furthermore, the CheckMate 017 trial included more male patients (82% in the nivolumab arm vs 71% in the docetaxel arm) than the BR.21 trial (65% in the erlotinib arm vs 66% in the placebo arm), and the TAILOR trial (66% in the docetaxel arm vs 71% in the erlotinib arm). The ERG considers that these differences may be due to the fact that the CheckMate 017 trial included squamous patients only, since squamous patients are more likely to be male and to be smokers than patients with non-squamous NSCLC.

Table 14 Summary of the baseline characteristics of studies included in the ICTs

Trial	Treatment arm	N	Median age (range) years	Male %	Current/ former smoker %	ECOG PS 0 %	ECOG PS 1 %	ECOG PS 2 %	ECOG PS 3 %	Disease stage %	Histology %	EGFR mutation status %
CheckMate 017	Nivolumab	135	62 (39 to 85)	82	90	20	79	0	0	Stage III: 22 Stage IV: 78	SQ: 100	Wild-type: 100*
	Docetaxel	137	64 (42 to 84)	71	94	27	73	0	0	Stage III: 18 Stage IV: 82		
TAILOR	Docetaxel	110	67 (35 to 83)	66	73	48	45	6	0	Not reported	SQ: 25 NSQ: 75	Wild-type: 100
	Erlotinib	109	66 (40 to 81)	71	83	48	44	8	0			
BR.21	Erlotinib	488	62 (34 to 87)	65	73	13	53	26	9	Stage III/IV: 100	SQ: 31 NSQ: 70	Wild-type: 77† Positive: 23†
	BSC	243	59 (32 to 89)	66	77	14	54	23	9	Stage III/IV: 100		

ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; NSQ=non-squamous; ECOG PS=performance status; SQ=squamous
*Assumed to be 100% since all patients had squamous NSCLC
†Not all patients were tested for EGFR status, number of tested, n=177 (24%)
Source: CS, adapted from Table 19 and Table 20

4.3.3 Assessment of risk of bias of the studies included in the indirect treatment comparisons

The company conducted an assessment of the risk of bias of the studies included in the ITCs and the results are presented in the CS and shown in Table 15.

While, overall, considered to be at a low risk of bias, both the CheckMate 017 and TAILOR trials were considered to be at a high risk of bias for blinding due to being open-label trials. However, the ERG notes that since nivolumab is infused every 2 weeks, docetaxel is infused every 3 weeks and erlotinib is given in tablet form, it would be challenging to compare any combination of these treatments with each other in a blinded manner. The BR.21 trial is described by its study authors as being double-blind (although details of blinding are not provided); it was considerably easier to introduce blinding in this trial comparing erlotinib with BSC since patients in both arms would receive an element of BSC and a placebo tablet was administered instead of erlotinib in the control arm.

In addition, as noted in Section 4.2.4, the ERG notes that in CheckMate 017, a relatively large proportion ([redacted]) discontinued docetaxel within the first week of starting treatment compared with [redacted] who withdrew treatment with nivolumab within the first week. The ERG considers that the rate of early discontinuation in the docetaxel arm may be higher than would be expected in clinical practice and could introduce bias from drop-outs. It is further noted that this information is derived from the CSR for CheckMate 017 and not reported in the published paper. Such information is rarely reported in published papers and so it is unclear if a similar situation occurred in either of the TAILOR or BR.21 trials.

Table 15 Summary of quality assessment of RCTs included in ITCs

Trial	JADAD score	Allocation concealment grade	Was randomisation carried out appropriately?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
CheckMate 017	3	A IVRS was used which ensures the allocation sequence is unknown	Low risk; the patients enrolled in the trial were randomised in a 1:1 ratio using IVRS, stratified by prior treatment with paclitaxel-based doublet vs. other doublet, and region (US vs. Europe vs. Rest of World)	Low risk; the baseline characteristics in the two groups were well balanced	High risk; this was an open-label trial	Low risk; study withdrawals were adequately reported	Low risk; the authors measured all outcomes as reported in the protocol	Low risk; ITT was used for efficacy analysis while mITT was used for safety analysis
TAILOR	2	B Method of allocation was not reported	Not clear; treatment was randomly allocated in a 1:1 ratio with a minimisation algorithm, which stratified treatment allocation by centre, stage, type of first-line platinum-based chemotherapy and ECOG status (0 to 1 vs 2)	Low risk; there was no significant difference in the baseline characteristics reported between the two treatment arms	High risk; this was an open label study	Low risk; the withdrawals and the specific reasons for withdrawal were reported	High risk; Author has not measured all the outcomes that have been listed in clinical trial registry	Low risk; the primary efficacy and safety analysis was done using mITT population
BR.21	3	A Patients were centrally allocated to the respective treatment	Not clear; this was a randomised study but the method of randomisation was not reported	Low risk; the baseline characteristics between the two treatment arms were well balanced	Not clear; Although this was stated to be a double-blind trial, the details of blinding were not reported	Not clear; Withdrawals and reasons for withdrawals were not reported	Low risk; the authors measured all outcomes as reported in the protocol	Low risk; the safety and efficacy analysis was performed using ITT population

ECOG=Eastern Cooperative Oncology Group; HR=high risk; LR=low risk; NR=not reported; IVRS=interactive voice response system; ITT=intention to treat; mITT=modified intention to treat
Source: CS, adapted from Table 21

4.3.4 Individual study findings from the studies included in the indirect treatment comparisons

Efficacy results from the studies included in the ITCs are provided in Table 16. The results presented for the BR.21 and TAILOR trials are from the respective subgroups of patients with squamous NSCLC. In summary:

- in the CheckMate 017 trial, a statistically significant improvement in OS and PFS was reported for nivolumab versus docetaxel
- a statistically significant improvement in OS was reported for erlotinib in comparison with BSC in the BR.21 trial; no comparison was made for PFS in the subgroup of squamous NSCLC patients
- in the TAILOR trial there was no statistically significant difference between erlotinib and docetaxel in terms of PFS or OS.

Table 16 Summary of data from trials included in indirect treatment comparisons

Trial	Treatment (N)	ORR n (%)	DCR n (%)	OS rate at 12 months n (%)	OS (Reported as median) (95% CI) months	OS (Reported as HR) (95% CI)	PFS (Reported as median (95% CI) months	PFS (Reported as HR) (95% CI)	Withdrawals due to treatment related AE n (%)
CheckMate 017	Nivolumab (135)	27 (20)	66 (49)	57 (42)	9.23 (7.33 to 13.27)	0.59 (0.43 to 0.81)	3.48 (2.14 to 4.86)	0.62 (0.47 to 0.81)	4 (3) Evaluable n=131
	Docetaxel (137)	12 (9)	59 (43)	32 (23)	6.01 (5.13 to 7.33)		2.83 (2.1 to 3.52)		13 (10) Evaluable n= 129
TAILOR	Docetaxel: squamous (23)	N/A	N/A	N/A	N/A	0.90 (0.49 to 1.65)	N/A	0.57 (0.32 to 1.03)	N/A
	Erlotinib: squamous (31)	N/A	N/A	N/A	N/A		N/A		N/A
BR.21	Erlotinib: squamous (144)	N/A	N/A	N/A	N/A	0.67 (0.5 to 0. 9)	N/A	N/A	N/A
	BSC: Squamous (78)	N/A	N/A	N/A	N/A		N/A	N/A	N/A

AE=adverse event; CI=confidence interval; DCR=disease control rate; HR=hazard ratio; PFS=progression-free survival; ORR=overall response rate; OS=overall survival; N/A=not available
Source: CS, Table 22

4.3.5 Results from indirect treatment comparisons

Summary of company's results

The results of the ITCs carried out by the company are provided in Table 17. The ERG notes that while the company has attempted to compare the efficacy of nivolumab with erlotinib and BSC, the company did not attempt to compare safety (e.g. incidence of AEs).

In the patient population of squamous patients who had received only one prior therapy, an ITC between nivolumab and erlotinib was performed. The results suggest that, when compared with erlotinib, nivolumab statistically significantly improves PFS, but not OS.

In the population of squamous patients who had received one or more prior therapies, an ITC between nivolumab and BSC was performed. The results suggest that, when compared with BSC, nivolumab significantly improves OS. It was not possible to compare PFS for nivolumab versus BSC due to there being no relevant comparison in the BR.21 trial. For the comparison of nivolumab with erlotinib, even if the criteria were widened to include studies that allowed additional lines of therapy, there were no new data available; therefore the results for nivolumab versus erlotinib are identical under both scenarios.

Table 17 Results of the ITCs

Outcome	Nivolumab vs erlotinib	Nivolumab vs BSC
	HR (95% CI); p-value	HR (95% CI); p-value
Patient population: squamous NSCLC in patients with one prior therapy only		
OS	[redacted]	
PFS	[redacted]	
Patient population: squamous NSCLC in patients with one or more prior therapies		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

BSC=best supportive care; CI=confidence interval; HR=hazard ratio; ITC=indirect treatment comparison; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival
Source: Table 23 of the CS

ERG critique of the company's results from the ITCs

The company states that the findings from the two ITCs should be treated with caution because of several differences identified across the included studies:

- the CheckMate 017 and TAILOR trials included patients who had received only one line of therapy, whilst patients in the BR.21 trial had received more than one previous treatment
- differences in the eligibility criteria of the included trials led to variations in the proportions of patients by ECOG PS across the included trials; patients included in the BR.21 trial were less fit than patients in the TAILOR and CheckMate 017 trials

- based on the characteristics of the whole populations in TAILOR and the BR.21 trials, the CheckMate 017 trial appears to have included a patient population with more current or former smokers and more males than the TAILOR and BR.21 trials.

The company concluded that the level of heterogeneity identified due to these differences affected the validity of the results of the ITCs. The ERG concurs with the company's view that these differences in patient characteristics are important and may render the results of the ITCs unreliable or even meaningless.

More importantly, the ERG considers that it was not appropriate for the company to conduct either of the ITCs due to the lack of informative survival data available from the TAILOR and BR.21 trials. For the comparison of nivolumab with erlotinib, data are available from the TAILOR trial as reported by Garassino *et al* 2013; in this paper, only a hazard ratio for OS is presented. For the comparison of nivolumab versus BSC, data are available from the BR.21 trial, as reported by Clark *et al* 2007; in this paper, only median OS data and a hazard ratio are available. These data are not sufficient to allow the required assumption of proportional hazards to be tested for either the PFS or OS outcomes. In addition, the ERG considers that data from the CheckMate 017 trial show that the proportional hazards assumption for PFS is violated and this means that the PFS results from the ITC comparing nivolumab with erlotinib are definitely not reliable. The ERG, therefore, considers that the results of the two ICTs conducted by the company are not reliable and that the clinical effectiveness of nivolumab versus erlotinib and nivolumab versus BSC remain unknown.

4.4 Summary and critique of supportive evidence from non-randomised studies

In addition to the Phase III RCT (CheckMate 017), evidence from two non-RCTs was also submitted by the company: a single-arm Phase I dose-escalation study (CheckMate 003) and a single-arm Phase II study (CheckMate 063). Results from the Phase I study led to the company adopting the 3mg/kg dose for nivolumab. The characteristics and findings relating to these trials are summarised by the ERG in the Appendices to this ERG report (Section 11.5, Table 46 and Table 47). The following observations are made by the ERG:

- for all efficacy endpoints, patients in the CheckMate 003 study appear to have more favourable outcomes than those in the CheckMate 063 study; this may be because the CheckMate 063 study only included patients with two or more previous lines of systemic therapy (20.5% had received four or more prior lines of therapy), whilst CheckMate 003 also included a minority of patients with only one prior therapy (46% had 1 to 2 prior therapies).
- the OS findings for squamous patients included in the CheckMate 003 study are broadly comparable with those reported for patients treated with nivolumab in the CheckMate 017 trial
- the safety profile of the CheckMate 063 study is broadly similar to that of the CheckMate 003 study and both non-randomised studies also appear to have a safety profile consistent with that of the CheckMate 017 trial
- given that the majority of patients in both the CheckMate 003 and CheckMate 063 studies were more heavily pre-treated than in CheckMate 017 (most had received three previous systemic therapies) but still had an ECOG PS of 0 or 1, the patients included in these non-randomised studies are unlikely to be typical of those seen in clinical practice in England.

4.5 Additional work on clinical effectiveness (safety) undertaken by ERG

4.5.1 Select AEs

As Select AEs are a category of irAEs that are not associated with traditional chemotherapy, the ERG has summarised the data on Select AEs for each of the nivolumab studies included in the CS: CheckMate 017, CheckMate 003 and CheckMate 063. In addition, data from CheckMate 153 [47] are also summarised. CheckMate 153 is referred to in the CS as an ongoing safety study ([redacted]) in which responders are randomised at 1 year to either stop nivolumab or to continue nivolumab treatment until progression. The company provided data describing 824 patients with either squamous or non-squamous NSCLC during the clarification process (see Appendices to this ERG report, Section 11.7, for more information about this study).

The ERG observes that the proportion of Select AEs by each type of category appears to be similar across all four studies, with a few exceptions (Section 11.6, Table 48):

- all cause skin AEs, all cause renal AEs and cause hypersensitivity/infusion reactions were markedly more common in the [redacted] study than in the CheckMate 003 study [redacted]
- the incidence of all cause Grade 3 to 4 pulmonary AEs and cause Grade 3 to 4 gastrointestinal AEs was markedly higher in the [redacted] study than in the CheckMate 003 study [redacted]
- [redacted] were markedly more common [redacted] than in the CheckMate 017 trial or CheckMate 153
- the incidence of drug-related pulmonary and renal AEs was markedly higher in the CheckMate 017 trial [redacted] than in CheckMate 153.

4.5.2 Comparison of the safety of nivolumab with erlotinib and BSC

In the absence of any comparison of the safety profiles of nivolumab with erlotinib or BSC, the ERG has extracted AE data from the recently published LUX-Lung 8 trial[16] which compared afatinib to erlotinib as a second-line treatment for a population of patients with advanced or metastatic squamous NSCLC (Section 11.8). In summary, the ERG observes that:

- from the data available, the results of a crude comparison suggest there appears to be little difference between nivolumab and erlotinib treatment in terms of overall incidence of AEs, with the exception of drug-related AEs which appeared to be much more common when patients are treated with erlotinib
- while both rash and diarrhoea have been highlighted as irAEs associated with treatment with nivolumab, the incidence of these drug-related AEs (both any Grade and Grade 3 to 4) in the CheckMate 017 trial for patients treated with nivolumab was much lower than the incidence reported for patients treated with erlotinib in LUX-Lung 8
- there were five drug-related deaths (1.3%) in the erlotinib arm of LUX-Lung 8; the patients died of interstitial lung disease, pneumonitis, pneumonia, intestinal obstruction and peritonitis; no drug-related deaths were reported for patients in the nivolumab arm of the CheckMate 017 trial.

Since BSC is a broad term for palliative treatment that can consist of a whole range of different palliative measures, the ERG agrees that it is impossible to establish a broad safety profile for BSC as a whole and, therefore, meaningful comparisons cannot be made. The ERG did not undertake any further work in this regard.

4.6 Conclusions of the clinical effectiveness section

The company has provided evidence from the CheckMate 017 trial suggesting that, after one previous line of chemotherapy, nivolumab improves OS for patients with squamous NSCLC when compared with docetaxel. Even though the proportional hazards assumption does not hold for PFS, data showing PFS rates at 12 and 18 months suggest that nivolumab results in better outcomes for patients compared with those treated with docetaxel. While nivolumab is a PD-1 inhibitor, there is no evidence from the CheckMate 017 trial to suggest that treatment should be targeted based on PD-L1 status.

The ERG notes that RECIST criteria were used to evaluate treatment response and PFS in the CheckMate 017 trial; these criteria may not be optimal for capturing response when using an immuno-oncology therapy such as nivolumab. In addition, a relatively large proportion (■) of patients discontinued treatment with docetaxel within 1 week; this rate appears to be higher than expected when used in clinical practice in England. Nivolumab appears to have a better safety profile than docetaxel and may result in improved HRQoL for patients. However, the HRQoL data are less robust than the clinical efficacy data as no statistically significant difference was reported in LCSS ASBI at Week 12 (the protocol defined point in time as which a statistical significance for disease-related symptom improvement rate was planned) and response rates for both LCSS ASBI and EQ-5D/VAS were low.

Patients in the CheckMate 017 trial are broadly similar to patients who would be treated in clinical practice in England. However, there are other patients who may also be seen in clinical practice and to whom the clinical effectiveness data do not apply. Namely, patients with ECOG PS>1 in particular, and patients using higher-dose corticosteroids.

Other comparators listed in the NICE scope and referenced in the company's decision problem were erlotinib and BSC. The ERG concurs with the company that docetaxel is the current standard of care for patients with squamous NSCLC who have been previously treated with one line of chemotherapy and that erlotinib and BSC are less relevant comparators. It was only possible to compare nivolumab with these comparators via ITCs. The company has acknowledged that the results of the ITCs should be treated with caution due to heterogeneity across the trials; the ERG concurs with the company's view. Moreover, the ERG considers the results of the company's ITCs to be unreliable as there are insufficient data available from the included studies to determine whether the assumption of proportional hazards, which underpins the reliability of results from any ITC, can be supported.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of prescribing nivolumab for the treatment of patients with locally advanced or metastatic squamous NSCLC previously treated with chemotherapy.

The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company also provided an electronic version of the economic model which was developed in Microsoft Excel.

5.1 ERG summary of the company's review of cost effectiveness evidence

5.1.1 Objective of the company's cost effectiveness literature review

The company's search was conducted to identify evidence to support the development of the company's cost effectiveness and budget impact models. The review focussed on identifying evidence relevant to patients with pre-treated locally advanced or metastatic NSCLC. Details of the search strategies employed by the company are provided in Appendix 11 of the CS. The data sources for the economic systematic review are outlined in Table 18. The searches were conducted in February 2015.

Table 18 Data sources for economic systematic review

Search strategy component	Sources	Date limits
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies	MEDLINE® MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL)	01 January 2000 to 23 February 2015
Conference proceeding	HTA International	2012, 2013, 2014
	International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	
	Society for Medical Decision Making	

Source: CS, Table 35

5.1.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria used to facilitate study selection are presented in Table 19.

Table 19 Economic evaluation inclusion/exclusion criteria

Parameter	Economic evaluations
Patient population	• Adults diagnosed with locally advanced or metastatic non-small cell lung cancer pre-treated with at least one previous line of chemotherapy
Intervention	• Nivolumab
Comparator	• Any pharmacological intervention • Placebo • Best supportive care • Afatinib • Docetaxel • Erlotinib • Gefitinib • Nintedanib (in combination with docetaxel) • Pemetrexed monotherapy • Ceritinib • Crizotinib • Platinum therapy in combination with gemcitabine, vinorelbine, pemetrexed, or a taxane
Outcome	• Studies will not be excluded based on the reported outcomes
Study design 1 (S1)*	• All economic evaluation studies based on models • Cost effectiveness analysis • Cost utility analysis • Cost minimisation analysis • Budget impact models
Study design 2 (S2)*	• Randomised controlled trials • Database studies • Prospective observational studies • Retrospective observational studies
Line of therapy	• Second- or further-line of therapy
Search timeframe	• 2000 to 2015 (last 15 years)
Language	• Only studies with the full-text published in English language included
Exclusion criteria	• Reviews, letter to the editors, and editorials • Studies reporting only cost and resource use data where no formal economic analysis has been undertaken
	• Animal/*in vitro* studies • Single-arm studies • Studies with no subgroup data for disease and adult population • Studies investigating first-line treatment for non-small cell lung cancer • Studies assessing included intervention as an adjuvant or neo-adjuvant therapy • Studies evaluating included intervention in combination with radiotherapy • Studies comparing different doses of the same intervention (i.e. dose-ranging studies), two formulations of the same intervention, and intervention with two different routes of administration
	• Conference abstracts prior to 2012 will be excluded.

*Within the single systematic review, two sets of study design criteria were used to identify relevant economic evaluations (S1) and relevant clinical studies (S2) reporting data on quality of life in second-line or later-line patients with NSCLC
Source: CS, Table 36

5.1.3 Included and excluded studies

None of the studies identified by the company's search evaluated the cost effectiveness of treatments in a squamous only population and, furthermore, no studies considered treatment with nivolumab. The company identified four relevant appraisals (Crizotinib [TA296[48]] Erlotinib [TA162[49]] Erlotinib and gefitinib [Review of TA162 and TA175)[17]] and Nintedanib [TA347[50]]) and these studies were used to inform the development of the economic model (see Table 38 of the CS). Two relevant UK-based cost effectiveness studies[51,52] were also identified by the company's search. Both included patients with NSCLC who had been previously treated (CS, Table 37); one study[51] compared docetaxel with BSC and the other[52] compared erlotinib with docetaxel. Holmes *et al* [51] reports an incremental cost per life year gained (LYG) for docetaxel versus BSC of £13,863. Lewis *et al* [52] found erlotinib to be dominant when compared with docetaxel. The models described in these two studies[51,52] and the four relevant models [17,48-50,53] submitted previously as part of technology appraisals report all used a three-state partitioned survival model representing progression-free (PF) disease, progressive disease (PD) and death.

5.2 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and is confident that there are no studies that fully meet the company's inclusion criteria. The databases searched and search terms used appear to be reasonable. The ERG considers the wider search for published economic literature (e.g inclusion of non-squamous patient population) to be appropriate when taking into account the shortage of relevant clinical and economic data for patient populations with advanced or metastatic squamous NSCLC.

The ERG acknowledges that the company reports the methods and results for searches carried out to identify HRQoL data relevant to the second-line, or later-line, treatment of patients with NSCLC, as well as resource requirements and costs associated with patient treatment. The ERG considers these details to be very helpful.

5.3 ERG's summary of company's submitted economic evaluation

5.3.1 Model structure

The company has developed a de novo economic model which is a cohort-based partitioned survival model comprised of three mutually exclusive health states: PF, PD and death. The model was developed in Microsoft Excel and the structure is consistent with previous economic evaluations submitted to NICE as part of appraisals of treatments for advanced NSCLC and other metastatic cancers (e.g. Nintedanib TA347,[50] Erlotinib TA258[53] and Bevacizumab TA212[54]). A schematic of the company's model is shown in Figure 3.

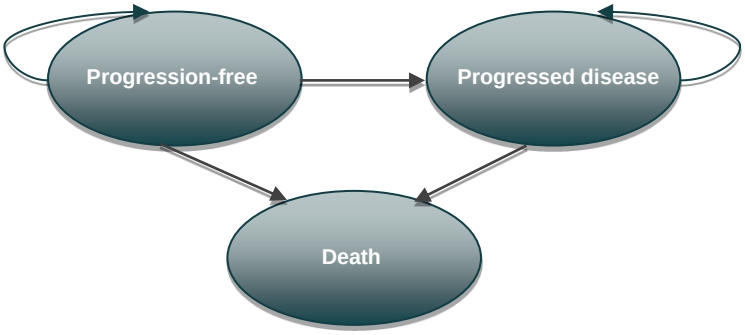


Figure 3 Schematic of company's model
Source: CS, Figure 14

The base case evaluates the cost effectiveness of nivolumab compared with docetaxel. Patients with locally advanced or metastatic squamous NSCLC who have failed platinum therapy enter the model in the PF health state. Patients who remain in PF are treated with either nivolumab or docetaxel. At the end of each cycle a patient can remain in the same health state or transition to PD or death. A restriction in the model is that patients cannot transition to an improved health state.

The number of patients in each health state was estimated using the partitioned survival method. The proportion of patients in the PD health state is calculated as the difference between OS and PFS. The partitioned survival approach allows for direct modelling of OS and PFS based on trial observed events. Cycle length is 1 week to accommodate the different dosing regimens of nivolumab (every 2 weeks) and docetaxel (every 3 weeks).

5.3.2 Population

The economic evaluation considers previously treated adult patients with advanced or metastatic squamous NSCLC, which is consistent with the population included in the CheckMate 017 trial. The company stated that typical weight distribution data for patients with lung cancer were not readily available for the UK population, so an indirect calculation, using the average body surface area (BSA) of patients with lung cancer receiving

chemotherapy in the UK, was used to derive an average body weight. The average weight (73kg) was used to calculate the nivolumab dose.

Although BSA data were captured in the CheckMate 017 trial, due to regional variations in patient characteristics, the Systematic Anti-Cancer Therapy (SACT) dataset[55] was considered to be more representative of patients with squamous NSCLC seen in UK clinical practice than patients in the CheckMate 017 trial. The average BSA used to calculate the dose of docetaxel was 1.82m^2.

5.3.3 Interventions and comparators

Nivolumab is implemented in the model in line with the anticipated licensed dose, i.e. 3mg/kg over 60 minutes as an intravenous infusion every 2 weeks.

The base case comparator in the economic analysis is docetaxel, administered at a dose of 75mg/m^2 every 3 weeks via intravenous infusion. Due to docetaxel being the current standard of care in previously treated patients with squamous NSCLC in the UK, it is the treatment that is most likely to be displaced by the introduction of nivolumab.

BSC was not included as a comparator in the base case analysis.

The company states that the use of erlotinib in this patient population in the UK is limited and declining. A comparison of nivolumab and erlotinib is only presented as a scenario analysis (Appendix 20 in the CS).

Subsequent treatments

The model assumes that nivolumab and docetaxel are second-line treatments and that patients can only receive one further line of therapy following progression (third-line therapy). The possible impact of this subsequent treatment on survival is not included in the model. Data from the CheckMate 017 trial were used to estimate the proportions of patients receiving third-line therapy and the distribution of those treatments. The CheckMate 017 trial, however, did not provide details about the duration of subsequent treatment. The duration of third-line therapy was derived from real world data, as reported in the observational study CA209-116[56] which investigated the treatment patterns, outcomes and healthcare resource use in patients with advanced NSCLC in Europe. In the model, the time until treatment discontinuation in patients in a third-line setting is [redacted] days.[56]

5.3.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services. The time horizon is set at 20 years, in line with previous

NICE STAs in this disease area (Table 39 of the CS) and taking into account the typical age of patients at diagnosis. Both costs and outcomes are discounted at a rate of 3.5% per annum.

5.3.5 Treatment effectiveness and extrapolation

The primary data source for the economic model was patient level data from the CheckMate 017 clinical trial. The follow-up period in this trial was shorter than the required length of the economic analysis (a lifetime equivalent) and extrapolation of the OS and PFS data from the trial was required to facilitate the partitioned survival (area under the curve [AUC]) approach. Extrapolation involved identifying parametric survival models for both OS and PFS.

Overall survival

Using patient level data from the CheckMate 017 trial, log-cumulative hazards, log-cumulative, odds, and standardised normal curve plots were generated to assess whether hazard rates of nivolumab and docetaxel were proportional (see CS Appendix 19, Figure 34). These analyses confirmed that the assumption of proportional hazards held for OS. The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit values for the selected parametric distributions were used to establish the best fitting parametric survival model. The company concluded that the two best fitting parametric survival models were the 2-knot spline hazards and a log-logistic distribution.

The method used to determine the base case parametric model for OS was based on validating the best fitting models (2-knot spline hazards and a log-logistic distribution) against both clinical trial data and real world data to ensure the clinical plausibility of the extrapolation. The 2-knot spline and log-logistic models both provided a good fit to the observed trial data from CheckMate 017. In addition, both distributions provided a good fit against additional data on OS (nivolumab) from the CheckMate 003 study (3 years) and the CheckMate 063 study (1 year).

Beyond 3 years, real world data from two registries were utilised in the model as there is no clinical survival evidence for the efficacy of treatment with nivolumab to facilitate long-term validation. These were the National Lung Cancer Audit (NLCA) registry (UK)[9] and the Surveillance, Epidemiology, and End Results Program (SEER) registry (US).[24] The NLCA data were available for up to 5 years and SEER data were available for up to 15 years. The company reported that the 2-knot spline model extrapolation consistently under-predicted conditional survival seen in the real world. In comparison, the log-logistic model was more closely aligned with real world conditional survival estimates. Based on all of the evidence

considered, the company determined that the log-logistic survival model should be used as the base case for OS extrapolation throughout the entire model timeframe.

Progression-free survival

Similar to the OS extrapolation, the choice of a parametric survival model for PFS was informed by assessment of whether the assumption of proportional hazards holds. This was carried out by visual inspection of the log-cumulative hazards, log-cumulative odds, and standardised normal curve plots. In addition, a Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time was used to test the proportional hazards assumption, which was highly significant (p=0.012), indicating that the null hypothesis for proportional hazards should be rejected.

The company reports that a single survival model adjusted for shape and scale, and independent survival models fitted to each trial arm were considered. The best fitting single survival model, in terms of visual inspection and AIC/BIC values, was the 2-knot spline hazard model with an adjustment on gamma 1. The best fitting independent survival models were the log-normal distribution and 1-knot spline hazard model for docetaxel and nivolumab respectively (Table 20).

Table 20 Summary of survival distributions for PFS and OS

Survival models explored	Best-fitting parametric curve
Progression-free survival	
Base case: single survival model adjusted for shape and scale	2-knot spline hazards
Scenario analysis: independent survival models	Docetaxel: Log-normal Nivolumab: 1-knot spline hazards
Overall survival	
Base case: single survival model	Log-logistic
Scenario analysis: single survival model	2-knot spline hazards

Source: CS, Table 50

As with OS, the survival parameters generated by these curves were compared with the in-trial survival estimates obtained from the CheckMate 003 and CheckMate 063 studies. As both dependent and independent survival functions provided a comparable and good fit to clinical trial data, and long-term real world data for PFS were not available to help validate long-term extrapolation for treatment with nivolumab, other factors were considered when selecting the best base case distribution. The company reports that to ensure randomisation was not broken by fitting independent curves to each treatment arm, and to account for a possible delayed response to treatment, the dependent curve option (2-knot spline hazards)

was selected as the base case survival curve for PFS. Table 20 provides a summary of the chosen survival distributions.

5.3.6 Health related quality of life

Systematic searches to identify HRQoL studies were performed as part of the company's systematic literature review. However, none of the identified studies evaluated nivolumab and none were performed in a UK-based population. Therefore, HRQoL data from the CheckMate 017 trial were used in the model. These data were collected in the trial using the EuroQol-5D preference-based health state utility questionnaire (EQ-5D utility index) and the EuroQol visual analogue scale (EQ-VAS) for overall health status.

Assessments were taken every other cycle (every 4 weeks) on Day 1 for the first 6 months of the study for nivolumab and every cycle (every 3 weeks) on Day 1 for the first 6 months of the study for docetaxel. Assessments were then taken every 6 weeks for the remainder of the trial period for both treatment arms (Table 21).

Table 21 EQ-5D assessment schedule in the CheckMate 017 trial

	Nivolumab & docetaxel		Nivolumab: on-study assessments	Docetaxel: on-study assessments	Nivolumab & docetaxel: follow-up assessments	Nivolumab & docetaxel: follow-up assessments
Assessments	**Screening visit**	**Cycle 1 Day 1 visit**	**Every other cycle (every 4 weeks) Day 1 (± 3 days)**	**Each cycle (every 3 weeks) Day1 (± 3 days)**	**Follow-up visits 1 (X01)[a] and 2 (X02)[b]**	**Further follow-up visits (beyond X02)[c]**
EQ-5D	✓	✓	✓	✓	✓	✓

[a] X01 to occur approximately 30 days (±5 days) after last dose or coinciding with the date of discontinuation (±5 days) if date of discontinuation is greater than 35 days after last dose
[b] X02 to occur approximately 70 days (±5 days) after X01
[c] Beyond 100 days from the last dose of study therapy, the EQ-5D will be administered every 3 months for the first 12 months, then every 6 months thereafter, as permitted by local law
Source: CS,Table 53

The EQ-5D completion rates were similar between treatment arms, being [redacted] and [redacted] for nivolumab and docetaxel, respectively, at baseline. For patients with baseline and at least one post-baseline visit, the completion rates correspondingly decreased to [redacted] and [redacted]. No adjustments were made for missing data when scoring the EQ-5D index. Data from screening visits (up to 28 days before) were used in place of any missing baseline data.

The mean utility values derived from analysis of data from the CheckMate 017 trial (using a UK scoring algorithm[57]) are 0.592 (PD); and 0.75 (PF). These compare with a mean utility value of 0.86 derived from a representative sample of adults drawn from the 2008 national Health Survey of England, which demonstrates that the HRQoL of patients with advanced

NSCLC is lower than that of the general population.[58] The utility values used in the economic model are summarised Table 22.

Adverse events

The economic model includes the quality of life impact of AEs of Grade 3 or higher severity, which occurred in ≥5% of patients in the CheckMate 017 trial. The disutility per episode for each of the included AEs is shown in Table 22. The expected disutility per patient associated with the incidence of the included AEs was applied separately in the first cycle only (i.e. without discounting).

Table 22 Summary of utility values used in the company's cost effectiveness analysis

	Utility value: mean (SD or SE)	95% confidence interval	Source
Progression-free (SD/PR/CR)	0.750 (0.236)	0.734 to 0.765	Derived from EQ-5D data collected in CheckMate 017 (BMS data on file)
Progressed disease	0.592 (0.315)	0.550 to 0.634	
Death	0	-	Assumption
Asthenia	-0.07346 (0.01849)	-	Assumed to be same as fatigue based on medical opinion
Dyspnoea	-0.05	-	Based on societal preferences for health states of patients with advanced NSCLC in England and Wales(Doyle and Walker, 2008)[59]
Fatigue	-0.07346 (0.01849)	-	Based on societal preferences for health states of patients with advanced NSCLC in England and Wales (Nafees *et al* , 2008)[60]
Febrile neutropenia	-0.09002 (0.01633)	-	
Neutropenia	-0.08973 (0.01543)	-	
Pneumonia	-0.008	-	Assumption that disutility is applicable to patients with advanced NSCLC (Marti *et al* , 2013)[61]

NSCLC=non-small cell lung cancer; SE=standard error; SD=standard deviation; CR=complete response; PR=partial response; SD=stable disease
Source: CS, adapted from Table 56

5.3.7 Resources and costs

Intervention costs

The drug acquisition costs by pack/vial size and acquisition costs of each treatment cycle for the comparative treatments are presented in Table 23 and Table 24 respectively. The company's analysis assumed that there was no vial sharing.

Table 23 Drug acquisition costs per pack/vial

Drug	Tablet dose/vial concentration	Pack size/vial volume	Cost per vial/pack	Source
Nivolumab	10mg/ml	4ml	£439.00 (£10.98/mg)	UK list price (CS Table 58)
		10ml	£1,097.00 (£10.98/mg)	
Docetaxel	10mg/ml	2ml	£138.33 (£6.92/mg)	BNF 2015[62]
		14ml	£900.00 (£6.43/mg)	

BNF=British National Formulary; BSC=best supportive care
Note: All BNF prices were accessed in June 2015
Source: CS, Table 58

Table 24: Drug acquisition cost per dose

Drug*	Total dose per administration	No. of vials/ packs	Method of administration	Total drug cost per dose	Frequency of administration
Nivolumab	3mg/kg x 73kg = 219mg	6 x 4ml vials	IV; no vial sharing (i.e. round up to nearest full vials)	£2,634	Every 2 weeks
Docetaxel	75mg/m^2 x 1.82 m^2 = 137mg	1 x 14ml vials	IV; no vial sharing (i.e. round up to nearest full vials)	£900	Every 3 weeks

BSC=best supportive care; IV=intravenous
* The 4ml vial (nivolumab) and 14ml vial (docetaxel) are used in the base case because these are the smallest and cheapest vial sizes, respectively
Source: CS, Table 59

Subsequent treatment

To ensure that the full cost of treatment for a progressed patient is accurately represented, the model includes costs of subsequent treatment for patients with PD based on the distribution of subsequent therapy observed in the CheckMate 017 trial (Table 52 in CS). Drug acquisition costs per dose for subsequent treatments for patients with an average BSA of 1.82m^2 are shown in Table 25. The cost of subsequent treatment was calculated by weighting the cost of the different third-line treatments assuming an average duration of treatment of [redacted] days (CS, page143). This weighted cost was applied as a one-off cost to all patients at the point in time at which they transitioned into the PD health state.

Table 25 Drug acquisition cost per dose (subsequent treatments)

Drug	Total dose required per administration	No. of vials / packs	Method of administration	Total drug cost per dose	Frequency of administration
Cisplatin	100mg/m^2 x 1.82m^2 =182mg	2 x 100ml vials	IV; no vial sharing	£100.44	Every 3 weeks
Carboplatin	400mg/m^2 x 1.82m^2 =728mg	2 x 45ml vials	IV; no vial sharing	£320.00	Every 4 weeks
Gemcitabine	1000mg/m^2 x 1.82m^2 =1820mg	2 x 1000mg vials	IV; no vial sharing	£309.24	Every 4 weeks (once per week for 3 weeks, followed by one week off-treatment)
Vinorelbine	30mg/m^2 x 1.82m^2 =55mg	6 x 1ml vials	IV; no vial sharing	£174.00	Every week
Docetaxel	75mg/m^2 x 1.82m^2 =137mg	1 x 14ml vials	IV; no vial sharing	£900.00	Every 3 weeks
Erlotinib	150mg	1/30 pack (30 x 150mg)	Oral	£54.38	Daily

BNF=British National Formulary; BSC=best supportive care; IV=intravenous; m^2=meters squared
Source: CS, Table 60

Treatment administration costs

Treatment administration costs for nivolumab and docetaxel are shown in Table 26

Nivolumab is expected to be administered in a hospital outpatient setting (day care basis), and is costed as a complex chemotherapy. The administration costs for subsequent therapies, i.e. those administered post progression are assumed to be the same as for docetaxel, i.e. simple chemotherapy.

Table 26 Cost per administration

Treatment	Type of administration*		Currency code	Cost per administration	Source
Nivolumab	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance	Outpatient setting	SB14Z	£269.94	NHS Reference Costs 2013/14[63]
Docetaxel	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z	£167.34	NHS Reference Costs 2013/14[63]

BSC=best supportive care
*All administration costs are assumed to be for first attendances in a cycle due to the length of time between administrations (for nivolumab and docetaxel, it is every 2 weeks and 3 weeks, respectively). All costs are inflated to June 2015 values
Note: erlotinib is an oral therapy and therefore, has no associated administration costs. Patients receiving erlotinib attend one outpatient appointment per month (considered in the monitoring costs), where they are assumed to obtain repeat prescriptions
Source: CS, Table 62

Health care costs

The cost of monitoring patients receiving nivolumab or docetaxel, disease management costs and terminal care costs are provided in Table 27. An end of life/terminal care cost is applied to patients who enter the death state as a one-off cost. The weighted cost reflects treatment received in various care settings.

Table 27 Health care costs

Type of cost	Health state	Cost*	Source
Monitoring cost - nivolumab or docetaxel	Progression-free	£151.89 per 4 weeks	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620][17]
Disease management	Progression-free	£313.55 per 4 weeks	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620][17] and Nintedanib NICE submission[50]
Disease management	Progressed disease	£766.62 per 4 weeks	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620][17] and Nintedanib NICE submission[50]
Terminal care	Death	£3,628.70 (one off)	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620][17]

MTA=Multiple Technology Assessment; NICE=National Institute for Health and Care Excellence; rev=review; TA=Technical Appraisal
*All costs have been inflated to June 2015 values
Source: Adapted from CS, Tables 63-67

Adverse event costs

Grade ≥3 AEs (regardless of causality) with a ≥5% incidence in the nivolumab or docetaxel arms of the CheckMate 017 trial are included in the base case analysis. The costs of treating AEs are per episode, and these costs were sourced from NHS Reference Costs (2013/14)[63] guided by the currency codes used in recent NICE submissions[7,17] for the treatment of NSCLC (Table 28).

Table 28 Cost of adverse events

AEs from CheckMate 017	Cost per episode	Mean number of episodes per AE treatment course	Source
Asthenia	£3,015.13	1	NHS Reference Costs (2013-14)[63]
Dyspnoea	£0.00	1	Assumption based on ipilimumab NICE STA submission for melanoma[7]
Fatigue	£3,015.13	1	NHS Reference Costs (2013-14)[63]
Febrile neutropenia	£5,489.94	1	Erlotinib & gefitinib (post chemotherapy) MTA (rev TA162, TA175) [ID620][17]
Neutropenia	£354.72	1	NHS Reference Costs (2013-14)[63]
Pneumonia	£1,822.85	1	NHS Reference Costs (2013-14)[63]

AE=adverse event; MTA=multiple technology appraisal; TA=technology appraisal
*All costs are inflated to June 2015 values
Source: CS, Table 69

5.3.8 Cost effectiveness results

Base case results

Total costs, LYG, QALYs, and incremental cost per QALY gained for nivolumab versus docetaxel are shown in Table 29. The base case analysis is based on the log-logistic curve for OS and the 2-knot spline function for PFS. Life years are undiscounted. In the base case, nivolumab generates 0.76 additional QALYs and 1.31 additional life years compared with docetaxel and the nivolumab-treated cohort has higher total lifetime costs. The incremental cost effectiveness ratio (ICER) for nivolumab versus docetaxel is £85,950 per QALY gained. Expected QALYs for nivolumab and docetaxel disaggregated by health state are shown in Table 30. Predicted (per patient) resource use costs included in the company's model are presented in Table 31.

Table 29 Base case results

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER per QALY (£)
Nivolumab	86,599	2.26	1.30	65,355	1.31	0.76	85,950
Docetaxel	21,243	0.95	0.54				

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, Table 72

Table 30 Summary of QALY gain per patient by health state

Health state	QALY intervention (nivolumab)	QALY comparator (docetaxel)	Incremental QALYs	% Absolute incremental QALYs
PF	0.63	0.26	0.37	48.9%
PD	0.68	0.33	0.34	45.1%
AE disutility	-0.01	-0.05	0.05	6.1%

Total	1.30	0.54	0.76	100%

AE=adverse event; PD=progressed disease; PF=progression-free; QALY=quality adjusted life year
Note: No utility is assigned to the death state
Source: CS, Table 74

Table 31 Cost per patient (disaggregated)

Health state	Cost intervention (nivolumab)	Cost comparator (docetaxel)	Incremental costs	% Absolute incremental costs
Disease management cost: PF	£3,425	£1,406	£2,019	3.1%
Disease management cost: PD*	£14,757	£9,164	£5,593	8.6%
Drug acquisition cost	£59,454	£6,636	£52,818	80.8%
Administration cost	£6,398	£1,486	£4,912	7.5%
Monitoring cost	£2,336	£1,248	£1,089	1.7%
AEs	£228	£1,304	-£1,076	-1.6%
Total treatment cost	£86,599	£21,243	£65,355	100%

AE= adverse event; PD=progressed disease; PF=progression-free
*Progressed disease includes the costs of managing patients who have progressed and end of life/terminal care. No costs are assigned to the death state
Source: CS, Table 75

5.3.9 Sensitivity analyses

Deterministic sensitivity analysis

One-way sensitivity analyses were undertaken by varying cost, utility and OS base case parameter values by their confidence intervals or +/-20%, based on data availability (Table 32). The ICER per QALY gained was most sensitive to the hazard ratio applied to modelled nivolumab OS. Additionally, the results were sensitive to average body weight, and the utility weights associated with the PF and PD health states. All other variables, including AE management, end of life care and monitoring costs had minimal impact on the size of the ICER per QALY gained.

Table 32 Results of deterministic analyses (nivolumab vs docetaxel)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		**65,355**	**0.7604**	**85,950**
Discount rate - costs	Lower	71,139	0.7604	93,556
	Higher	62,141	0.7604	81,723
Discount rate - outcomes	Lower	65,355	0.9061	72,130
	Higher	65,355	0.6849	95,428
Average body weight	Lower	55,658	0.7604	73,197
	Higher	75,053	0.7604	98,704
BSA	Lower	65,400	0.7604	86,008
	Higher	60,248	0.7604	79,233
Costs				
Cost - PF state	Lower	64,952	0.7604	85,419
	Higher	65,759	0.7604	86,481
Cost - PD state	Lower	64,201	0.7604	84,433
	Higher	66,510	0.7604	87,468
Terminal cost	Lower	65,391	0.7604	85,997
	Higher	65,320	0.7604	85,904
Administration cost – nivolumab	Lower	64,163	0.7604	84,382
	Higher	66,548	0.7604	87,519
Administration cost – docetaxel	Lower	65,544	0.7604	86,199
	Higher	65,167	0.7604	85,702
Monitoring cost – nivolumab	Lower	65,159	0.7604	85,691
	Higher	65,890	0.7604	86,653
Monitoring cost - docetaxel	Lower	65,438	0.7604	86,059
	Higher	65,273	0.7604	85,842
Outcomes				
Utility weight, PFS	Lower	65,355	0.7525	86,855
	Higher	65,355	0.7678	85,119
Utility weight, PD	Lower	65,355	0.7361	88,790
	Higher	65,355	0.7847	83,287
Survival				
HR on OS - nivolumab	Lower	75,118	1.3522	55,554
	Higher	58,495	0.3457	169,225

BSA=body surface area; CI=confidence interval; HR=hazard ratio; OS=overall survival; PD=progressed disease; PF=progression-free; PFS=progression-free survival; QALY=quality adjusted life year
Source: CS, Table 93

Scenario analyses

Scenario analyses were undertaken by the company. These involved varying the survival modelling approaches applied to OS and PFS data, duration of treatment, vial optimisation and use of erlotinib as an alternative comparator. The influence of each change on the size of the ICER per QALY gained is presented in Table 33. Nivolumab was found to be more expensive (+£69,698) and more effective (+0.81 QALYs) than erlotinib and this analysis yielded an ICER of £85,862 per QALY gained.

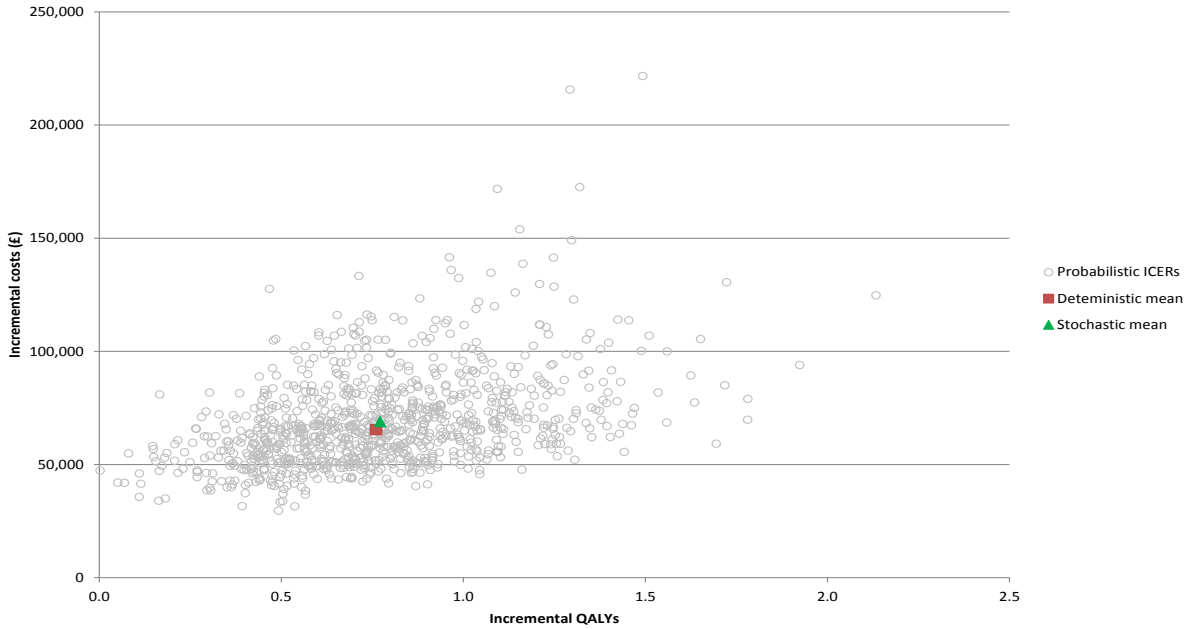
Table 33 Scenario analyses results

Description	ICER per QALY gained
Base case	£85,950
Survival analysis	
2-knot spline distribution for OS	£108,096
Applying independent survival curves for PFS	£87,925
Treatment discontinuation	
1-year treatment stopping rule	£45,470
2-year treatment stopping rule	£60,923
Vial optimisation	
Optimal combination of vials	£79,559
Alternative comparator	
Erlotinib	£85,862

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year
Source: CS, adapted from Tables 96, 99, 102, 105 and Appendix 20 (Table 41)

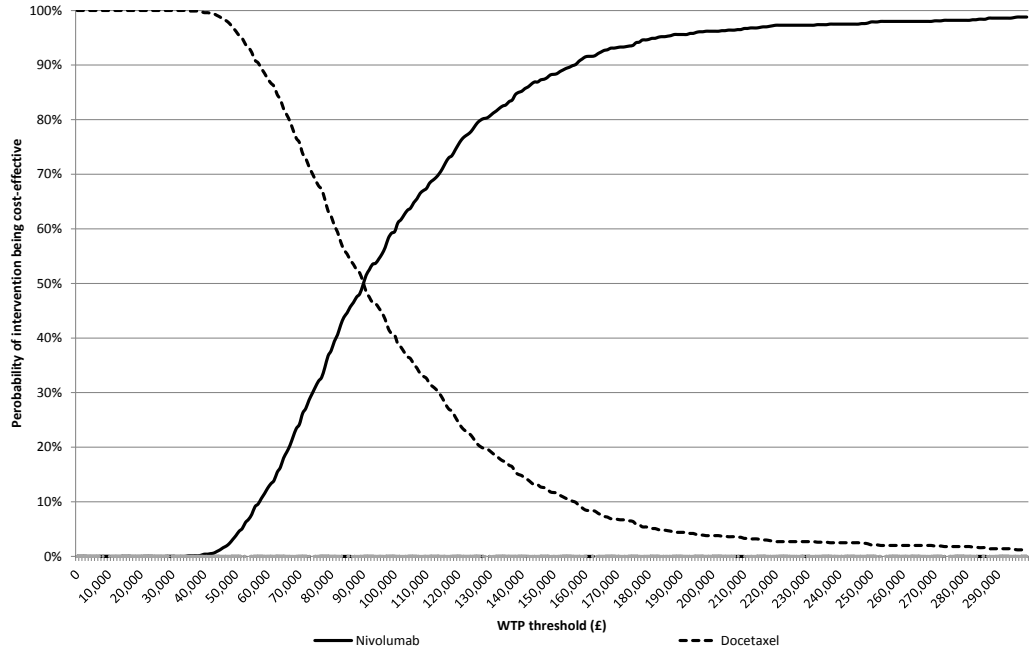
Probabilistic sensitivity analysis

The company undertook probabilistic sensitivity analysis (PSA) to derive the mean ICER per QALY gained for nivolumab vs docetaxel. The PSA was run for 1000 iterations. The probabilistic ICER is £89,343 per QALY gained (with a 0% probability of being cost effective at a threshold of £30,000 per QALY gained and a 3.8% probability of being cost effective at a threshold of £50,000 per QALY gained) compared with £85,950 per QALY gained in the deterministic analysis. For this comparison, the cost effectiveness plane is shown in Figure 4 and the cost effectiveness acceptability curve (CEAC) is shown in Figure 5.



ICER = incremental cost effectiveness ratio
Source: CS, Figure 28

Figure 4 Cost effectiveness plane (nivolumab vs docetaxel, 1000 iterations)



WTP=willingness to pay
Source: CS, Figure 29

Figure 5 Cost effectiveness acceptability curve (nivolumab vs docetaxel)

5.3.10 Model validation and face validity check

The company states that their survival models were validated against data from the CheckMate 017 trial, CheckMate 003 and CheckMate 063 studies, the NLCA[9] dataset and the SEER[64] database. In addition, during model development, external clinical and health economic experts attended three workshops and provided advice during ad hoc consultations.

5.4 ERG's detailed critique of the company's economic evaluation

5.4.1 NICE reference case checklist

Table 34 NICE reference case checklist

Attribute	Reference case [25]	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial. Erlotinib was only included as a scenario analysis. BSC was not subject to a full economic evaluation due to paucity of data
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Patient related direct health effects are considered. No impact on carers has been considered in the model
Perspective on costs	NHS and PSS	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 20 year time horizon
Synthesis of evidence on health effects	Based on systematic review	Yes – data primarily taken from a single clinical trial
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs and the EQ-5D instrument has been used to collect HRQoL data
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Yes - HRQoL data were collected as part of the Check Mate 017 trial. The mixed international trial population may show heterogeneity of response
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and effects (currently 3.5%)	Benefits and costs have been discounted at the 3.5% rate

EQ-5D=Euroqol 5D; HRQoL=health related quality of life; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PSS=Personal Social Services; QALY=quality adjusted life year

5.4.2 Drummond checklist

Table 35 Critical appraisal checklist for the company's economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Partially	CheckMate 017 was stopped early due to benefit. Limited data available from this trial
Were all the important and relevant costs and consequences for each alternative identified?	Yes	Key costs and outcomes were identified
Were costs and consequences measured accurately in appropriate physical units?	Partially	Costing does not take account of age/sex-specific variation on body metrics, and wrongly assumes different acquisition costs
Were the cost and consequences valued credibly?	Partially	The ERG considers that the company's OS and PFS projections lack clinical credibility and overestimate the effectiveness of nivolumab
Were costs and consequences adjusted for differential timing?	Yes	Discount rate of 3.5% per annum
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICER calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic, scenario and probabilistic sensitivity analyses were undertaken, although the deterministic analyses were not comprehensive
Did the presentation and discussion of study results include all issues of concern to users?	Yes	The results are presented and discussed in detail and an end of life treatment case has been proposed by the company

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; OS=overall survival

5.4.3 The company's model

The company's Microsoft Excel spreadsheet model is constructed according to conventional practice and is generally implemented correctly. However, the coding used to drive the model is very inefficient, meaning that the model takes a long time to run. Furthermore, the coding used to implement the company's survival model functions was not readily accessible, meaning that the ERG was unable to determine whether it had been implemented correctly.

5.4.4 Estimating survival: the primary issue in this appraisal

The results of univariate deterministic sensitivity analyses relating to the primary comparison between nivolumab and docetaxel are presented in the CS. Eleven parameters were selected for testing by the company, and the largest variation was shown for uncertainty in the estimated hazard ratio between the two treatments in the CheckMate 017 trial, which showed results ranging from a 36% reduction in the size of the estimated ICER per QALY gained to a 95% increase in the size of the estimated ICER per QALY gained.

The company model does not include the facility to carry out deterministic one-way sensitivity analyses on all of the individual model parameter values. However, the ERG has tested the effect of varying one of the log-logistic OS model parameters (the shape parameter) between its lower and upper confidence limits and found a large impact on the size of the estimated ICER per QALY gained for the comparison of nivolumab with docetaxel, from a 13% reduction to an 18% increase. These results suggest that both the hazard ratio estimate and the method of survival projection are implicated in generating serious uncertainty in the economic model results.

It is particularly noteworthy that in the company's base case analysis the majority (59%) of the estimated survival gain is attributable to the period after disease progression has been confirmed (Table 36).

Table 36 Mean survival gain estimated in company base case analysis

Survival composition (months)	Nivolumab	Docetaxel	Survival gain
Progression-free survival (PFS)	10.7	4.3	+6.5 (41%)
Post-progression survival (PPS)	16.4	7.2	+9.2 (59%)
Overall survival	27.2	11.5	+15.7 (100%)

This implies that additional benefit continues to accrue to patients whose disease has progressed on nivolumab despite no longer receiving the randomised treatment. Since the sole evidence for this phenomenon is from the CheckMate 017 trial with very limited follow-up (up to 2 years), it must be considered whether this degree of benefit may be merely an artefact of the type of parametric survival projection function chosen by the company analysts.

Figure 6 compares the company's base case OS models (based on log-logistic parametric functions) with the ERG's exploratory OS models (detailed in Sections 5.5.2 to 5.5.4 of this report) using simple exponential functions, in terms of annual mortality rates. The obvious difference between the two formulations is that mortality rates remain constant after the first year in the ERG models, but the company's log-logistic method results in rapidly falling mortality rates indefinitely. As the mean baseline age of patients in the CheckMate 017 trial is 63.3 years, it is expected that over time mortality rates in this group of patients would increase rather than decrease. In particular, Figure 6 indicates that mortality rates in the company's base case model fall below those experienced by the general population [65] after 18 years in the nivolumab cohort and after 22 years in the docetaxel cohort. Indeed, this analysis implies that a few months of treatment with either nivolumab or docetaxel confers a

life-long reduction in mortality risk from *all* causes of death. The ERG considers this to be wholly implausible, and inconsistent with any clinical evidence of treating metastatic disease.

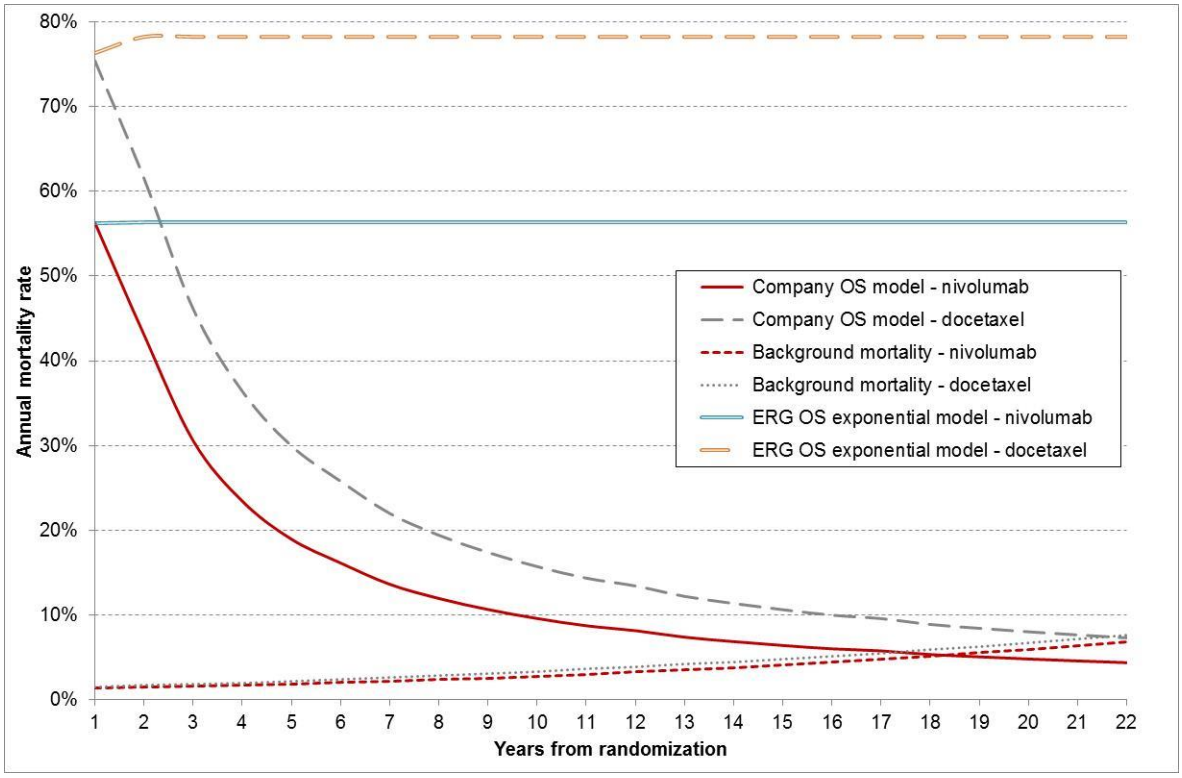


Figure 6 Comparison of long-term mortality rates between company OS models and ERG exponential models

5.4.5 Post-progression survival

The ERG requested a K-M analysis of the CheckMate 017 trial data (using a revised censoring algorithm) for the survival of patients following documented disease progression from the company (Figure 7). This analysis indicates that there is no meaningful difference in long-term survival following disease progression that is attributable to the choice of second-line treatment (log-rank test, p=0.544).

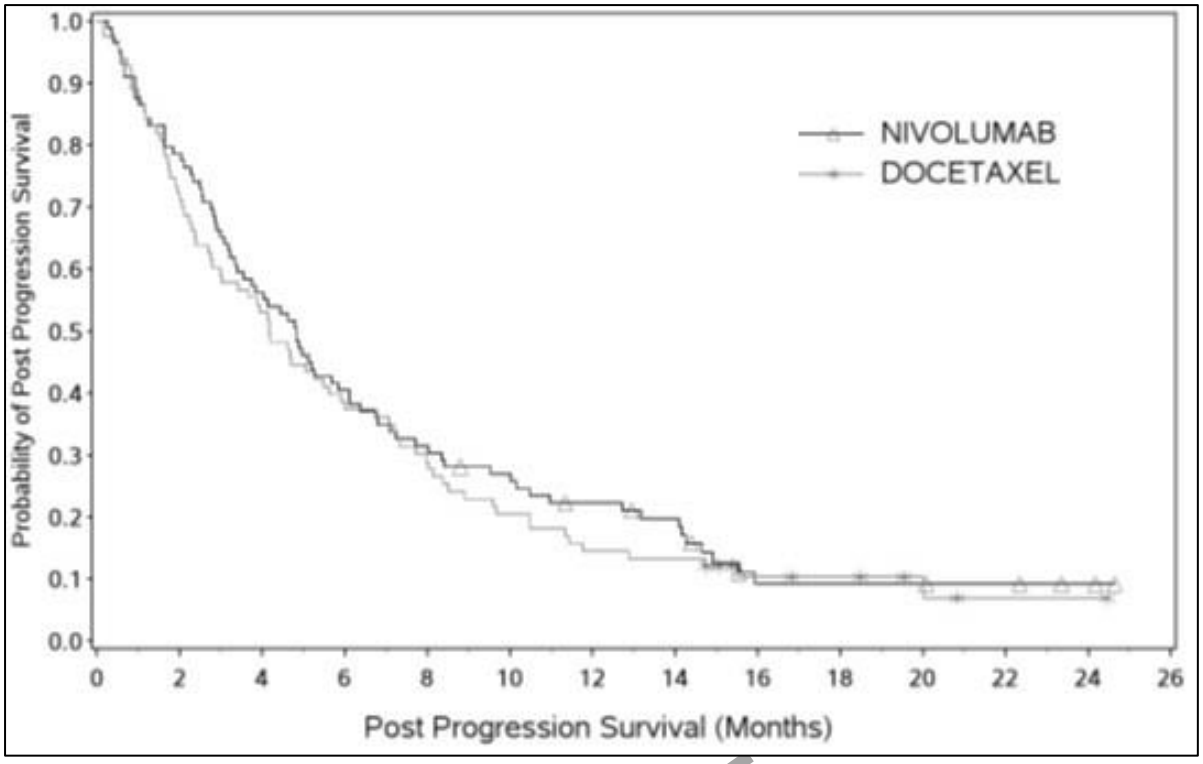


Figure 7 Post-progression survival in the CheckMate 017 trial

At first sight these data may suggest that none of the 9.2 months post-progression survival (PPS) gain generated by the company model (Table 36) is supported by the trial evidence. However, some differential PPS can arise if there is a difference in the proportion of patients who die prior to overt disease progression, and who would therefore not feature in the PPS analysis. Information in the CSR for the CheckMate 017 trial (CSR, Table S.5.13) indicates that [redacted] such deaths occurred in the nivolumab arm than in the docetaxel arm. Using a 2-phase exponential function to represent accurately the joint PPS trial data (Figure 8), the difference in pre-progression deaths leads to a notional mean gain in PPS of 1.15 months rather than 9.2 months in the company base case (Table 36), and a corresponding reduction in OS gain from 15.7 months to 7.65 months. This modification to the company model would be expected to increase substantially the size of the estimated ICER per QALY gained for nivolumab versus docetaxel.

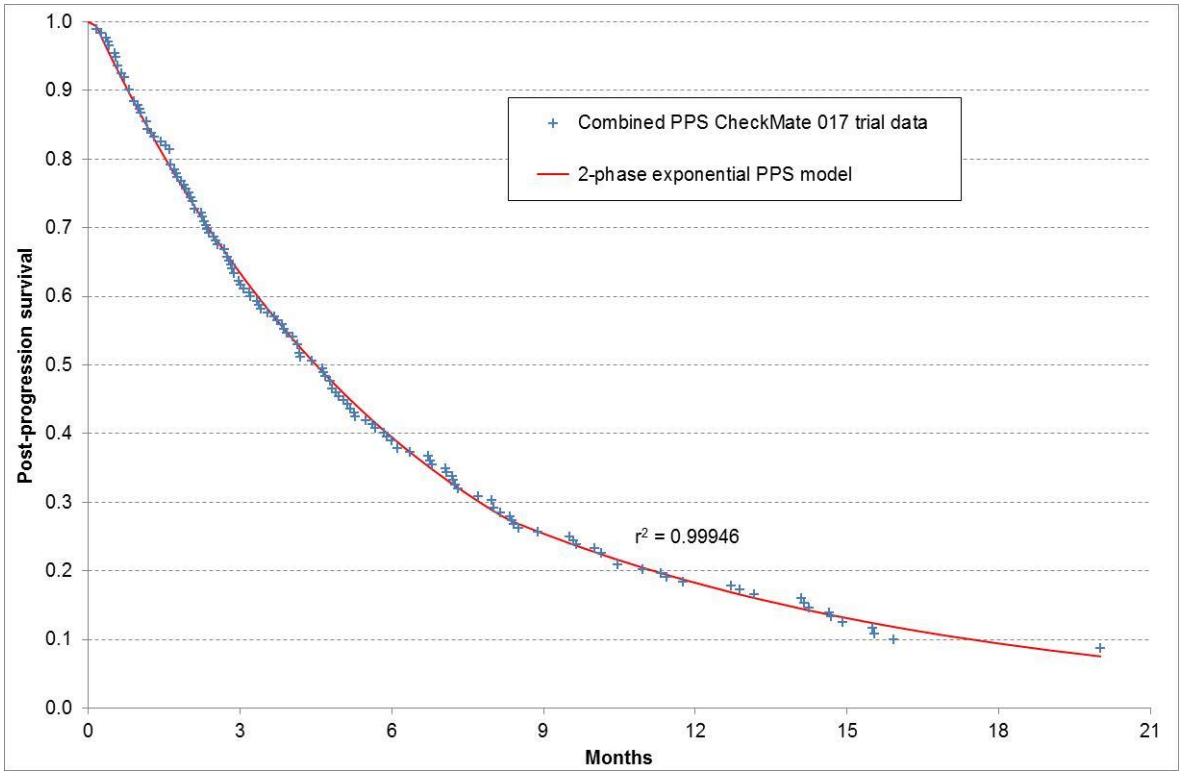


Figure 8 Post-progression survival 2-phase exponential model fitted to all patients in the CheckMate 017 trial who progressed alive on either treatment

5.4.6 Pre-progression survival

The ERG requested a K-M analysis of CheckMate 017 data (using a revised censoring algorithm) for the pre-progression survival of trial patients from the company. Figure 9 shows that there was no difference between the trial arms up until 2.2 months (9 to 10 weeks), when the first scheduled tumour assessments occurred. Immediately following this time the two survival curves diverge steadily, with roughly constant but different event rates in each arm. This demonstrates clearly that the assumption of time-invariant proportional hazards is violated, so that the use of hazard ratios to model PFS in all comparators in the company model is invalid.

The ERG successfully fitted simple exponential models separately to the trial arms from 2.2 months onwards. PFS estimates for both treatments in the CheckMate 017 trial were obtained by calculating the area under the PFS curve (AUC) directly for the trial data, and then appending the area under the fitted curve from a point at which the trial data and fitted model estimate matched closely.

This approach yielded mean PFS estimates of 7.57 months for nivolumab and 3.93 months for docetaxel, with a net PFS gain of 3.63 months attributable to nivolumab treatment compared to docetaxel. These values are considerably smaller than those estimated by the

company model (Table 36), so that the estimated PFS gain falls from 6.5 months to less than 4 months.

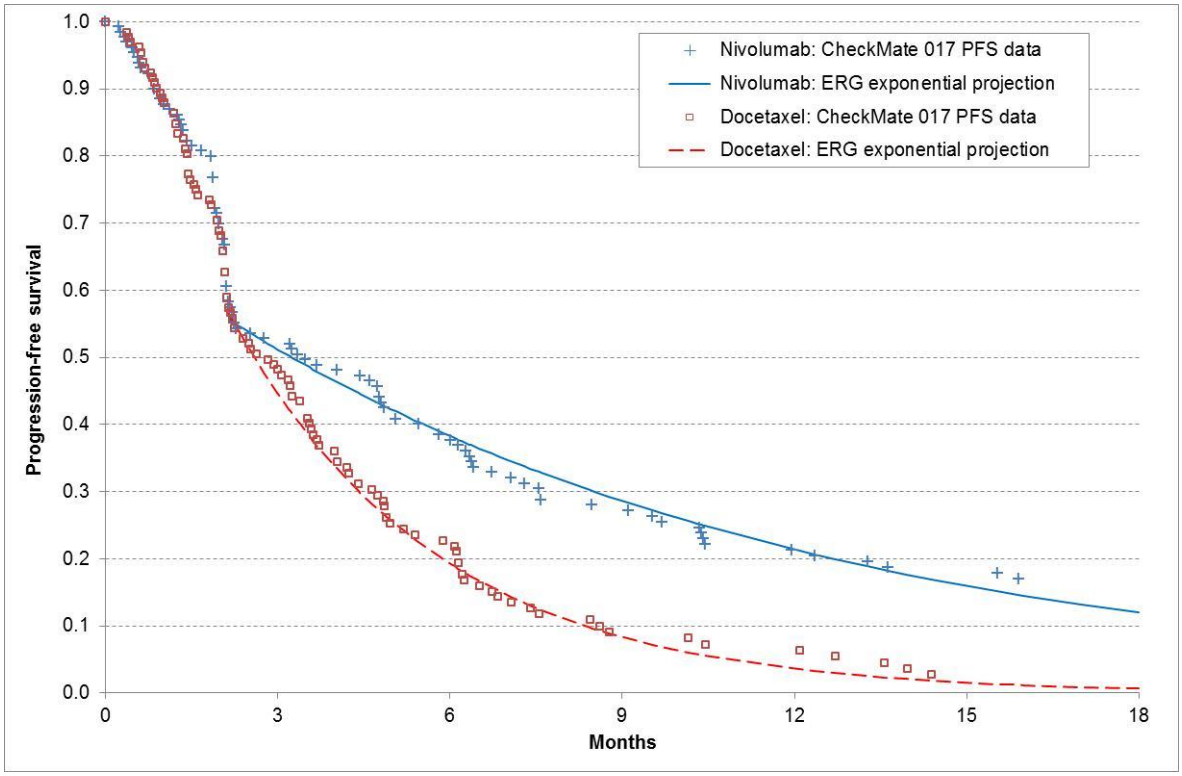


Figure 9 Progression-free survival exponential projection models fitted to patients alive and progression-free after 2.2 months treatment in the CheckMate 017 clinical trial

5.4.7 Overall survival

Similarly, the ERG requested a K-M analysis of CheckMate 017 data (using a revised censoring algorithm) for OS from the company. Examination of the cumulative hazard plot shows that long-term linear trends were established from 40 weeks onwards in both trial arms, indicating that exponential models are the best fit to the trial data and are therefore the best option as a basis for projective survival estimation (Figure 10). This was carried out by the ERG using the AUC method for the recorded trial data from 0 to 40 weeks, and using the projection model from 40 weeks to 20 years.

This approach yielded mean OS estimates of 16.06 months for nivolumab and 8.89 months for docetaxel, with a net OS gain of 7.17 months attributable to nivolumab treatment compared to docetaxel. These values are considerably smaller than those estimated by the company model (15.7 months in Table 36).

The company model is structured to calculate estimates of PFS and OS at each time point, and then infer the corresponding PPS value by subtraction (PPS = OS – PFS). However, the

ERG's separate analyses of PFS, PPS and OS permit two methods of reconciling these three sets of results:

1) use of the same method as the company (use OS and PFS data to infer PPS)

2) use PFS and PPS data to infer OS by addition (allowing for patients alive at progression).

Table 37 Mean survival gain estimated by ERG using two different methods

Survival composition (months)	Nivolumab	Docetaxel	Survival gain
Original method			
PFS	**7.57**	**3.93**	**+3.63**
PPS	*8.50*	*4.96*	*+3.54*
OS	**16.06**	**8.89**	**+7.17**
Alternative method			
PFS	**7.57**	**3.93**	**+3.63**
PPS	**6.14**	**4.99**	**+1.15**
OS	*13.71*	*8.92*	*+4.79*

Figures in **bold** represent directly estimated values, figures in *italics* represent inferred values by addition/subtraction

It is possible to propose arguments in favour of either approach, but on balance the ERG prefers to retain the original method since it uses the trial data directly in respect of the most important and reliable trial outcome – OS. Either method leads to more than halving the incremental survival gain, resulting in an increased ICER.

The impact of the ERG approach to survival modelling on the size of the estimated ICER for nivolumab compared with docetaxel is substantial, but differs for PFS and OS:

- applying the ERG PFS estimates alone reduces the incremental cost per patient by nearly £15,000. However, this approach reduces the incremental QALYs per patient by less than 4%, so that the estimated ICER is reduced by nearly 20% to £68,912 per QALY gained
- by contrast applying only the ERG OS estimate also reduces the incremental cost per patient, but by less than 8%. However, the incremental QALY gain per patient is reduced by 40%, so that the estimated ICER increases to £131,979 per QALY gained.

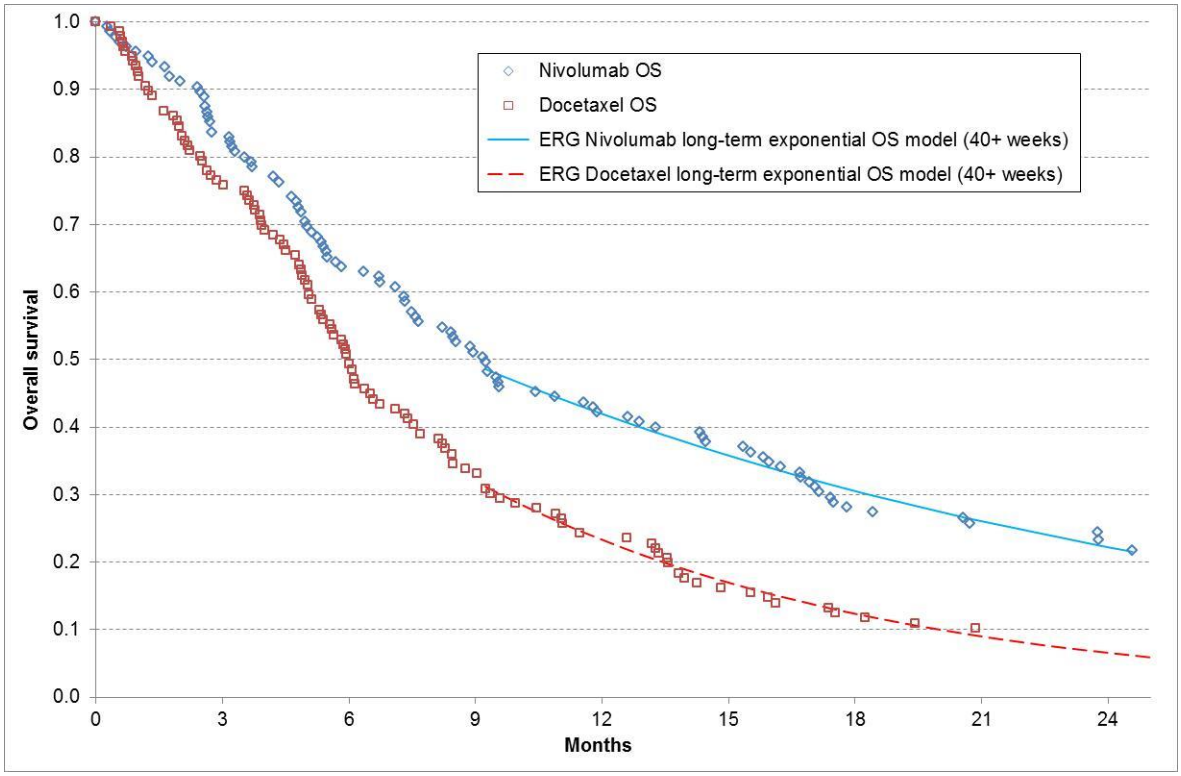


Figure 10 Overall survival exponential projection models fitted to all patients in the CheckMate 017 clinical trial

5.4.8 Treatment cost calculations

The company model ignores gender differences in the default setting, using a mean body weight of 73kg and a mean BSA of 1.82 m^2 for all patients, derived from the CheckMate 017 trial population. This is incorrect for several reasons:

- females are generally smaller and lighter than males and therefore require lower doses of chemotherapy, whether doses are calculated by body weight or body surface area
- there are wide variations in body size within each gender group, so that using a single group average dose calculation is always inaccurate. Doses should be estimated at an individual level and the use of different sized vials optimised to minimise the acquisition cost of each individual dose delivered
- the body metric averages drawn from the CheckMate 017 trial are unrepresentative of the UK population considered in this appraisal (only [redacted] UK patients were included in the randomised trial population, all of whom were males).

In the company model average BSA values were drawn from the SACT database study which reported results for an undifferentiated cohort of lung cancer patients undergoing chemotherapy. This is inappropriate for this appraisal since the SACT patients are dominated by the majority of patients receiving first-line chemotherapy, who will generally have suffered less from cumulative health degradation than those undergoing subsequent treatments. By contrast Sacco *et al* 2010[66] identified separately those patients receiving

palliative chemotherapy which are more likely to correspond to those undergoing second-line treatments. The estimated values for this group are UK mean body weight of 63.4kg for females and 74.7kg for males, with mean BSA of 1.66m^2 for females and 1.89m^2 for males for UK lung cancer patients. The cost of all treatments in the company's model will be overestimated unless UK population gender-specific data are used.

Additionally, chemotherapy regimens used as comparators to nivolumab, or for subsequent post-progression additional lines of treatment are all assigned unit costs in the company model based on published list prices. In many cases these products may be obtained at lower cost to the NHS either as generic equivalent products, or based on NICE-approved patient access scheme discounted prices. The ERG has re-estimated the mean cost per dose for each treatment based on UK gender-specific population values without vial sharing and using NHS average unit costs (Table 38).

Applying these parameter value amendments (for both second and third-line treatments) to the company's model leads to an increase in the size of the estimated ICER by over £6,000 per QALY gained when comparing nivolumab to docetaxel.

Table 38 Mean acquisition costs of modelled treatments

Treatment	Mean cost per dose: published list price	Mean cost per dose: at NHS price	Basis of NHS price
Docetaxel	£900.00	£47.09[#]	Generic product*
Gemcitabine	£972.72	£19.01	Generic product*
Vinorelbine	£278.00	£25.66	Generic product*
Cisplatin	£100.44	£31.60	Generic product*
Carboplatin	£300.00	£36.32	Generic product*

including 3 days co-medication with dexamethasone per dose of docetaxel
* Electronic market information tool[67] (average prices in 2014)

5.4.9 Treatment administration costs

The company model uses a higher unit cost for the administration of nivolumab than for docetaxel, assuming that nivolumab involves 'complex chemotherapy including prolonged infusional treatment' (NHS Reference Cost SB14Z: £269.94[63]) and that administration of docetaxel is 'simple parenteral chemotherapy' (NHS Reference Cost SB12Z: £167.34[63]). On clinical advice, based on experience with both regimens, the ERG considers that the nivolumab cost is inappropriate, and the lower figure should be used for both treatments. Applying this modification results in a £2,266 reduction in the incremental cost per patient and a £2,981 reduction in the size of the estimated ICER per QALY gained.

5.4.10 Duration of treatment

In the CheckMate 017 trial treatment with docetaxel and nivolumab was planned to continue until disease progression was confirmed. The company model is based on the assumption that PFS is the sole determinant of whether patients continue on their randomised treatment. In practice, patients suffering serious AEs on treatment may delay or withdraw from treatment without evidence of disease progression. Thus the recorded time to treatment discontinuation (TTD) may be a more reliable measure of the true cost of treatment.

Analysis of the trial data (Figure 11) indicates that although PFS and patients still on treatment (TTD) follow a closely similar profile in the nivolumab arm of the trial, this is not the case for patients randomised to docetaxel, who consistently discontinue treatment earlier than would be expected by their PF status. After 62 weeks the two measures converge in both arms of the trial.

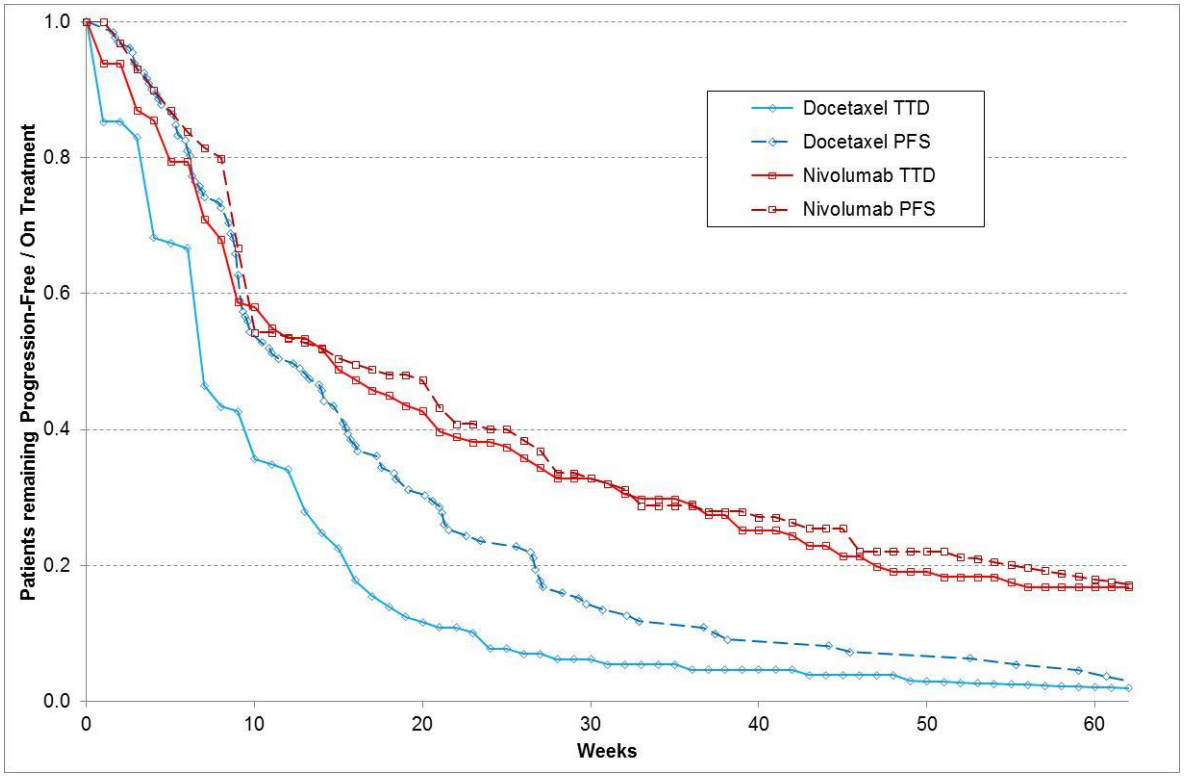


Figure 11 PFS and time to treatment discontinuation in the CheckMate 017 clinical trial

It appears from Figure 11 that applying TTD estimates in the decision model rather than PFS estimates in the calculation of treatment costs should favour docetaxel, since the reduction in the volume of treatments given is much greater for docetaxel than for nivolumab. However, this is more than outweighed by the much greater differential in unit costs of treatment (drug acquisition plus administration). As a result, the costs of treatment fall by

20% for nivolumab but only fall by 9% for docetaxel, so that the incremental cost per patient and the size of the estimated ICER reduce by more than 23%.

5.4.11 Restricted use of docetaxel

In the UK, the use of docetaxel chemotherapy in second-line NSCLC is restricted to a maximum of four cycles, due to the risk of AEs (especially febrile neutropenia). Applying this restriction on docetaxel use in the model and assuming that this affects only the cost of treatment (i.e. has no impact on outcomes), this change reduces the cost of docetaxel treatment and thereby increases the incremental cost of using nivolumab so that the estimated ICER for nivolumab compared to docetaxel increases by £4,213 per QALY gained.

5.4.12 Timing of chemotherapy

Treatment costs (acquisition and administration) are estimated in the company model by applying a unit cost to the average number of patients on treatment across each cycle. However, both the intervention and the comparator treatments are given on the first day of each cycle and should be costed accordingly. When this correction is applied the cost per patient increases in both arms, and the size of the estimated ICER increases by £704 per QALY gained.

5.4.13 Health state utility

Although EQ-5D data were collected in the CheckMate 017 trial, the response rates were poor and patchy. Less than [redacted] of randomised patients completed the baseline EQ-5D assessment, and participation fell to [redacted] at [redacted] and [redacted] at [redacted], despite approximately [redacted] and [redacted] of patients remaining alive at these time points. Inevitably, the decision to continue responding to the EQ-5D questionnaire will have been influenced by a variety of factors, but it must be of concern that those who continued to participate will have been self-selecting and are unlikely to be typical of the initial cohort. In particular, claims to improvements in mean utility scores over time, or significant differences attributable to the randomised treatment cannot be considered reliable. The ERG considers that it is likely that continuing responders will have been those with the better health status and ECOG PS scores and the ERG therefore considers that mean health state utility estimates are likely to be overstated.

In the company model, it is assumed that patients with stable disease or showing a response to treatment experience a mean utility score of 0.75, whereas those who have suffered disease progression have a mean utility score of 0.592. These values were derived from the CheckMate 017 trial EQ-5D data. The ERG has tested the effect of substituting alternative

values (based on the study by Nafees *et al* 2008[60]) previously used for patients treated with second-line chemotherapy in a systematic review and economic evaluation of first-line chemotherapy for NSCLC;[68] 0.65 for the PF state and 0.43 for the PD state. These changes reduce the incremental QALYs gained per patient by 19%, and increase the size of the estimated ICER by 23%.

5.4.14 Adverse event utility decrements

The effects of AEs on health-related utility are represented in the company model by six selected AEs. The associated disutility estimates are derived from three sources: the Nafees study[60] for asthenia, fatigue, neutropenia and febrile neutropenia, a study by Marti[61] for pneumonia, and a study by Doyle and Walker[59] for dyspnoea. The Marti *et al* study is a standard gamble exercise involving South and Central American parents of hospitalised children aged 3 to 36 months, considering the disutility of a 7 day stay followed by recovery to full health. Clearly this cannot be considered relevant to elderly patients with metastatic lung cancer undergoing second-line chemotherapy. The Doyle and Walker study[59] was less sophisticated than the Nafees *et al* study,[60] including only three symptoms and omitting PD. It is therefore inappropriate to select a single estimated parameter value from the Doyle and Walker model[59] and combine it with the Nafees *et al* model parameters.[60]

The method of applying the disutility effects of AEs in the company model is unsatisfactory. It involves multiplying the Grade 3 to 5 incidence rates of the selected AEs with the corresponding disutility values and summing them to a single disutility quantum, which is applied only to week 1 of the model. This involves two strong assumptions:

- that any patient experiencing a specific AE only suffers a single episode (because the incidence rate per person is used instead of the event rate)
- that, on average, all AE events and their sequelae last for no more than one week.

As a consequence, the estimated disutility effect of AEs in the model is necessarily understated to an unknown extent. The ERG is not able to assess the potential size of this problem due to lack of data, but considers it is unlikely to be large relative to the other issues previously highlighted.

5.5 Summary of ERG's review of the company model

For the comparison of nivolumab versus docetaxel, the ERG has made revisions in all three areas of interest: clinical outcomes, especially in survival analysis; cost estimation and implementation for drug treatments; and the selection of appropriate health-related utility values. In particular, the ERG considers that estimation of OS gain in the company's model

is flawed and that this is the primary issue of concern in this appraisal. The company's estimation of PFS, the use of PFS rather than TTD data to estimate drug costs, and the choice of AE utility values are also of particular concern to the ERG.

5.6 Comparing the clinical and cost effectiveness of nivolumab with other treatments

The ERG considers that there is no reliable approach that could allow the use of the currently available clinical evidence to populate the company model in order to generate meaningful cost effectiveness results comparing nivolumab with either erlotinib or BSC. This is because the company model is structured to rely on the application of time-invariant hazard ratios to data from the CheckMate 017 trial in order to represent the relative performance of erlotinib and BSC; this forms the basis of the company's approach to estimating net outcome benefits attributable to nivolumab. However, the evidence network required to generate the necessary hazard ratios must be considered 'broken' by the absence of any time profiles of clinical outcomes for the squamous subgroup of patients in the TAILOR trial. Lack of such informative evidence from the TAILOR trial precludes the indirect comparison of nivolumab versus erlotinib and versus BSC. In addition, the necessary time profile for the squamous subgroup in the BR.21 trial is only available for the OS outcome, so that populating the model for PFS is not possible.

The possibility of exploratory 'unlinked' comparisons using a single hazard ratio was investigated by the ERG in relation to OS, and the ERG concluded that although this might be possible in relation to BSC, it is clearly inappropriate for erlotinib. Full details of the ERG's additional analyses are presented in Appendix 11.9.

5.7 Conclusions of the cost effectiveness section

The various changes implemented by the ERG for the comparison of nivolumab versus docetaxel yield a mixture of effects. When implemented individually, these revisions both increase and decrease the size of the ICER per QALY gained. However, the combined effect of all of the changes yields an ICER of £132,089 per QALY gained.

The ERG considers that the company's base case result substantially underestimates the size of the most probable ICER per QALY gained for nivolumab versus docetaxel in previously treated patients with squamous NSCLC. The ERG was unable to compare the cost effectiveness of nivolumab versus erlotinib or nivolumab versus BSC for this patient population due to the limited clinical effectiveness data available.

6 IMPACT ON THE ICER OF ADDITIONAL ANALYSES UNDERTAKEN BY THE ERG

The ERG has made the following changes to the submitted model to address the points raised in Section 5:

- use of ERG' s preferred PFS estimates
- use of ERG's preferred OS estimates
- revision of second-line drug treatment costs
- revision of third-line treatment costs
- use of the same administration costs for nivolumab and docetaxel
- use of docetaxel restricted to 4 cycles
- drugs administered at the start of each cycle
- revised treatment duration (based on TTD)
- use of alternative health state utility values.

Details of all Microsoft Excel revisions made by the ERG to the company's model are presented in the Appendices to this report (Section 11.10).

6.1.1 Summary of ERG's revisions to company model

The cost effectiveness results obtained by applying each of the ERG's model revisions are summarised in Table 39. Revisions R7 and R8 are mutually exclusive, since R8 includes the effect of using patient numbers at the beginning of a cycle for costing treatment. The ERG's preferred revised base case analysis (B) uses R8 on the grounds that it more closely reflects how treatment is delivered in clinical practice. For the comparison of nivolumab versus docetaxel, the ERG's revised base case analysis yields an ICER of £132,989 per QALY gained which is £47,039 per QALY gained higher than the company's original ICER. The ERG's revised base case generates both costs (- £17,827) and benefits (- 0.103 QALYS) that are lower than those generated by the company for this comparison.

Table 39 Cost effectiveness results (nivolumab 3mg/kg Q2W vs docetaxel 75mg/m^2 Q3W): ERG revisions to company base case comparison

Model scenario ERG revision	**Nivolumab 3mg/kg Q2W**			**Docetaxel 75mg/m^2 Q3W**			**Incremental**			**ICER**	**ICER**
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change**
A. Company's base case	**£86,599**	**1.299**	**2.261**	**£21,243**	**0.539**	**0.953**	**+ £65,355**	**+ 0.760**	**+ 1.308**	**£85,950**	**-**
R1) ERG PFS estimates	£71,172	1.265	2.261	£20,738	0.533	0.953	+ £50,434	+ 0.732	+ 1.308	£68,912	**- £17,038**
R2) ERG OS estimates	£79,923	0.894	1.343	£19,572	0.437	0.743	+ £60,366	+ 0.457	+ 0.600	£131,979	**+ £46,029**
R3) Revised costs of 2nd line drugs	£85,597	1.299	2.261	£15,742	0.539	0.953	+ £69,854	+ 0.760	+ 1.308	£91,867	**+ £5,917**
R4) Revised costs of 3rd line drugs	£86,089	1.299	2.261	£20,550	0.539	0.953	+ £65,539	+ 0.760	+ 1.308	£86,192	**+ £241**
R5) Common administration cost	£84,332	1.299	2.261	£21,243	0.539	0.953	+ £63,089	+ 0.760	+ 1.308	£82,970	**- £2,981**
R6) Restricted use of docetaxel (4 cycles)	£86,599	1.299	2.261	£18,040	0.539	0.953	+ £68,559	+ 0.760	+ 1.308	£90,164	**+ £4,213**
R7) Timing of chemotherapy: drugs given at the start of each cycle	£87,311	1.299	2.261	£21,420	0.539	0.953	+ £65,891	+ 0.760	+ 1.308	£86,654	**+ £704**
R8) Drug costs based on time to treatment discontinuation data	£69,196	1.299	2.261	£19,359	0.539	0.953	+ £49,837	+ 0.760	+ 1.308	£65,542	**- £20,409**
R9) Use utilities from Nafees *et al* publication	£86,599	1.031	2.261	£21,243	0.414	0.953	+ £65,355	+ 0.617	+ 1.308	£105,915	**+ £19,964**
B. ERG revised base case A+R1 to R6, R8, R9	**£60,292**	**0.689**	**1.343**	**£12,780**	**0.332**	**0.743**	**+ £47,512**	**+ 0.357**	**+ 0.600**	**£132,989**	**+ £47,039**

Costs and QALYs discounted; life years undiscounted
ERG=Evidence Review Group; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years

7 END OF LIFE

The company makes the following case for nivolumab to be considered under NICE's end of life criteria:

- patients with advanced or metastatic squamous NSCLC have a life expectancy of less than 24 months
- data from CheckMate 017 demonstrate that nivolumab extends life by more than 3 months compared with docetaxel
- patient population eligible for nivolumab treatment in England is expected to be small (n=853).

The ERG agrees with the company that nivolumab is a treatment that is indicated in patients with a short life expectancy and that the expected size of the patient population is small. The ERG also considers that nivolumab offers an extension to life of at least an additional 3 months compared to current NHS treatment; the ERG estimates a mean OS gain of more than 6 months for patients treated with nivolumab compared to patients treated with docetaxel.

8 DISCUSSION

8.1 Summary of clinical effectiveness issues

8.1.1 Evidence from the CheckMate 017 trial

The company presented clinical evidence from the CheckMate 017 trial to support the clinical case for the use of nivolumab as a second-line treatment option for patients with advanced or metastatic squamous NSCLC. The ERG makes the following observations:

- the ERG considers this trial to be a well-conducted trial with high quality design and reporting methods. However, a relatively large proportion ([redacted]) of patients discontinued treatment with docetaxel within one week – this appears to be a relatively high discontinuation rate when compared with clinical practice
- the ERG considers the comparator in this trial (docetaxel) to be the most appropriate comparator
- the ERG notes that RECIST criteria were used to evaluate response in the CheckMate 017 trial which may not be the optimal method for capturing response with the use of an immuno-oncology therapy such as nivolumab
- nivolumab is a PD-1 inhibitor, however, there is no evidence from the CheckMate 017 trial to suggest that treatment should be targeted based on PD-L1 status
- considering the limited number of patients aged 75 years and over in CheckMate 017, the relative efficacy of nivolumab with docetaxel is not known in this age group
- given the small sample sizes (<20 patients responding) in the nivolumab arm after [redacted] and docetaxel arm after only [redacted], the on-treatment HRQoL data should be treated with caution; response rates for LCSS ASBI and EQ-5D/VAS at 30 days and 100 days follow-up were also relatively low ([redacted] and [redacted] respectively)
- there is currently a lack of data for the efficacy for patients with ECOG PS >1.

In summary, the ERG agrees with the company that, from a clinical effectiveness perspective, nivolumab offers previously treated patients with advanced or metastatic squamous NSCLC an effective treatment option compared with the current standard of care.

8.1.2 Evidence generated by the indirect treatment comparisons

The company and the ERG agree that the efficacy findings of the ITCs comparing nivolumab with erlotinib and nivolumab with BSC are unreliable due to heterogeneity across the trials. In addition, the ERG considers that based on the OS and PFS data available, the ITCs appear to be based on flawed methodology; this means that the clinical and cost effectiveness of nivolumab versus erlotinib or BSC is unknown.

The safety of nivolumab was not compared by the company with either erlotinib or BSC. A crude comparison of AEs reported in the CheckMate 017 and LUX-Lung 8 trials conducted by the ERG suggests that nivolumab may be a safe alternative to erlotinib.

The ERG reiterates that it does not consider erlotinib or BSC to be as relevant as docetaxel as a second-line treatment option for patients with advanced or metastatic squamous NSCLC.

8.1.3 Nivolumab in clinical practice in England

Treatment duration

Patients recruited to the CheckMate 017 trial could receive nivolumab until disease progression (mean number of administrations was eight; range 1 to 48). It is unclear whether any limits will be placed on the number of treatments available to patients if nivolumab is recommended for use in the NHS; the effect on patient benefit of any reduction in number of administrations is unknown. There are no data available to suggest how many treatments might be optimal in clinical practice. Results from the ongoing CheckMate 153 trial will be particularly informative here.

Treatment beyond progression

One fifth of patients in CheckMate 017 remained on treatment with nivolumab after disease progression as defined by RECIST criteria; around one third of these (6.7% of all patients treated with nivolumab) continued to receive benefit in terms of tumour response with treatment. How these 'non-conventional benefitters' would be identified and treated in clinical practice in England is unclear. Whether they would need to be identified is also unclear as the ERG speculates that these 'non-conventional benefitters' may still benefit even if therapy is stopped at progression since an immune response may already have been initiated. Results from the ongoing CheckMate 153 trial may again be informative here.

8.1.4 Available treatment options

The ERG agrees that there are few effective treatment options available for patients with squamous NSCLC (there has been very little progress made in treating patients with squamous NSCLC since the approval of docetaxel for this patient population 10 years ago) and, if the results of CheckMate 017 are borne out in the long term, compared with docetaxel, nivolumab will offer a significant new treatment option for patients with squamous NSCLC. While the ERG does not consider a robust comparison with erlotinib or BSC is possible, it is noted that the safety profile of nivolumab appears to be no worse and possibly even better than that of erlotinib.

The ERG notes that another pharmaceutical company (Boehringer Ingelheim) has announced that they have submitted filing applications for afatinib for the treatment of patients with advanced squamous NSCLC for second-line treatment to the US Food and Drug Administration and to the EMA. Like erlotinib, afatinib is a tyrosine-kinase inhibitor. The

ERG notes that the recently published LUX-Lung 8 trial reported statistically significantly improved median PFS and OS for afatinib compared with erlotinib but afatinib appears to result in an increase in drug-related Grade 3 AEs of diarrhoea, stomatitis and rash/acne over erlotinib.

8.2 Summary of cost effectiveness issues

8.2.1 Cost effectiveness of nivolumab vs docetaxel

An analysis of the company's base case model results shows that, when treatment with nivolumab is compared with docetaxel, 89.4% of the incremental cost is attributable to differences in direct treatment costs (drug acquisition and administration). This means that the cost of nivolumab plays a pivotal role in determining the incremental cost per patient, and that all other costs have no real effect on the size of the ICER per QALY gained.

There are two aspects to determining the cost of treatment with nivolumab – the price charged to the NHS and the length of time patients receive the drug. The company determines the price paid by the NHS for new products, and this is either the list price or a price agreed through a patient access scheme with the Department of Health. In the submitted economic model, the length of time patients receive treatment is determined by the estimated time spent in the PFS state. The ERG considers that the length of time on treatment (TTD) is a more accurate measure of usage and, on request, the company supplied the ERG with an analysis of these CheckMate 017 trial data. This analysis shows that one fifth of patients (n=28) in the nivolumab arm of the trial continued to receive nivolumab after disease progression, and nine of these patients continued to receive benefit. However, despite nivolumab being an immune-oncological therapy, analyses of CheckMate 017 trial data carried out by the ERG have highlighted that there is no evidence to show that, for the majority of patients, nivolumab delivers benefit post-treatment cessation. When considering whether to recommend the use of nivolumab, it is important to estimate the number of patients in England likely to receive nivolumab post-progression as such treatment would have a substantial impact on the magnitude of the cost incurred by the NHS.

The benefits of treatment with nivolumab and docetaxel are measured using QALYs. The magnitude of a QALY depends on patients' perception of their own health (utility) and how long patients live. In the company's model different levels of utility have been used for the pre-progression and post-progression phases of the model, with quality of life (the utility value used) being lower in the post-progression phase. In determining quality of life benefit, however, there is uncertainty regarding the reliability of the utility values used by the

company. In CheckMate 017, data were collected using the EQ-5D questionnaire and response rates were low, which suggests self-selection bias. This bias may have been due to the fact that those patients who were very sick were unable, or unwilling, to complete the questionnaires. This view is consistent with the observation that the PFS utility value estimated by the company is very similar to the UK population age-specific figure estimated by Kind *et al* .[69] Bearing in mind that, at baseline, the population in CheckMate 017 had already undergone one line of chemotherapy treatment this level of similarity seems implausible. The ERG, therefore, used alternative estimates, ones which have previously been used in NSCLC NICE appraisals. In terms of the base case results, when using the alternative utility values for estimating QALYs, the ERG's ICER is approximately £20,000 per QALY gained higher than the company's estimate.

In determining length of life, because data from the CheckMate 017 trial are only available up to 2 years, trial data have been extrapolated to allow patient survival to be estimated up until 20 years (patient lifetime). This means that 90% of the modelled survival is an estimate. The uncertainty around the survival estimates is exemplified by the very different values resulting from the PFS and OS estimation methods employed by the company and the ERG, with the incremental difference in LYG between nivolumab and docetaxel being 1.308 and 0.6 LYG using the company and ERG methods respectively. When the ERG's preferred approach to the estimation of utilities is also implemented in the model, the corresponding QALYs are 0.760 (company value) and 0.357 (ERG value).

After all of the ERG's modifications have been made to the company's model, both the ERG's estimated ICER (£132,989 per QALY gained) and the company's ICER (£85,950 per QALY gained) exceed the willingness to pay thresholds employed in the appraisal of other treatments considered under NICE's end of fife criteria.

8.2.2 Cost effectiveness of nivolumab vs either erlotinib or BSC

In terms of other treatment comparisons, the company considers the cost effectiveness of nivolumab versus erlotinib as a scenario analysis but does not consider the cost effectiveness of nivolumab versus BSC. The ERG considers that although erlotinib and BSC are relevant comparators to nivolumab (but less relevant than the docetaxel which is the current standard of care), there is no reliable clinical evidence to allow the comparison of nivolumab with these two treatments in previously treated patients with squamous NSCLC.

9 OVERALL CONCLUSIONS

For patients with advanced or metastatic squamous NSCLC previously treated with one line of chemotherapy, treatment with nivolumab appears to improve OS and PFS compared with docetaxel, which is the current standard of care for such patients. Improvements were also apparent in terms of ORR but the results from the HRQoL analyses should be treated with caution due to relatively low numbers of patents who completed the assessments. The safety profile of nivolumab also appears to be better than that of docetaxel. It is not currently possible to carry out a robust comparison of nivolumab with the less common treatment options of erlotinib and BSC (in patients previously treated with chemotherapy). However, the limited data that are available suggest that nivolumab may be a safe alternative to erlotinib.

In terms of cost effectiveness, the ERG considers that the company's base case result substantially underestimates the size of the most probable ICER per QALY gained for nivolumab versus docetaxel in previously treated patients with squamous NSCLC. The company's base case result is £85,950 per QALY gained, which is £47,039 less than that estimated by the ERG (£132,989 per QALY gained).

The ERG was unable to compare the cost effectiveness of nivolumab with either erlotinib or BSC for this patient population due to only limited clinical effectiveness data being available.

9.1 Implications for research

The crucial outcomes required for the clarification of the nature and magnitude of patient benefit from use of nivolumab and other treatments for patients with squamous NSCLC are long-term survival, HRQoL and AEs. Long-term data, if collected from Cancer Registries and NHS audits, will provide a very valuable resource for both the clinical research community and for healthcare decision makers.

In the meantime, given nivolumab is an anti-PD-1 agent, data from ongoing studies of nivolumab may be useful for improving the evidence base regarding treatment efficacy and PD-L1 and PD-L2 status. If a relationship were found to exist, further research into the clinical utility of using this biomarker to tailor treatment for patients with locally advanced and metastatic squamous disease would be required.

Data from the CheckMate 017 trial has highlighted a small group of patients referred to as 'non-conventional benefitters'. These are patients who continue to receive benefit (in terms of tumour response) after disease progression (as defined by RECIST criteria). More research is required to identify the characteristics that explain why disease progression in this group of patients is non-conventional and whether the benefits experienced by these patients could be experienced by other patients. Further exploration of how to more accurately compare treatment response and PFS for patients treated with immuno-oncological therapies such as nivolumab compared with more conventional therapies such as docetaxel is also required.

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11 APPENDICES

11.1 Trials included in the company's systematic review

Fourteen trials were included in the company's systematic review. All of the RCT publications reported analyses of outcome data from patients with pre-treated squamous NSCLC (CS, Figure 6 and Table 8). The characteristics of the 14 included studies are summarised here in Table 40. Three trials (CheckMate 017, LUX-Lung 8[16] and EMPHASIS[34]) included only patients with squamous NSCLC. All of the other studies included a minority (20% to 43%) of patients with squamous NSCLC. The numbers of patients with squamous NSCLC varied widely (n=19 to 795) across the included studies. The company notes that only one study (CheckMate 017) included nivolumab as an intervention; in this study nivolumab was compared with docetaxel.

Two of the included studies[38,42] included a comparison of pemetrexed with pemetrexed + carboplatin or gefitinib. Pemetrexed, pemetrexed + carboplatin and gefitinib are not relevant comparators to nivolumab. However, as the company planned to conduct ITCs, the inclusion of these trials was appropriate, as they may have been required to complete the evidence network. A description and critique of the company's ITCs is provided by the ERG in Section 4.3.

Table 40: Characteristics of trials included in the company's systematic review

Trial	RCT type and location(s)	Intervention and comparators	Patient population and previous treatment	Squamous NSCLC (%)	Squamous NSCLC (n)
CheckMate 017[8]	Open-label, active-controlled Phase III study Multicentre: 95 sites in 21 countries	Nivolumab (n=135) Docetaxel (n=137)	Stage IIIB or IV NSCLC Recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease	100.0	272
TAILOR[31]	Open-label, active-controlled Phase III study Multicentre: 105 sites in Italy	Docetaxel (n=110) Erlotinib (n=109)	Locally advanced or metastatic NSCLC Recurrence or progression after platinum-based chemotherapy	34.7	76
BR.21[32]	Double-blind, placebo-controlled Phase III study Multicentre: 15 countries	Erlotinib (n=488) Placebo (BSC) (n=243)	Stage IIIB or IV NSCLC One or two prior chemotherapy	30.5	223
HORG[37]	Open-label, active-controlled Phase III study Multicentre: 9 sites in Greece	Pemetrexed (n=166) Erlotinib (n=166)	Stage IIIB or IV NSCLC Progression after one or two chemotherapy lines	22.5	75
JMID[42]	Open-label, active-controlled Phase III study Multicentre: 7 sites in China	Pemetrexed (n=104) Docetaxel (n=107)	Stage IIIB or IV NSCLC Second-line treatment (after chemotherapy)	24.6	52
Li 2012[39]	Active-controlled study Multicentre: 13 sites in China	Pemetrexed (n=102) Docetaxel (n=106)	Stage IIIB or IV NSCLC Only one prior chemotherapy regimen for advanced disease	21.8	45
LUME-LUNG 1[40]	Open-label, active-controlled Phase III study Multicentre: 211 sites in 27 countries	Nintedanib+docetaxel (n=655) Docetaxel (n=659)	Stage IIIB or IV recurrent NSCLC Relapse of failure of one previous first-line chemotherapy	42.2	555
Kim 2015[38]	Open-label, active-controlled Phase II study Single-centre in Korea	Pemetrexed (n=47) Gefitinib (n=48)	Stage IIIB or IV NSCLC Progression after 1st or 2nd line chemotherapy	20.0	19
NVALT-7[41]	Active-controlled Phase II and pharmacogenetic study Sites nor location not reported	Pemetrexed (n=121) Carboplatin+pemetrexed (n=119)	NSCLC Progression after cytotoxic therapy, which included a platinum compound, with the last cycle administered ≥3 months before entry	32.0	74

Trial	RCT type and location(s)	Intervention and comparators	Patient population and previous treatment	Squamous NSCLC (%)	Squamous NSCLC (n)
NVALT-10[35]	Open-label, active-controlled Phase II study Multicentre: 14 sites in Netherlands	Erlotinib (n=115) Erlotinib+docetaxel or pemetrexed (n=116)*	Locally advanced or metastatic NSCLC Progressed on first-line platinum-based chemotherapy	25.0	60
Juan *et al* 2014[43]	Double-blind, placebo-controlled Phase III study Multicentre: 7 sites in Spain	Docetaxel+erlotinib (n=33) Erlotinib (n=35)	Stage IIIB or IV NSCLC PD with previous chemotherapy	43.0	29
EMPHASIS[34]	Active-controlled Phase III study Multicentre: 12 countries (Europe and Israel)	Erlotinib † Docetaxel †	Advanced NSCLC patients Progression after standard platinum-based chemotherapy doublet	100.0	80 †
TITAN[36]	Open-label, active-controlled Phase III study Multicentre: 77 sites in 24 countries	Erlotinib (n=221) Docetaxel/Pemetrexed (n=203)	Advanced NSCLC Progression after standard platinum-based chemotherapy doublet	36.3	154
LUX-Lung 8[33]	Active-controlled Phase III study Multicentre: 23 countries	Afatinib (n=397) Erlotinib (n=398)	Stage IIIB or IV NSCLC Failure of platinum-based chemotherapy	100.0	795

CNS=Central Nervous System; CT=Computerised Tomography; ECOG=European Cooperative Oncology Group; EGFR=Epidermal Growth Factor Receptor; KPS=Karnofsky Performance Status; MRI=Magnetic Resonance Imaging; ECOG PS=Performance Status; NSCLC=Non-Small Cell Lung Cancer; PD=Progressive Disease; RCT=randomised controlled trial; RECIST= Response Evaluation Criteria in Solid Tumors; TKI=Tyrosine-Kinase Inhibitor

* In the comparator arm of NVALT-10, all patients with squamous NSCLC received erlotinib + docetaxel and all patients with non-squamous NSCLC received erlotinib + pemetrexed

† EMPHASIS aimed to recruit 500 patients but was closed prematurely due to low accrual. To date, results have been presented based on 80 patients with serum protein status defined as good or poor based on the VeriStrat test. Results have been presented for patients with erlotinib good or poor status and docetaxel good or poor status and not for all patients treated with erlotinib or all patients treated with docetaxel

Source: CS, adapted from Table 8, Table 12 and Table 13 of Appendices to CS (of Appendix 7.12 and Appendix 7.13 respectively)

Excluding CheckMate 017, 11 trials included one of the comparators specified in the NICE scope and data from these trials are summarised in Table 41.

Table 41 Summary of findings from trials that include relevant comparators to nivolumab

Relevant trial(s)	Treatment comparison	Summary of findings
TAILOR[31] subgroup (n=54)	Docetaxel vs erlotinib	No statistically significant differences between arms in terms of OS (HR=0.90; 95% CI: 0.49 to 1.65) or PFS (HR=0.57; 95% CI: 0.32 to 1.03)
BR.21[32] subgroup (n=233)	Erlotinib vs placebo (BSC)	Favours erlotinib over placebo for OS (HR=0.67; 95% CI: 0.5 to 0.9)
HORG[37] subgroup (n=75)	Pemetrexed vs erlotinib	Time to tumour response favours erlotinib over pemetrexed (HR=1.97; 95% CI: 1.20 to 3.23)
JMID[42] subgroup (n=52)	Pemetrexed vs docetaxel	No relevant findings
Li 2012[39] subgroup (n=45)	Pemetrexed vs docetaxel	No relevant findings
LUME-LUNG 1[40] subgroup (n=555)	Nintedanib+docetaxel vs docetaxel	No statistically significant difference between arms for OS (HR=1.01; 95% CI: 0.85 to 1.21) but PFS was significantly improved in the nintedanib+docetaxel arm (HR=0.77; 95% CI: 0.62 to 0.96)
NVALT-10[35] subgroup (n=74)*	Docetaxel+erlotinib vs erlotinib	Median OS was similar between arms (6.1 months and 6.2 months) with median PFS numerically higher in the erlotinib arm (4.1 and 4.9 months)
Juan *et al* 2014[43] subgroup (n=29)	Docetaxel+erlotinib vs erlotinib	No statistically significant difference between arms in terms of PFS (HR=0.67; 95% CI: 0.30 to 1.50)
EMPHASIS[34] (n=80)	Docetaxel vs erlotinib	Data from EMPHASIS only reported findings based on serum protein status as defined by the VeriStrat test and not for all patients treated with docetaxel or for all patients treated with erlotinib
TITAN[36] subgroup (n=76)	Erlotinib vs docetaxel or pemetrexed	No statistically significant difference between arms for OS (HR=0.86; 95% CI: 0.61 to 1.23)
LUX-Lung 8[33] (n=795)	Afatinib vs erlotinib	OS and PFS were statistically significantly improved with afatinib (OS: HR=0.81; 95% CI: 0.69 to 0.95; PFS: HR=0.89; 95% CI: 0.69 to 0.96); median OS 7.9 vs 6.8 months and median PFS 2.6 vs 1.9 months

OS=overall survival; HR=hazard ratio; PFS=progression-free survival;
* In the comparator arm of NVALT-10, all patients with squamous NSCLC received erlotinib+docetaxel and all patients with non-squamous NSCLC received erlotinib+ pemetrexed
Source: CS, adapted from Table 15 of Appendices to CS (Appendix 7.14)

11.2 Eligibility criteria for entry into CheckMate 017

CheckMate 017 enrolled men and women aged ≥18 years who signed informed consent, and met key target disease and other criteria as summarised in Table 42.

Table 42 Eligibility for entry into CheckMate 017 trial

Inclusion criteria	Exclusion criteria
• Patients with histologically- or cytologically-documented squamous cell non-small cell lung cancer who present with Stage IIIB/ Stage IV disease or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease) • Disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease • Maintenance therapy following platinum doublet-based chemotherapy was not considered as a separate regimen of therapy • Patients who received platinum-containing adjuvant, neo-adjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy were eligible • Patients with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, were eligible • Patients must have had measurable disease by computed tomography or magnetic resonance imaging per Response Evaluation in Solid Tumours 1.1 criteria; Radiographic Tumour Assessment performed within 28 days of randomisation. Target lesions may have been located in a previously irradiated field if there was documented (radiographic) disease progression in that site • Eastern Cooperative Oncology Group performance status of ≤1 • A formalin-fixed, paraffin-embedded tumour tissue block or unstained slides of tumour sample (archival or recent) must have been available for biomarker evaluation. Specimens must have been received by the central laboratory prior to randomisation. Biopsy should have been excisional, incisional or core needle. Fine needle aspiration was insufficient	• Patients with untreated central nervous system (CNS) metastases. Patients were eligible if CNS metastases had been treated and patients had neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrolment. In addition, patients must have been either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) • Patients with carcinomatous meningitis • Patients with active, known or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enrol • Patients with a condition requiring systemic treatment with either corticosteroids (>10mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomisation. Corticosteroids with minimal systemic absorption (inhaled or topical steroids), and adrenal replacement steroid doses >10 mg daily prednisone equivalent, were permitted in the absence of active autoimmune disease • Prior therapy with anti- programmed death-1, anti-programmed death-ligand 1, anti-programmed death-ligand, anti-CD137, or anti-cytotoxic T-lymphocyte-associated protein4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) • Prior treatment on the first-line ipilimumab trial CA184104 • Prior treatment with docetaxel • Patients with interstitial lung disease that was symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity • All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have been resolved to Grade 1 or baseline before administration of study drug • Treatment with any investigational agent within 14 days of first administration of study treatment

Source: CS, adapted from Table 10

11.3 Trial characteristics of CheckMate 017

Key trial characteristics of CheckMate 017 are summarised in Table 43.

Table 43 Trial characteristics of CheckMate 017

Characteristic	Description
Location	95 sites in 21 countries worldwide (four sites in UK): Argentina, Australia, Austria, Canada, Chile, Czech Republic, France, Germany, Hungary, Ireland, Italy, Mexico, Netherlands, Norway, Peru, Poland, Romania, Russian Federation, Spain, United Kingdom, and US
Design	Global, Phase III, randomised, open-label trial. Patients were randomised via IVRS in a ratio of 1:1. Randomisation was stratified according to prior treatment with paclitaxel-based doublet versus other doublet, and region (US/Canada vs Europe vs Rest of the World)
Population	Adult (≥18 years) patients with advanced or metastatic squamous cell NSCLC after failure of prior platinum doublet-based chemotherapy
Intervention and comparator	Nivolumab at 3mg/kg by IV infusion Q2W (N=135) Docetaxel at 75mg/m^2 by IV infusion Q3W (N=137)
Concomitant medication	Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption); adrenal replacement steroid doses >10mg daily prednisone were permitted in the absence of active autoimmune disease; brief (less than 3-week) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen) was permitted; physiologic replacement doses of systemic corticosteroids were permitted even if >10mg prednisone equivalent dose was administered Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) was allowed if initiated prior to first dose of study therapy (prior radiotherapy must have been completed at least 2 weeks prior to randomisation). Palliative radiotherapy was allowed, but not recommended while receiving nivolumab. If palliative radiotherapy was required, then nivolumab was to be withheld for at least 1 week before, during, and 1 week after radiation. Only non-target bone lesions that did not include lung tissue in the planned radiation field or CNS lesions were to have received palliative radiotherapy while on study treatment
Outcomes	Primary: OS* Secondary: Investigator-assessed PFS, ORR, DOR, TTR Exploratory: Incidence and severity of AEs, HRQoL, immunogenicity
Dates of recruitment	October 2012 to November 2014
Timing of assessments	Radiographic assessments of tumour response were performed at Week 9 (+/- 5 days) and every 6 weeks (+/- 5 days) thereafter until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond progression) or other protocol defined reasons
Duration of follow-up	From start of randomisation to final analysis was approximately 38 months (14 months of accrual + 24 months of follow-up). Last patient last visit occurred on 17 November 2014, providing a minimum follow-up of 10.6 months

AE=adverse event; BOR=best objective response; DOR=duration of response; HRQoL=health related quality of life; NSCLC=non-small cell lung cancer ; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; ORR=objective response rate; TTR=time to treatment response; IVRS=interactive voice response system
*It should be noted that the primary endpoint was changed on 25 April 2014 from a co-primary endpoint including both OS and ORR to a single primary endpoint of OS. This amendment was based on data from the CheckMate 003 study
Source: CS, adapted from Table 10

11.4 Adverse events reported in CheckMate 017

Adverse events were typically lower with nivolumab than with docetaxel, the most obvious exception being pneumonitis (Table 44). Although fatigue, an AE normally reported for traditional chemotherapies, was the most common AE reported by patients treated with nivolumab (16%) it was much more common in the docetaxel arm (33%) as were asthenia and diarrhoea, two other AEs associated with traditional chemotherapies. The drug-related incidence of other AEs associated with traditional chemotherapies (alopecia, neutropenia, febrile neutropenia, neutrophil count decreased, white blood cell count decreased, leukopenia, anaemia and peripheral neuropathy) were all ≤2% in the nivolumab arm.

Table 44 Most common (≥5%) drug-related adverse events in CheckMate 017

Type of AE	Patients with each type of AE, n (%)			
	Nivolumab (n=131)		Docetaxel (n=129)	
	Any Grade	Grade 3 to 5	Any Grade	Grade 3 to 5
Total patients with an event	76 (58)	9 (7)	111 (86)	74 (57)*
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhoea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	1 (1)	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Vomiting	4 (3)	0	14 (11)	1 (1)
Mucosal inflammation	3 (2)	0	12 (9)	0
Anaemia	2 (2)	0	28 (22)	4 (3)
Myalgia	2 (2)	0	13 (10)	0
Oedema peripheral	2 (2)	0	8 (6)	0
Constipation	2 (2)	0	8 (6)	0
Abdominal pain	2 (2)	0	7 (5)	1 (1)
Dizziness	2 (2)	0	7 (5)	0
Paraesthesia	2 (2)	0	7 (5)	0
Neutropenia	1 (1)	0	42 (33)	38 (30)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Alopecia	0	0	29 (22)	1 (1)
Febrile neutropenia	0	0	14 (11)	13 (10)
Neutrophil count decreased	0	0	8 (6)	6 (5)
White blood cell count decreased	0	0	7 (5)	5 (4)

AE=adverse event
NOTE: a patient may be recorded as having more than one adverse event within a category
* There were only three patients with a drug-related Grade 5 AE, all in the docetaxel arm: [redacted]
Source: adapted from CS, Table 28 and CSR, Table 8.1-1 and Table S.6.5

11.5 Evidence from non-randomised studies identified by the company

In addition to the Phase III RCT (CheckMate 017), evidence from two non-RCTs was also submitted by the company: a single-arm Phase I dose-escalation study (CheckMate 003) and single-arm Phase II study (CheckMate 063). Results from the Phase I study led to the company adopting the 3mg/kg dose for nivolumab.

11.5.1 Characteristics of the non-randomised studies

The characteristics of the non-random studies included in the CS are summarised in Table 45. Of note, CheckMate 003 included patients with squamous and non-squamous NSCLC alongside patients with other solid tumours. The number of patients with NSCLC was 129 of whom 37 received the subsequently licensed 3mg/kg dose of nivolumab; 54 patients had squamous NSCLC of whom 18 patients received the 3mg/kg dose of nivolumab.

Table 45 Study characteristics of non-randomised studies

Characteristic	CheckMate 003	CheckMate 063
Location	US	France, Germany, Italy and US
Design	Single-arm Phase I study	Single-arm Phase II study
Population	Patients with selected solid tumours that are advanced or recurrent and progressing after prior treatment with other therapies and for which there is no alternative curative option available (NSCLC n=129; squamous NSCLC n=54)	Patients with advanced or metastatic squamous cell NSCLC who have received first-line platinum doublet chemotherapy and at least one FDA- or EMA-approved subsequent line of systemic therapy (n=117)
Intervention	Nivolumab 1-, 3-, 10-mg/kg Treatment discontinued after 96 weeks	Nivolumab 3mg/kg
Outcomes	Primary Safety (incidence and severity of AEs, SAEs, AEs leading to discontinuation, AEs leading to dose delay, treatment-emergent AEs, AEOSIs including irAEs) Secondary: IRC assessed ORR, BOR, DOR, disease control rate, PFS, TTR Exploratory: immune-related ORR, BOR, DOR and biomarkers of immune response including PD-L1 expression levels	Primary: IRC assessed ORR, BOR, DOR Secondary: Investigator assessed ORR, BOR, DOR Exploratory: OS, PFS, TTR and potential association between programmed death ligand 1 (PD-L1) expression level and efficacy observations; safety and tolerability outcomes including frequency of deaths, AEs, SAEs, AEs leading to discontinuation, AEs leading to dose delay, Select AEs , Clinical laboratory assessments (haematology, serum chemistry, and liver and thyroid function tests), and vital sign measurements, PD-L1 biomarker immunogenicity
Duration of follow-up	Median follow-up was 39 months (range: 32 to 66 months)	Study will end when OS analysis is completed, up to 5 years beyond analysis of primary endpoint; at August 2014 database lock, minimum follow-up was around 11 months

AEs=adverse events; AEOSI=adverse events of special interest; BOR =best objective response; DOR= duration of response EMA=European Medicines Agency; FDA=Food And Drug Administration; irAE=immune related adverse event; IRC=independent radiology review committee; NSCLC=non-small cell lung cancer; ORR=objective response rate; PD-L1=programmed death-ligand 1; PFS=progression-free survival; OS=overall survival; SAEs=serious adverse events; TTR=time to response
Source: adapted from CS, pages 81 to 82 and CS, Appendix 16.1 (Table 26)

Baseline patient characteristics are presented for CheckMate 003 and CheckMate 063 in the Appendices to the CS. For CheckMate 003, baseline data are presented for all 129 patients with NSCLC, regardless of their histology and nivolumab dose. In some respects, the characteristics of patients in both CheckMate 003 and CheckMate 063 studies were similar to those in CheckMate 017:

- the median age of all patients with NSCLC in both trials was 63 years; in CheckMate 017 the median age was 62 in the nivolumab arm
- there were a majority of males with NSCLC in CheckMate 003 (61%) and CheckMate 063 (73%); in CheckMate 017 the proportion of males was 82% in the nivolumab arm
- patients with NSCLC had ECOG PS 0 or 1 in CheckMate 003 (98%) and CheckMate 063 (100%); all patients in CheckMate 017 had ECOG PS 0 or 1.

It is, however, of note that in both of the non-randomised studies, patients were more heavily pre-treated than in CheckMate 017: in CheckMate 003, [redacted] of patients with NSCLC (and [redacted] of patients with squamous NSCLC) had received two or more prior systemic therapies and in CheckMate 063, all patients had received two or more prior systemic therapies; in CheckMate 017 no patient received two or more prior systemic therapies. Furthermore, in CheckMate 003, 54% received three or more prior therapies and in CheckMate 063 the proportion was 65%.

The ERG notes that given the majority of patients in both CheckMate 003 and CheckMate 063 had received three previous systemic therapies but still had an ECOG PS of 0 or 1, the patients included in these studies are unlikely to be typical of those seen in clinical practice in England.

11.5.2 Quality assessment of the non-randomised studies

The findings of the company's assessment of methodological quality are summarised in Appendix 8 of the CS. Both studies scored favourably using the Downs and Black[28] checklist.

11.5.3 Results from the non-randomised studies

A summary of the efficacy findings from CheckMate 003 and CheckMate 063 are presented in Table 46. For all endpoints, patients in CheckMate 003 appeared to have more favourable outcomes than in CheckMate 063. This may be because CheckMate 063 only included patients with two or more previous lines of systemic therapy, unlike CheckMate 003 which included a minority of patients with only one prior therapy. Indeed, the OS findings for squamous patents in CheckMate 003 are broadly more comparable with those reported for patients treated with nivolumab in CheckMate 017.

Table 46 Summary of efficacy findings from non-randomised studies

Endpoint	CheckMate 003			CheckMate 063
	All patients with NSCLC (all doses) (n=129)	Squamous NSCLC (all doses) (n=54)	Squamous NSCLC (3mg/kg) (n=18)	Squamous NSCLC (3mg/kg) (n=117)
OS				
Median months (95% CI)	9.9 (7.8 to 12.4)	9.2 (7.3 to 12.5)	[redacted]	8.2 (6.1 to, 10.9)
1-year survival rate, % (95% CI)	42 (33 to 50)	41 (27 to 54)	49 (23 to 71)	40.8 (31.6 to 49.7)
2-year survival rate, % (95% CI)	24 (17 to 33)	24 (14 to 37)	35 (13 to 58)	N/A
3-year survival rate, % (95% CI)	18 (11 to 25)	19 (9 to 32)	28 (9 to 51)	N/A
PFS				
Median months (95% CI)	2.3 (1.8 to 3.7)	3.8 (1.8 to 7.2)	[redacted]	1.9 (1.8 to 3.2)
1-year survival rate, % (95% CI)	22 (15 to 30)	27 (15 to 41)	30 (10 to 53)	20.0 (12.7 to 28.5)
2-year survival rate, % (95% CI)	9 (4 to 15)	13 (5 to 26)	23 (6 to 46)	N/A
Tumour response				
ORR, % (95% CI)	17.1 (11.0 to 24.7)	16.7 (7.9 to 29.3)	22.2 (6.4 to 47.6)	14.5 (8.7 to 22.2)
Median DOR, months (95% CI)	17 (1.4 to 30.8+)	NtR (3.7 to 30.8+)	NtR (3.7 to 30.8+)	NtR (1.9+ to 11.5+)

Source: adapted from Gettinger *et al* 2015[23] (Table 2, Table S1, Figure S2-B), CheckMate 003 CSR[70] (Table S.5.2.1A) and CS, page 85 and Table 25

A summary of AEs from the two non-randomised studies is provided by the company in the CS. For CheckMate 003 the following observations are made by the company:

- 71% of patients had experienced drug-related AE of any Grade
- the most common drug-related AEs were: fatigue (24%); decreased appetite (12%); and diarrhoea (10%)
- 18 patients who responded to nivolumab discontinued treatment as a result of AEs
- Grade 3 or 4 treatment-related AEs occurred in 14% of patients
- drug-related Select AEs of any Grade were observed in 41.1% of 129 patients with NSCLC, most commonly skin (15.5%), gastrointestinal (11.6%) and pulmonary events (7.0%)
- four patients had treatment-related Grade 3 or higher pneumonitis, including one with Grade 5 pneumonitis
- drug-related deaths occurred in three patients (2%); all were associated with pneumonitis
- no clear relationships between the occurrence of pneumonitis and dose level or treatment duration were noted.

For CheckMate 063, the company makes the following observations:

- almost three-quarters (74%) of patients reported a drug-related AE of any Grade; most commonly, fatigue (33%), decreased appetite (19%) and nausea (15%)
- Grade 3 to 4 drug-related AEs and Grade 3 to 4 drug-related SAEs were reported by 20 (17%) and nine (7.7%) of nivolumab patients, respectively; the most frequent Grade 3 to 4 drug-related AE was fatigue (4%) and the most frequent treatment-related Grade 3 to 4 SAE was [redacted], of which none were Grade 4
- drug-related AEs led to discontinuation for 12% of patients: most commonly for pneumonitis (4%) or fatigue (2%)
- the drug-related pneumonitis AE rate was 5% and drug-related Grade 3 pneumonitis rate was 3%; no cases were Grade 4 or 5
- all pneumonitis cases were manageable with corticosteroids and none required infliximab
- the majority of Select AEs were of low Grade, manageable and resolved, including those for which corticosteroids were initiated; the most frequently reported Select AE categories were: [redacted]
- two deaths (both of which occurred in patients with multiple comorbidities and in the setting of progressive disease) were assessed by the investigator to be related to nivolumab treatment; one death was as a result of drug-related hypoxic pneumonia at 28 days following the last nivolumab dose and the other was a drug-related ischaemic stroke 41 days after the first and only administered nivolumab dose.

Overall the company states that in CheckMate 063: “The nature, frequency and severity of treatment-related AEs, SAEs, Select AEs, and AEs leading to discontinuation are consistent with prior nivolumab trials in squamous NSCLC” (CS, page 94). The ERG concurs that the safety profile of CheckMate 063 is broadly similar to that of CheckMate 003 and that both non-randomised studies also appear to have a safety profile consistent with that of CheckMate 017.

11.6 Pooled safety and immunogenicity data

The ERG notes that the EPAR[1] includes data from a pooled analysis of AEs from CheckMate 017 and CheckMate 063 (n=248). Most frequent AEs (any Grade) are reported to be as follows:

- fatigue (39.5%)
- dyspnoea (37.1%)
- cough (31.5%)
- decreased appetite (29.4%)
- nausea (21.8).

The most frequent Grade 3 to 4 AEs are reported to be:

- dyspnoea (6.9%)
- fatigue (4.4%)
- nausea (2.0%)
- cough (1.6%)
- decreased appetite (1.6%).

Select AEs have also been identified according to four guiding principles:

- AEs which may differ in type frequency, or severity from AEs caused by non-immunotherapies
- AEs which may require immunosuppression (e.g., corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity
- AEs for which multiple event terms maybe used to describe a single type of AE, thereby necessitating the pooling of terms for full characterisation.

Endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, nephritis, and rash are currently considered to be Select AEs.

A summary of the pooled Select AEs is presented in Table 47. In addition, the EPAR also highlights that in CheckMate 003, pneumonitis was reported in 3/37 (8.1%) patients with NSCLC receiving nivolumab 3mg/kg. This includes a case of Grade 4 pneumonitis in one patient.

A comparison of the types of Select AEs in the CheckMate 017 trial, non-randomised CheckMate 003 and CheckMate 063 studies and ongoing CheckMate 153 is presented in Table 48. For more information on CheckMate 153, see Section 11.7.

Table 47 Drug related Select AEs taken from pooled analysis of CheckMate 017 (n=272) and CheckMate 063 (n=248) reported in EPAR

Type of Select AE	Severity of AE		Resolution of AEs	Treatment for AEs*	
	Any Grade	Grade 3 to 5		Corticosteroids*	Discontinuation*
Endocrinopathies (Endocrine AEs)	12 (4.8%)	1 (0.4%) †	6 (50.0%)	3	1 †
• Thyroid disorders (including hypothyroidism or thyroiditis)	11 (4.4%)	0	5 (45.5%)	3	0
• Adrenal insufficiency	1 (0.4%)	1 (0.4%) †	1 (100.0%)	0	1 †
• Hypophysitis	0	0	NA	NA	NA
• Diabetes mellitus	0	0	NA	NA	NA
• Diabetic ketoacidosis	0	0	NA	NA	NA
Diarrhoea/colitis (Gastrointestinal AEs)	23 (9.3%)	NR	19 (82.6%)	3	1
• Diarrhoea	NR	5 (2.0%)	NR	NR	1
• Colitis	NR	4 (1.6%)	NR	NR	0
Hepatitis (Hepatic AEs)	3 (1.2%)	0	2 (66.7%)	0	1 §
Pneumonitis, including interstitial lung disease (Pulmonary AEs)	13 (5.2%)	4 (1.6%) ¥	13 (100.0%)	11	8 ¥
Nephritis (Renal AEs)	8 (3.2%)	1 (0.4%) †	5 (71.4%)	2 †	0
Rash (Skin AEs)	30 (12.1%)	2 (0.8%) ‡	24 (80.0%)	0	2 ‡
Hypersensitivity/infusion reactions	4 (1.6%)	2 (0.8%) ‡	4 (100.0%)	2	2 ‡

NA=not applicable; NR=not reported; AE=adverse event
Note: With the exception of one patient with Grade 4 hypersensitivity/infusion reactions AEs, the highest severity of AE was Grade 3 in either study
* Corticosteroids at least 40mg prednisone equivalents or permanent discontinuation
† all Grade 3 AEs required corticoids
§ due to Grade 2 increases in transaminases
¥ all Grade 3 to 5 AEs required permanent discontinuation of treatment
‡ one patient with Grade 3 AE required permanent discontinuation of treatment
Source: pooled analysis of Select AEs reported in the text of pages 89 to 91 of EPAR

Table 48 Summary of Select AEs reported with nivolumab in patients with NSCLC

Select AEs	CheckMate 017, squamous NSCLC (3mg/kg) (n=131)		CheckMate 003, squamous and non-squamous NSCLC (all doses) (n=129)		CheckMate 063, squamous NSCLC (3mg/kg) (n=117)		CheckMate 153, squamous and non-squamous NSCLC (3mg/kg) ECOG PS 0 to 1 (n=742)		CheckMate 153, squamous and non-squamous NSCLC (3mg/kg) ECOG PS 2 (n=65)	
	Any Grade n (%)	Grade 3 to 4 n (%)	Any Grade n (%)	Grade 3 to 4 n (%)	Any Grade n (%)	Grade 3 to 4 n (%)	Any Grade n (%)	Grade 3 to 4 n (%)	Any Grade n (%)	Grade 3 to 4 n (%)
Endocrine										
• All cause	[redacted]	[redacted]	8 (6.2)	0	[redacted]	[redacted]	NR	NR	NR	NR
• Drug-related	5 (3.8)	0	NR	NR	[redacted]	[redacted]	37 (5.0)	2 (0.3)	1 (1.5)	0
Gastrointestinal										
• All cause	[redacted]	[redacted]	15 (11.6)	1 (0.8)	[redacted]	[redacted]	NR	NR	NR	NR
• Drug-related	11 (8.4)	1 (0.8)	NR	NR	[redacted]	[redacted]	50 (6.7)	3 (0.4)	4 (6.2)	0
Hepatic										
• All cause	[redacted]	[redacted]	6 (4.7)	1 (0.8)	[redacted]	[redacted]	NR	NR	NR	NR
• Drug-related	2 (1.5)	0	NR	NR	[redacted]	[redacted]	26 (3.5)	4 (0.5)	2 (3.1)	1 (1.5)
Pulmonary										
• All cause	[redacted]	[redacted]	9 (7.0)	3 (2.3)	[redacted]	[redacted]	NR	NR	NR	NR
• Drug-related	7 (5.3)	1 (0.8)	NR	NR	[redacted]	[redacted]	6 (0.8)	2 (0.3)	0	0
Renal										
• All cause	[redacted]	[redacted]	4 (3.1)	0	[redacted]	[redacted]	NR	NR	NR	NR
• Drug-related	4 (3.1)	1 (0.8)	NR	NR	[redacted]	[redacted]	2 (0.3)	0	0	0
Skin										
• All cause	[redacted]	[redacted]	20 (15.5)	0	[redacted]	[redacted]	NR	NR	NR	NR
• Drug-related	12 (9.2)	0	NR	NR	[redacted]	[redacted]	69 (9.3)	3 (0.4)	6 (9.2)	1 (1.5)
Hypersensitivity/infusion reaction										
• All cause	[redacted]	[redacted]	5 (3.9)	1 (0.8)	[redacted]	[redacted]	NR	NR	NR	NR
• Drug-related	1 (0.8)	0	NR	NR	[redacted]	[redacted]	8 (1.1)	2 (0.3)	1 (1.5)	0

AE=adverse event; NSCLC=non-small cell lung cancer; ECOG=Eastern Cooperative Oncology Group; PS=performance status
Source: adapted from: CS, Table 29, Table 32 and Table 33; CheckMate 017 CSR Table 8; and company's response to clarification letter, Table 8

The following observations are made in the EPAR with regard to AEs and immunogenicity:

- nivolumab is most commonly associated with immune-related adverse reactions (irAEs)
- most irAEs (including severe reactions) resolved following initiation of appropriate medical therapy or withdrawal of nivolumab
- the summary of product characteristics (SmPC) Sections 4.2 and 4.4 and 4.8 contain the recommendations on how to manage irAEs
- in the absence of data for patients with baseline performance score ≥ 2, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry, nivolumab should be used with caution in these populations after careful consideration of the potential risk-benefit on an individual basis. In addition, these populations have been included in the risk-management plan as missing information
- data in subjects with severe renal impairment and moderate or severe hepatic impairment is limited; caution should be exercised when using nivolumab in these patient populations
- no sound conclusions can be drawn regarding the potential relationship between nivolumab toxicity and age. Safety of nivolumab in the elderly will be followed up in the post-marketing setting
- severe infusion reactions have been reported in clinical trials. In case of a severe infusion reaction, nivolumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab with close monitoring (see Section 4.4 and 4.8 of the SmPC). This risk has been included in the risk-management plan as an important identified risk
- nivolumab shows a low immunogenicity potential
- however, given the low number of patients tested, the risk of developing anti-drug antibodies was considered not yet fully investigated. For suspected irAEs, adequate evaluation should be performed to confirm aetiology or exclude other causes
- based on the severity of the AE, nivolumab should be withheld and corticosteroids administered. Upon improvement, nivolumab may be resumed after corticosteroid taper
- nivolumab must be permanently discontinued for any severe irAE that recurs and for any life threatening irAE (see sections 4.4 and 4.8 of the SmPC)
- the risk of immunogenicity has been included in the risk-management plan as an important potential risk.

It is concluded that the AEs experienced by patients treated with nivolumab appear to be mostly low Grade and manageable and the safety profile is acceptable. However, more information is required from future studies for:

- Select AEs
- immunogenicity.

11.7 Ongoing CheckMate 153 study

In its response to the ERG during the clarification process, the company presented findings from the ongoing Checkmate 153 study which, the company states, is expected to generate data to support optimal duration of treatment with nivolumab. This is because patients who remained progression free at 1 year were randomised to one of two cohorts: Cohort A continued to receive nivolumab until disease progression and Cohort B stopped receiving nivolumab at 1 year but could be re-treated with nivolumab upon disease progression. CheckMate 153 is ongoing and plans to recruit 1380 patients with squamous and patients with non-squamous NSCLC. A summary of AEs reported for the 824 patients so far recruited are presented in Table 50 and drug-related Select AEs, by ECOG status, in Table 51. Data have not been presented by histology:

- the company observed that ECOG PS2 patients experienced a higher rate of SAEs but a similar incidence of drug-related AEs or SAEs compared with ECOG PS 0 to1 patients; there were no Grade 5 drug-related AE or SAE events
- the ERG notes Grade 3 to 4 AEs and all cause AEs leading to discontinuation were also more common in patients with PS 2
- a subgroup analysis of safety data by ECOG PS status showed that the frequency of treatment-related SAEs and select AEs was similar between patients with ECOG PS 0 to 1 and ECOG PS 2.

Table 49: Summary of deaths and treatment discontinuations in CheckMate 153

Characteristics	Nivolumab 3mg/kg N=824
Patients treated, n	824
Patients still on treatment, n (%)	483 (59)
Patients off treatment, n (%)	341 (41)
Reason off treatment, n (%)	
Progressive disease	195 (24)
Death	56 (7)
Other	28 (3)
Patient request to discontinue study treatment	21 (3)
Patient withdrew consent	19 (2)
Patient no longer meets study criteria	9 (1)
Adverse event unrelated to study drug	6 (<1)
Study drug toxicity	5 (<1)
Maximum clinical benefit	1 (<1)
Not reported	1 (<1)
Total patients who died, n (%)	182 (22)
Disease-related	156 (19)
Other [a]	18 (2)
Unknown	8 (1)
Study drug toxicity	0

[a] other includes: respiratory failure due to multifactorial etiology; hypoxic respiratory failure; cardiac arrest, myocardial infarction, congestive heart failure; pulmonary embolism; cardiopulmonary failure; suicide; aspiration respiratory failure; intracranial hemorrhage; hypotension; disease progression; respiratory arrest, and pneumonia
Source: Company's response to clarification letter, Table 6

Table 50: Summary of deaths and treatment discontinuations in CheckMate 153

	Nivolumab 3mg/kg All patients (n=824)		Nivolumab 3mg/kg ECOG PS 0 to 1 (n=742)		Nivolumab 3mg/kg ECOG PS 2 (n=65)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
All adverse events	762 (93)	311 (38)	683 (92)	268 (36)	62 (95)	33 (51)
All serious adverse events (SAEs)	309 (38)	223 (27)	257 (35)	185 (25)	42 (65)	29 (45)
All select adverse events	282 (34)	37 (5)	253 (34)	32 (4)	22 (34)	3 (5)
All treatment-related adverse events	439 (53)	59 (7)	403 (54)	52 (7)	27 (42)	4 (6)
All treatment-related SAEs	23 (3)	19 (2)	18 (2)	14 (2)	3 (5)	3 (5)
All treatment-related select AEs	199 (24)	20 (2)	181 (24)	16 (2)	14 (22)	2 (3)
All AEs leading to discontinuation	87 (11)	53 (6)	69 (9)	42 (6)	16 (25)	9 (14)
All treatment-related SAEs leading to discontinuation	14 (2)	12 (2)	11 (2)	9 (1)	2 (3)	2 (3)
All treatment-related select AEs leading to discontinuation	12 (2)	11 (1)	9 (1)	8 (1)	2 (3)	2 (3)

Source: Company's response to clarification letter, Table 7

Table 51: Summary of treatment-related Select AEs by ECOG PS in CheckMate 153

Type of Select AE	ECOG PS 0- to 1 Nivolumab 3mg/kg (n=742)		ECOG PS 2 Nivolumab 3mg/kg (n=65)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Endocrine disorders	37 (5.0)	2 (0.3)	1 (1.5)	0
• Hypothyroidism	28 (3.8)	1 (0.1)	0	0
• Hyperthyroidism	8 (1.1)	1 (0.1)	0	0
• Blood thyroid-stimulating hormone increased	0	0	1 (1.5)	0
Gastrointestinal disorders	50 (6.7)	3 (0.4)	4 (6.2)	0
• Diarrhoea	48 (6.5)	2 (0.3)	4 (6.2)	0
• Enterocolitis	1 (0.1)	1 (0.1)	0	0
Hepatic disorders	26 (3.5)	4 (0.5)	2 (3.1)	1 (1.5)
• Autoimmune hepatitis	1 (0.1)	1 (0.1)	0	0
• Hepatotoxicity	0	0	1 (1.5)	1 (1.5)
Respiratory disorders	6 (0.8)	2 (0.3)	0	0
• Pneumonitis	6 (0.8)	2 (0.3)	0	0
Renal disorders	2 (0.3)	0	0	0
• Interstitial nephritis	0	0	0	0
Skin disorders	69 (9.3)	3 (0.4)	6 (9.2)	1 (1.5)
• Rash	14 (1.9)	0	1 (1.5)	0
Infusion reaction	8 (1.1)	2 (0.3)	1 (1.5)	0
• Hypersensitivity	2 (0.3)	0	0	0

ECOG= Eastern Cooperative Oncology Group; PS=performance status
Source: adapted from Company's response to clarification letter, Table 8

Overall, the company states the safety data from CheckMate 153 are consistent with results from other clinical trials of nivolumab in patients with NSCLC and more specifically for patients with squamous NSCLC. The ERG concurs that broadly speaking, the safety profile of CheckMate 153 is similar to that of the non-randomised studies, CheckMate 003 and CheckMate 063 and also that of CheckMate 017.

11.8 Adverse events associated with erlotinib

Table 52 summarises the broad types of AEs experienced by patients treated with erlotinib in LUX-Lung 8 alongside the corresponding data from CheckMate 017 for nivolumab. From this crude comparison, drug-related AEs appear to be more common with erlotinib than with nivolumab. Drug related deaths were only reported for patients treated with erlotinib but not with nivolumab.

Table 52 Summary of safety profiles of nivolumab and erlotinib from two recent trials

Type of AE	Proportion of patients with each type of AE (%)	
	CheckMate 017: nivolumab (n=131)	LUX-Lung 8: erlotinib (n=395)
All cause and any Grade AE	97	98
Drug-related AE	58	81
All cause AE leading to discontinuation	11	17
All cause Grade 3 to 5 AE*	51	57
All cause and any Grade SAE	47	44
Death from drug-related AE	0	1

AE=adverse event; SAE=serious adverse event
Source: For CheckMate 017 data (nivolumab), adapted from pages 87 to 89 (including Table 27) of CS except * taken from EPAR,[1] page 96 and † taken from CSR, [44] Table 8.1-1; for LUX-Lung 8 data (erlotinib) taken from oral presentation of results from LUX-Lung 8[33]

The most common drug-related AEs with erlotinib in LUX-Lung 8 are summarised in Table 53. Adverse events occurring in ≥20% of patients were rash or acne and diarrhoea. While both rash and diarrhoea have been highlighted as irAEs associated with nivolumab, the incidence of these AEs (both any Grade and Grade 3 to 4) in CheckMate 017 for patients treated with nivolumab was much lower than reported for patients treated with erlotinib in LUX-Lung 8. Pruritis, dry skin, fatigue and decreased appetite were the next most common AEs reported for patients treated with erlotinib in LUX-Lung 8. Crudely comparing the AE rates from CheckMate 017 with LUX-Lung 8 suggests fatigue may be slightly more common with nivolumab than with erlotinib, decreased appetite is similar across the two drugs and pruritus and dry skin are more common with erlotinib than with nivolumab; skin-related Select AEs are more likely to be identified with nivolumab.

Table 53 Most common drug-related adverse events with erlotinib in LUX-Lung 8

Type of AE	Patients with each type of AE, n (%) in erlotinib arm (n=395)			
	Grade 1	Grade 2	Grade 3	Grade 4
Rash or acne	142 (36%)	83 (21%)	41 (10%)	0 (0%)
Diarrhoea	94 (24%)	28 (7%)	9 (2%)	1 (<1%)
Pruritus	37 (9%)	10 (3%)	0 (0%)	0 (0%)
Dry skin	34 (9%)	7 (2%)	0 (0%)	0 (0%)
Fatigue	24 (6%)	17 (4%)	7 (2%)	0 (0%)
Decreased appetite	24 (6%)	15 (4%)	2 (<1%)	0 (0%)

AE=adverse event
* AEs that occurred in >10% of patients with Grade 1 to 2 adverse events in either the erlotinib or afatinib arms of the trial
Source: Adapted from Table 3 of Soria *et al* 2015 (published paper)[16]

11.9 Evidence network, proportional hazards and implications for decision analysis

Proportional hazards and decision modelling

If there are no direct comparisons from RCTs comparing the intervention treatment (in this case nivolumab) with relevant comparators (docetaxel, erlotinib and BSC), it may be possible to establish a chain of evidence through multiple RCTs that together allow indirect comparisons to be made between the intervention and each of the comparators. In such cases the common method of applying such indirect comparisons in a decision model is to estimate single hazard ratios to represent the relative clinical efficacy of the intervention relative to each comparator in turn, and then to use such hazard ratios to adjust the intervention arm of the primary trial to represent each comparator as if it had been an additional arm in the primary trial.

This use of a single hazard ratio is commonly used for single observation outcomes (e.g. the number of patients suffering a repeat stroke within 30 days of an index stroke), and for this purpose the method is generally reliable. However, when modelling a series of events over an extended time period this naïve method is inappropriate since it takes no account of differential timing of events during the trial which frequently occurs due to the contrasting modes of action of the treatments being compared. The use of a single time-invariant hazard ratio relies on the assumption that event hazards are directly proportional at all times between the arms of the trial.

Moving from a single trial to an evidence network of trials, the same proportional hazards assumption is required throughout the network to provide confidence that the indirect comparisons made by use of a chain of single hazard ratios accurately reflect the relative performance of each comparator compared to the intervention. However, the failure of one or more of the links in an evidence chain to fully comply with the proportional hazards assumption does not necessarily indicate that a comparison between the intervention and any individual comparator may not in fact itself provide an accurate result, but only by happenstance should deviations from the proportional hazards assumption in individual linked trials counter each other.

Broken network

In the CS, an evidence network (Figure 12) has been proposed to allow comparisons to be made between the intervention of interest (nivolumab) and additional comparators specified in the scope for this appraisal: erlotinib and BSC. This involves two clinical trials in addition to CheckMate 017:

- the TAILOR trial which compared erlotinib and docetaxel
- the BR.21 trial which compared erlotinib and placebo (best supportive care).

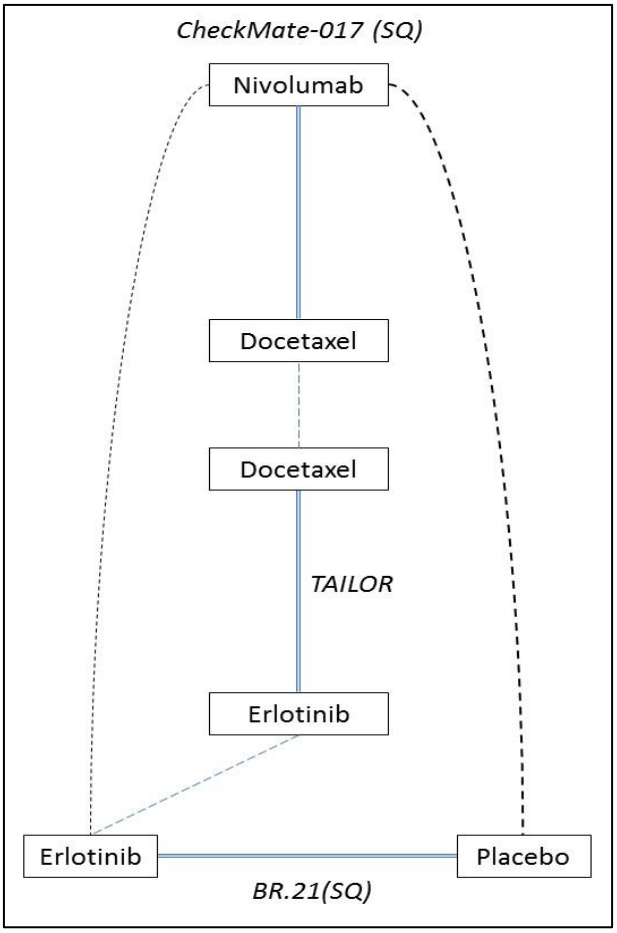

Figure 12 Evidence network

However, there is a serious problem with this network concerning the contrasting patient populations in the three trials. CheckMate 017 features only patients with squamous disease. The BR.21 and TAILOR trials enrolled patients with both squamous and non-squamous disease. A retrospective analysis of the BR.21 trial OS results by Clark *et al* 2007 looked at various subgroups, including squamous versus non-squamous disease, and demonstrated important differences in OS outcomes including quite different time-varying hazard profiles. This indicates that evidence from the TAILOR trial could only be included in the network for OS if detailed time-varying profile results were available from its squamous subgroup, but unfortunately currently the results of this type of analysis have not been published.

For PFS the situation is even less satisfactory, since the Clark *et al* 2007 re-analysis of the BR.21 trial results relates only to OS, so no corresponding temporal PFS hazard profile is available for squamous patients.

Thus, the proposed evidence network is effectively 'broken' for both OS and PFS by the mixed population of the TAILOR trial, and also for PFS by the lack of any subgroup analysis of BR.21 for PFS.

Unlinked comparisons

As the conventional basis for establishing a viable evidence network cannot be established, is it still possible to make viable 'unlinked' comparisons between nivolumab and the two comparators which did not feature in the CheckMate 017 trial (shown in the network diagram above by curved dashed lines)?

Figure 13 shows the relationship between the hazard profiles of nivolumab (CheckMate 017) and erlotinib (BR.21) compared to the simple pattern required to satisfy the proportional hazards assumption. Clearly there is a serious discrepancy evident which indicates that the use of a single time-invariant hazard ratio within the decision model to represent erlotinib would be misleading and inappropriate.

Similarly, Figure 14 shows the relationship between the hazard profiles of nivolumab (CheckMate 017) and BSC (BR.21) compared to the simple pattern required to satisfy the proportional hazards assumption. In this case, the trial data suggest that there is better correspondence between the time-varying profiles of the separated arms of the two trials. This might suggest that an exploratory comparison could be possible using a single time-invariant hazard ratio in respect to OS.

Figure 13 Test of proportional hazards assumption between nivolumab OS (CheckMate 017) and erlotinib OS (BR.21)

Figure 14 Test of proportional hazards assumption between nivolumab OS (CheckMate 017) and BSC OS (BR.21)

Unlinked comparisons

The company model is structured to rely on the application of time-invariant hazard ratios to data from the CheckMate 017 trial to represent the relative performance of erlotinib and BSC as a basis for estimating net outcome benefits in OS and PFS attributable to nivolumab. However the evidence network must be considered 'broken' by the absence of any time profiles of clinical outcomes for the squamous subgroup in the TAILOR trial. In addition, the necessary time profile for the squamous subgroup of the BR.21 trial is only available for the OS outcome.

The possibility of exploratory 'unlinked' comparisons using a single hazard ratio was explored by the ERG in relation to OS, and showed that though this might be possible in relation to BSC, it is clearly inappropriate for erlotinib.

The ERG therefore concludes that there is no generally reliable approach that could allow the use of the currently available clinical evidence to populate the company model to generate meaningful cost effectiveness results comparing nivolumab with either erlotinib or BSC.

11.10 ERG Revisions to company's model: Nivolumab STA

All revisions are activated by a logic switch with 0 = unchanged, 1 (or any non-zero number) = apply ERG modification.

Logic switches are indicated by range variables Mod_*n* where n = 1 – 10 (n=2 not used).

A menu of revisions/Mod numbers appears on the 'Results' worksheet together with summary results as used to transfer to the ERG report.

ERG Table 23 Row Title	Binary switch	Associated detail	Implementation instructions
R1. ERG PFS estimates	Mod_4	ERG_survival_estimates.xlsx Copy the range A1:F1048 and paste into Sheet 'Response and Survival' at cell AP32 of the company model	In Sheet 'Response and survival', Replace formula in cell G39 by =IF(INT_PFS="Spline", spline(INT_PFSsplineform, INT_PFSnosplines, INT_PFSsplineparams, INT_PFSknots, INT_PFSsplinecoef, $E39), Survival_func(INT_PFS, INT_PFS_Scale, INT_PFS_Shape, 'Response and survival'!$E39, INT_PFS_Q))*IF(Mod_4=0,1,0)+AP39*IF(Mod_4=0,0,1) Copy formula in cell G39 to range G40:G1079 Replace formula in cell I39 by =IF(TRT1_PFS="spline",spline(TRT1_PFSsplineform,TRT1_PFSnosplines, TRT1_PFSsplineparams,TRT1_PFSknots,TRT1_PFSsplinecoef,$E39),Survival_func(TRT1_PFS,TRT1_PFS_scale,TRT1_PFS_shape,'Response and survival'!$E39,TRT1_PFS_Q))*IF(Mod_4=0,1,0)+AS39*IF(Mod_4=0,0,1) Copy formula in cell I39 to range I40:I1079
R2. ERG OS	Mod_10	ERG_survival_estim	In Sheet 'Response and survival',

ERG Table 23 Row Title	Binary switch	Associated detail	Implementation instructions
estimates		ates.xlsx (as above)	Replace formula in cell H39 by =IF(TRT1_OS="Spline", IF(spline(TRT1_OSsplineform, TRT1_OSnosplines, TRT1_OSsplineparams, TRT1_OSknots, TRT1_OSsplinecoef,E39)^INT_HR_OS>$G39, spline(TRT1_OSsplineform, TRT1_OSnosplines, TRT1_OSsplineparams, TRT1_OSknots, TRT1_OSsplinecoef,E39)^INT_HR_OS, $G39), IF(Survival_func(TRT1_OS, TRT1_OS_scale, TRT1_OS_shape, 'Response and survival'!$E39, TRT1_OS_Q)^INT_HR_OS > $G39, Survival_func(TRT1_OS, TRT1_OS_scale, TRT1_OS_shape, 'Response and survival'!$E39, TRT1_OS_Q)^INT_HR_OS,$G39))*IF(Mod_10=0,1,0)+AQ39*IF(Mod_10=0,0,1) Copy formula in cell H39 to range H40:H1079 Replace formula in cell J39 by =IF(TRT1_OS="Spline",IF(spline(TRT1_OSsplineform,TRT1_OSnosplines, TRT1_OSsplineparams,TRT1_OSknots,TRT1_OSsplinecoef,$E39)>$I39,spline(TRT1_OSsplineform,TRT1_OSnosplines,TRT1_OSsplineparams,TRT1_OSknots,TRT1_OSsplinecoef,$E39),$I39),IF(Survival_func(TRT1_OS,TRT1_OS_scale,TRT1_OS_shape,'Response and survival'!$E39,TRT1_OS_Q)>$I39,Survival_func(TRT1_OS,TRT1_OS_scale,TRT1_OS_shape,'Response and survival'!$E39,TRT1_OS_Q),I39))*IF(Mod_10=0,1,0)+AT39*IF(Mod_10=0,0,1) Copy formula in cell J39 to range J40:J1079
R3. Recost main drugs (ERG revised 2nd line treatment costs)	Mod_1	ERG_dosing_calculations.xls	In Sheet 'Model parameters', Replace formula in cell G276 by =IF(Mod_1=0,INT_acq_user,2619.69) Replace formula in cell G277 by =IF(Mod_1=0,trt1_acq_user,47.09)
R4. Recost 3rd line drugs	Mod_3	ERG_dosing_calculations.xls	In Sheet 'Model parameters', Replace formula in cell G284 by =IF(Mod_3=0,Costs!N112,31.6)

ERG Table 23 Row Title	Binary switch	Associated detail	Implementation instructions
(ERG revised treatment costs)			Replace formula in cell G285 by =IF(Mod_3=0,Costs!N114,36.32) Replace formula in cell G286 by =IF(Mod_3=0,Costs!N116,19.01) Replace formula in cell G287 by =IF(Mod_3=0,Costs!N118,25.66)
R5. Common admin costs (use same administration cost for nivolumab and docetaxel)	Mod_7	-	In Sheet 'Costs', Replace formula in cell I128 by =IF(Mod_7=0,269.940925288571,I136)

ERG Table 23 Row Title	Binary switch	Associated detail	Implementation instructions
R6. 4 cycles docetaxel (limit Tx to UK maximum)	Mod_5	Modifications combined in same cell range	In Sheet 'Cost', Replace formula in cell N10 by .. =((TRT1_acq*(IF(Mod_8=0,'Patient flow - 1'!$AH14,'Patient flow - 1'!$V14)))*$C10 + (0*('Patient flow - 1'!$AI14))*$C10) + (TRT1_subtrt_cost*TRT1_subtrt_prop*('Patient flow - 1'!$AI14)*C10)
R7/R8. Drugs given at the start of cycle / Drug costs based on time on treatment data	Mod_8		Replace formula in cell N11 by .. =IF(MOD($A11, TRT1_periodicity) = 0, 1, 0)*((TRT1_acq*IF(Mod_8=0,'Patient flow - 1'!$AH15,'Patient flow - 1'!$V15))*$C11 + (0*('Patient flow - 1'!$AI15))*$C11) + (TRT1_subtrt_cost*TRT1_subtrt_prop*MAX(0,('Response and survival'!I38-'Response and survival'!I39))*C11) + N10 Replace formula in cell N12 by .. =IF(MOD($A12, TRT1_periodicity) = 0, 1, 0)*((TRT1_acq*CHOOSE(Mod_8+1,'Patient flow - 1'!$AH16,'Patient flow - 1'!$V16,'Response and survival'!AU39))*$C12 + (0*('Patient flow - 1'!$AI16))*$C12) + (TRT1_subtrt_cost*TRT1_subtrt_prop*MAX(0,('Response and survival'!I39-'Response and survival'!I40))*C12) + N11 Replace formula in cell N13 by =IF(MOD($A13, TRT1_periodicity) = 0, 1, 0)*((TRT1_acq*CHOOSE(Mod_8+1,'Patient flow - 1'!$AH17,'Patient flow - 1'!$V17,'Response and survival'!AU40))*$C13 + (0*('Patient flow - 1'!$AI17))*$C13)*IF(Mod_5=0,1,IF(A13>9,0,1)) + (TRT1_subtrt_cost*TRT1_subtrt_prop*MAX(0,('Response and survival'!I40-'Response and survival'!I41))*C13) + N12 Copy cell N13 to range N14:N1049

ERG Table 23 Row Title	Binary switch	Associated detail	Implementation instructions
		-	In Sheet 'Cost', Replace formula in cell O10 by .. =((TRT1_admin*(IF(Mod_8=0,'Patient flow - 1'!$AH14,'Patient flow - 1'!$V14)))*$C10 + (0*('Patient flow - 1'!$AI14))*$C10) + (TRT1_subtrt_admin_cost*TRT1_subtrt_prop*('Patient flow - 1'!$AI14)*C10) Replace formula in cell O11 by .. =IF(MOD($A11, TRT1_periodicity) = 0, 1, 0)*((TRT1_admin*IF(Mod_8=0,'Patient flow - 1'!$AH15,'Patient flow - 1'!$V15))*$C11 + (0*('Patient flow - 1'!$AI15))*$C11) + (TRT1_subtrt_admin_cost*TRT1_subtrt_prop*MAX(0,('Response and survival'!I38-'Response and survival'!I39))*C11) + O10 Replace formula in cell O12 by .. =IF(MOD($A12, TRT1_periodicity) = 0, 1, 0)*((TRT1_admin*CHOOSE(Mod_8+1,'Patient flow - 1'!$AH16,'Patient flow - 1'!$V16,'Response and survival'!AU39))*$C12 + (0*('Patient flow - 1'!$AI16))*$C12) + (TRT1_subtrt_admin_cost*TRT1_subtrt_prop*MAX(0,('Response and survival'!I39-'Response and survival'!I40))*C12) + O11 Replace formula in cell O13 by =IF(MOD($A13, TRT1_periodicity) = 0, 1, 0)*((TRT1_admin*CHOOSE(Mod_8+1,'Patient flow - 1'!$AH17,'Patient flow - 1'!$V17,'Response and survival'!AU40))*$C13 + (0*('Patient flow - 1'!$AI17))*$C13)*IF(Mod_5=0,1,IF(A13>9,0,1)) + (TRT1_subtrt_admin_cost*TRT1_subtrt_prop*MAX(0,('Response and survival'!I40-'Response and survival'!I41))*C13) + O12 Copy cell O13 to range O14:O1049
		-	In Sheet 'Cost',

ERG Table 23 Row Title	Binary switch	Associated detail	Implementation instructions
			Replace formula in cell F10 by .. =IF(econ_dose_cap_on, IF(B10 <= econ_dose_cap, 1, 0), 1)*IF(dose_cap_on, IF(B10 <= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B10 <= trt_cap, 1,0), 1)*(IF(Mod_8=0, INT_acq*('Patient flow - 1'!$P$14),INT_acq*'Patient flow - 1'!$D$14)*1 + (0*('Patient flow - 1'!$Q14))*$C10) + (INT_PD_Trt*INT_PD_doses*INT_acq*('Patient flow - 1'!$Q14) + INT_subtrt_cost*INT_subtrt_prop*('Patient flow - 1'!$Q14)*C10) Replace formula in cell F11 by .. =IF(MOD($A11, INT_periodicity) = 0, 1, 0)*IF(econ_dose_cap_on, IF(B11 <= econ_dose_cap, 1, 0), 1)*IF(dose_cap_on, IF(B11 <= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B11 <= trt_cap, 1,0), 1)*(INT_acq*CHOOSE(Mod_8+1,('Patient flow - 1'!$P15),('Patient flow - 1'!$D15),'Response and survival'!AR39)*$C11 + (0*('Patient flow - 1'!$Q15))*$C11) + (INT_subtrt_cost*INT_subtrt_prop*MAX(0, (('Response and survival'!G38) - ('Response and survival'!G39)))*C11) + INT_PD_Trt*INT_PD_doses*INT_acq*MAX(0,(('Response and survival'!G38) - ('Response and survival'!G39))*C11) + F10 Copy cell F11 to range F12:F1049

ERG Table 23 Row Title	Binary switch	Associated detail	Implementation instructions
		-	In Sheet 'Cost', Replace formula in cell G10 by .. =IF(dose_cap_on, IF(B11 <= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B11 <= trt_cap, 1,0), 1)*(INT_admin * IF(Mod_8=0,'Patient flow - 1'!$P14,'Patient flow - 1'!$D14)*$C10 + (0*('Patient flow - 1'!$Q14))*$C10) + (INT_PD_Trt*INT_PD_doses*INT_admin*('Patient flow - 1'!$Q14)*C10) + (INT_subtrt_admin_cost*INT_subtrt_prop*('Patient flow - 1'!$Q14)*C10) Replace formula in cell G11 by .. =IF(MOD($A11, INT_periodicity) = 0, 1, 0)*IF(dose_cap_on, IF(B11 <= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B11 <= trt_cap, 1,0), 1)*((INT_admin*CHOOSE(Mod_8+1,'Patient flow - 1'!$P15,'Patient flow - 1'!$D15,'Response and survival'!AR39))*$C11 + (0*('Patient flow - 1'!$Q15))*$C11) + (INT_PD_Trt*INT_PD_doses*INT_admin*MAX(0,(('Response and survival'!G38) - ('Response and survival'!G39)))*C11) + (INT_subtrt_admin_cost*INT_subtrt_prop*MAX(0, (('Response and survival'!G38) - ('Response and survival'!G39)))*C11) + G10 Copy cell G11 to range G12:G1049
R9. Use Nafees utilities (health state utility values)	Mod_9	-	In sheet 'Outcomes', Replace formula in cell F12 by =IF(Mod_9=0,0.75,0.65) Replace formula in cell F13 by =IF(Mod_9=0,0.592,0.43)

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811]

You are asked to check the ERG report from LRiG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday 29 October** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Revised ERG OS extrapolation (page 93)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report concludes that due to the cumulative hazards plot showing long-term linear trends from 40 weeks onwards in both trial arms that an exponential model from 40	The ERG has not provided clinical validation of the revised approach for survival extrapolation. When examining the long-term survival projections of the base-case parametric model for OS (log-logistic); the sensitivity analysis parametric model for	Data is not consistent with the long-term follow-up data for nivolumab or real-world survival data for advanced NSCLC patients	This is not a factual error. The justification for the ERG approach is that it has been found to give consistent results in a number of appraisals of advanced cancer treatments including

weeks is the best option as a basis for projective survival estimation	OS (2-spline hazard); and the ERG model for OS in comparison to the long-term nivolumab trial data and real-word studies it is evident that the ERG OS extrapolation approach consistently under predicts survival – refer to Table 1 below. Based on the evidence provided (as outlined below), we recommend the institute apply the most clinically plausible OS extrapolations (i.e. BMS base-case analyses) to inform the base case analyses. There are three clinical trials available to provide a validation of the OS extrapolation approaches in the BMS submission – CheckMate 017, CheckMate 003, and CheckMate 063; 1.5 years of follow-up are available in CheckMate 017 and CheckMate 063, and 4 years of follow-up is available in CheckMate 003. The long-term clinical validation of the various OS extrapolation approaches are outlined in Table 1 below. What is evident in this Table is that within the various OS extrapolations explored there is a consistent proportion alive at 2 years which is in line with the clinical trial data for nivolumab across CheckMate 017,		those for 2nd line NSCLC patients. The company has selected a projective model design for overall survival which maximises the apparent survival of patients in both trial arms, leading to extended survival gains over many years. The company has then chosen to focus on registry data, which may or may not be relevant to this appraisal. The ERG note that neither the NCLA report nor the SEER analysis distinguish squamous lung cancer from other types of NSCLC, and the US data may be confounded by the different nature and intensity of how treatments are used in the US. By contrast the ERG have considered primarily the only direct trial evidence for the use of nivolumab in patients with advanced/metastatic squamous lung cancer which allows a comparison

	CheckMate 003, and CheckMate 063. However, after 2 years the ERG model significantly under predicts the long-term OS data available from CheckMate 003. Specifically, the ERG model is predicting only 11.9% and XXXX of patients alive at 3 years and 4 years respectively, in comparison to 18% and XXX seen in CheckMate 003. This would be considered clinically implausible as the ERG model would imply that across the nivolumab trials for which OS data is available – CheckMate 017, CheckMate 003, and CheckMate 063 – survival for patients are similar up to 2 years but following this only patients in the CheckMate 017 study would experience a significant decline in OS. In addition, the parametric models submitted were validated against real-world conditional survival data from SEER and the NLCA – Table 42 of the submission document. The NLCA data estimated that conditional survival from Year 3 to Year 4 and Year 4 to Year 5 for Stage IV NSCLC patients is 78.6% and 90.9% respectively. The log-logistic model for OS for nivolumab estimated a conditional survival of 69.4% and 76.6% respectively. The ERG model for OS predicts conditional survival of 53.4% and 52.9% respectively. This		with docetaxel. This reveals that there is no meaningful difference in prognosis for patients living with progressed disease following treatment with either nivolumab or docetaxel. This calls into serious question the reliability of the company's approach to projective modelling of overall survival, which predicts a very large post-progression survival gain which therefore appears implausible.

	relationship is also seen when comparing the ERG OS model to the SEER dataset – the ERG model consistently under predicts OS data seen in the real-world setting. In comparison, the log-logistic model is the closest to the conditional survival seen in NLCA and SEER.		

Table 1. Validation of long-term extrapolation of ERG OS model

Data source	Curve	Proportion alive (%)										Median OS (months)	MeanOS (months)
		6 months	1 year	1.5 years	2 years	3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Log-logistic (base case)	Nivolumab OS	66.8%	43.7%	31.8%	24.9%	17.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.9	27.2
	Docetaxel OS	50.4%	24.6%	14.4%	9.5%	5.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.2	11.5
2-knot spline hazards	Nivolumab OS	65.9%	43.4%	32.8%	25.6%	16.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.7	20.5
	Docetaxel OS	49.3%	24.2%	15.0%	9.9%	4.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.0	10.3
ERG OS extrapolation	Nivolumab OS	63.7%	42.1%	30.6%	22.3%	11.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.5	16.2
	Docetaxel OS	50.7%	23.4%	12.5%	6.6%	1.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.2	9.0
CheckMate 017 (WCLC 2015)	Nivolumab OS	63.70%	42.10%	28%	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.2	-
	Docetaxel OS	50.40%	23.70%	13%	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6	-
CA-209-003 (BMS Data on File)	Nivolumab OS	NA	42%	31%	24%	18%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.9	-
CA-209-063 (WCLC 2015)	Nivolumab OS	60%	39%	27%	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.1	-

Issue 2 Rate of mortality (page 87)

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>The ERG notes that as the baseline age of patients in CheckMate 017 trial is 63.3 years, it is expected that over time the mortality rates in this group of patients would increase rather than decrease over time</td>
<td>The rate of mortality predicted by the parametric model is more consistent with the nature of the disease and the survival profile of lung cancer patients which survive to landmark points.</td>
<td>The 1-year conditional survival for advanced NSCLC patients seen within the NLCA and SEER dataset indicates that from diagnosis conditional survival increases over time. This is consistent with the clinical rationale that once advanced NSCLC patients achieve particular landmark survival points their OS profile improves and their mortality rate will move towards baseline mortality the further the time from diagnosis. The log-logistic model shows that over time as patients are alive longer from point of randomization that their mortality rate moves towards baseline mortality. The ERG model assumes that regardless of time from randomization that the mortality rate of a NSCLC patient would always be significantly higher than baseline mortality.
NLCA Stage IV 1-year conditional survival
<table>
<tr><th>Year from diagnosis</th><th>1-year conditional survival</th></tr>
</table>
</td>
<td>See response to Issue 1</td>
</tr>
</table>

			Year 0	20.5%
			Year 1	46.3%
			Year 2	73.7%
			Year 3	78.6%
			Year 4	90.9%

SEER Stage IIIb –IV 1-year conditional survival

Year from diagnosis	1-year conditional survival
Year 0	15.6%
Year 1	36.0%
Year 2	59.3%
Year 3	69.3%
Year 4	79.1%
Year 5	81.3%
Year 6	83.8%
Year 7	89.5%
Year 8	83.8%
Year 9	92.5%
Year 10	91.9%

Issue 3 Completion rates for HRQoL assessment and potential for selection bias (page 95-96)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG conclusion that EQ-5D data collected in the CheckMate 017 trial had low compliance rate and therefore, the possibility of selection bias in the sample.	Completion rates are higher than stated by ERG and therefore, ERG calculations are inappropriate and need to be amended to reflect an appropriate denominator of patients still receiving either investigational agent or control.	The "week 12" assessment refers to assessments at week 12 for patients remaining on treatment; post-treatment assessments are described as follow-up assessments number 1 and 2. For example, for Nivolumab, 71 patients remained on treatment at week 12 and 50 completed the EQ-5D at the week 12 on-treatment assessment, which is a completion rate of [redacted] (reported in the DoF Table 2); the ERG describes compliance at week 12 as [redacted] dividing the assessments by all randomized subjects. Therefore, potential for selection bias in the on-treatment assessments is much lower than stated by the ERG.	See amended text of Section 5.4.13 and new Addendum (Addendum 2). It is not possible for the ERG to assign Follow-up data to specific time points. Calculations of compliance rates therefore relate solely to patients in the progression-free health state.

Issue 4 ERG substitution and preference of utility values based on the study by Nafees *et al* 2008[60] (page 95)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG conclusion and preference to use of utilities from Nafees *et al* publication to inform the base-case cost effectiveness analyses is at odds with NICE methods guide and reference case.	In line with NICE methods guide and BMS submission, CheckMate 017 trial based utility data should be used as the primary evidence base for this appraisal.	The health state is defined by RECIST 1.1 criteria in CheckMate 017 study and is not based on literature or oncologist description of a PFS or PD patient (as described in Nafees at al 2008). Using direct trial based data enables a clinically more precise definition of a pre-progression vs. post-progression patient to be captured. Moreover, CheckMate 017 study provides data collected from actual patients where Nafees et al derives values based on information from the general public.	See response to Issue 3

Issue 5 Proportion of patients previously treated with an experimental drug (table 6)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states 2% of patients in the docetaxel were previously treated with an experimental treatment this is incorrect	The correct proportion of patients treated with an experimental drug in the docetaxel arm was 1%	Data is reported incorrectly.	This is a typographical error in the ERG report. The ERG agrees the percentage should be 1%. Data amended in erratum document (Table 6)

Issue 6 OS survival reported from the EMPHASIS trial is incorrect (page 39)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states a median OS of 4.8 months in patients with poor classification; this is incorrect	The correct median OS for docetaxel is 4.4months	Data is reported incorrectly	This is a typographical error in the ERG report. The ERG agrees the median should be 4.4 months. Text amended in erratum document (page 39)

Issue 7 Subsequent therapy (page 40)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Number of patients receiving subsequent therapy in the docetaxel arm is incorrectly reported as 24%	The proportion of patients treated with docetaxel receiving subsequent therapy is 30%	Data is reported incorrectly	The ERG extracted data on subsequent treatment therapy from the appendix (Table S3) to the Brahmer et al 2015 publication. The numbers of patients reported by the ERG (page 40) actually refer to systemic therapy (nivolumab: 49 [36%] and docetaxel 41 [30%]) and the ERG should have cited the numbers of patients receiving subsequent chemotherapy in the nivolumab and docetaxel arms which were 48 and 33 respectively. Hence the percentages presented by the ERG are correct but the number of patients in each arm was incorrect. Text amended accordingly in erratum document (page 40)

Issue 8 Subsequent therapy (page 40)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Number of patients receiving subsequent chemotherapy, the ERG incorrect report 95% receiving a taxane in the nivolumab arm	The proportion of patients treated with nivolumab receiving subsequent taxane is 29%. If this is calculated as from the proportion of patients receiving chemotherapy this should be 81%	Data is reported incorrectly	This is an error in the ERG report. The ERG agrees the proportion should be 81%. Text amended in erratum document (page 40)

Issue 9 Subsequent therapy (page 40)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Number of patients receiving subsequent chemotherapy, the ERG incorrect report 17% receiving a taxane in the docetaxel arm	The proportion of patients treated with nivolumab receiving subsequent taxane is 5%. If this is calculated as from the proportion of patients receiving chemotherapy this should be 21%	Data is reported incorrectly	This is an error in the ERG report since the wrong denominator was used (patients who received systemic therapy as opposed to those who received chemotherapy). Text amended in erratum document (page 40)

Issue 10 Median time to onset of drug related Select AEs, weeks (table 10)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The upper limit of the median time to onset of drug-related Select AEs for patients treated with docetaxel is reported as 17.6. This is incorrect.	The upper limit of the range for Median time to onset of drug-related Select AEs for docetaxel should be 17.7	Data is reported incorrectly	This is a typographical error in the ERG report. The ERG agrees the upper limit of the range should be 17.7. Data amended in erratum document (Table 10)

Issue 11 Summary of drug-related Select adverse events in Checkmate 017(table 11)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The data reported for the incidence of Pulmonary events is incorrect.	The correct values should be	Data is reported incorrectly	The final column of this table in the ERG report is Grade 3 to 5 AEs and Table 29 of the CS states that these are Grade 5 AEs. Therefore the data in the final column are correct, however the data in the penultimate column are not. Data amended in erratum document (Table 11)

Pulmonary	7 (5)	1 (1)	0	1 (1) †
Pneumonitis	6 (5)	1 (1)	0	0
Lung infiltration	1 (1)	0	0	0
Interstitial lung disease	0	0	0	1 (1) †

Pulmonary	7 (5)	1 (1)	1 (1)*	0
Pneumonitis	6 (5)	1 (1)	0	0
Lung infiltration	1 (1)	0	0	0
Interstitial lung disease	0	0	1 (1)*	0

Issue 12 Characteristics of included clinical studies (table 40)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There are a number of errors reported in table 40 of the report. Corrected values are given in the next column	HORG study – number of patients randomised to pemetrexed and erlotinib should be 178 and 179 respectively (not 166 and 166) JMID study – number of patients randomised to pemetrexed should be 80, not 104 Li 2012 study – number of patients randomised to pemetrexed should be 107 not 102, and patients randomised to docetaxel should be 104 not 106 Li 2012 study – proportion of patients with squamous NSCLC should be 57% not 45% NVALT-7 study – number and proportion of patients with squamous NSCLC should be 60 (not 32) and 25% (not 74%) NVALT-10 study - number and proportion of patients with squamous NSCLC should be 57 (not 60) and 32% (not 25%) Juan 2014 - Number of patients randomised to docetaxel+erlotinib should be 34 not 33. Number of patients randomised to Erlotinib should be 36 not 35. LUX-Lung study - Number of patients randomised to Afatinib should be 398 not 397 and number of patients randomised to erlotinib should be 397 not 398	Data is reported incorrectly	The ERG extracted much of the data reported in this table from Tables 12 to 14 in Appendices to CS (Appendix 7.12 and Appendix 7.13). The numbers of patients in Tables 12 and 13 are not equivalent, presumably because Table 12 cites patients randomized and Table 13 those for whom data were available at baseline. The ERG has extracted the numbers of patients at baseline (from Table 13) and hence all these data are correct with the exception of the data for LUX-Lung 8 where the company is correct. The ERG has made this explicit in the relevant column heading in the erratum and amended data for LUX-Lung 8 (Table 40). Regarding the % of patients with squamous NSCLC, the ERG disagrees with the company regarding Li 2012: Table 14 in the company's Appendices state this is 21.8% as originally cited by the ERG (n=45) – however from Table 1 of the Li 2012 publication, the ERG notes the number should be 44 which is equivalent to 21.2%. The ERG agrees with the company in relation to the errors noted relating to the NVALT trials and has amended these data (Table 40)

Issue 13 Baseline characteristics of included clinical studies (table 14)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The proportion of patients with squamous NSCLC in the TAILOR studies is incorrectly reported in table 14.	The proportion of patients with squamous NSCLC in the TAILOR study should be 35%	Data is reported incorrectly	The ERG believes that the company is incorrect. There were 219 patients in the TAILOR trial of whom 54 had squamous NSCLC: 54/219=24.7%

Issue 14 Drug related select AEs taken from pooled analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The proportion of patients with rash – resolution of AEs is incorrectly reported as 80.0%	The proportion of patients with rash – resolution of AEs should be 83%	Data is reported incorrectly	The ERG notes from the EPAR that 30 patients were reported to have rash and for 24 patients, this was resolved, which equates to a proportion of 80%. However, the ERG also notes the EPAR does state the proportion was 83% and so has altered the data in the Table (Table 47)

Issue 15 Difference in the number of event between docetaxel and nivolumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report incorrectly reports 15.9% fewer deaths in the nivolumab arm compared to the docetaxel arm	This correct value is 15.8%.	Data is reported incorrectly	This is a typographical error in the ERG report. The ERG agrees that there were 15.8% fewer deaths. Data amended in erratum document (page 88)

Issue 16 Net PFS gain (page 90)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report incorrectly reports a net PFS gain of 3.63 month attributable to nivolumab. This is incorrect.	This correct value is 3.64.	Data is reported incorrectly	The correct value may appear to be 3.64 (7.57 – 3.93) but due to rounding, the value of 3.63 is correct

STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated locally advanced or metastatic squamous non-small cell lung cancer [ID811]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/05

Erratum completed 6 November 2015

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 16 issues in relation to factual errors in the original ERG report. Twelve issues (Issues 3, 5 to 12 and 14 to 16) were considered by the ERG to require minor changes to the text. The pages of the report affected are presented here. Text that remains unaltered is greyed out.

not consider that these differences are likely to lead to major bias and/or favour one arm over another.

Table 6 Baseline characteristics more common in one arm than another (CheckMate 017)

Trial characteristic	More common (≥5%) in nivolumab arm (nivolumab vs docetaxel)	More common (≥5%) in docetaxel arm (nivolumab vs docetaxel)
Age	Age <65 years (59% vs 53%)	Age ≥75 years (8% vs 13%)
Sex	Male (82% vs 71%)	Female (18% vs 29%)
Race		White (90% vs 95%)
ECOG PS	ECOG PS 1 (79% vs 73%)	ECOG PS 0 (20% vs 27%)
Prior surgery		Had prior surgery (51% vs 56%)
Previous treatment	Previously treated with an experimental drug (7% vs 1%) Previously treated with etoposide (13% vs 8%) Most recent platinum therapy was cisplatin (40% vs 26%)	Previously treated with gemcitabine (44% vs 52%) Most recent platinum therapy was carboplatin (60% vs 74%)
Previous best response to therapy	Previous best response to disease was a complete or partial response (36% vs 31%)	Previous best response to disease was stable disease (24% vs 34%)

Source: adapted from CS, Table 13 and from appendix to published paper, Table S1

Palliative radiotherapy to bone or central nervous system (CNS) lesions was allowed per protocol in the CheckMate 017 trial. Clinical advice received by the ERG is that radiotherapy within clinical trials of immune therapies is not atypical and preclinical data suggest that radiotherapy may even improve efficacy of drug treatments (although the ERG is unaware of any published clinical evidence to support this). A total of six patients in the nivolumab arm and one patient in the docetaxel arm received concurrent palliative radiotherapy. In addition, it is stated in the CSR (page 94) that:

Overall, aside from the caveat that, in general, patients who participate in RCTs tend to be slightly younger and fitter than patients seen in clinical practice, the ERG considers that the patient population in the CheckMate 017 trial is likely to be similar to patients treated in routine clinical practice in England for the following reasons:

- eligibility criteria for entry into this trial appear to be reasonable (see Appendices to ERG report, Section 11.1)
- drug dose for docetaxel in the trial is the same as the drug dose used in England
- clinical opinion received by the ERG is that baseline characteristics of included patients are similar to those who would be considered for treatment with nivolumab or docetaxel in England.

Overall survival

At the time of the December 2014 data-cut, the risk of death in the nivolumab arm was 41% lower than in the docetaxel arm. Median OS was improved by 3.2 months, with 42% of patients still alive at 12 months in the nivolumab arm, an increase of 18% compared with patients in the docetaxel arm. At the time of the [redacted] data-cut, the risk of death was very similar (38% lower in the nivolumab arm than that in the docetaxel arm) and median OS was still improved in the nivolumab arm by 3.2 months. The difference in survival rates between arms at 18 months (15%) was similar to the difference in survival rates between arms at 12 months (18%).

At the time of the December 2014 data-cut, the majority of results from subgroup analyses (including PD-L1 status) also appeared to favour nivolumab with the exception of patients aged 75 years and over and patients grouped as 'Rest of the World' (i.e. Argentina, Australia, Chile, Mexico, and Peru) where the findings appeared to favour docetaxel. For both subgroups, confidence intervals were wide and crossed 1 due to small sample sizes (n=29 and n=31 respectively) and therefore numbers of events were few. [redacted] [redacted] a subgroup analysis conducted for age which suggested that patients aged 75 years and over experience no treatment benefit from nivolumab over docetaxel (HR=1.85; 95% 0.76 to 4.51). The company conducted three subgroup analyses for age, categorising patients as (i) <65 and ≥65 (ii) <75 and ≥75 and (iii) <65, ≥65 and <75 and ≥75. [redacted]

In Section 4.2.3, the ERG stated that it considered the patient population in the CheckMate 017 trial to be similar to patients treated in clinical practice in England. Additional evidence to support this assertion may be drawn from comparing the OS estimate in patients treated with docetaxel in the CheckMate 017 trial with estimates typically observed in clinical practice or reported in other trials. Clinical opinion received by the ERG is that patients treated with docetaxel typically have similar, possibly even worse, OS than patients included in the CheckMate 017 trial. Docetaxel OS data are available from the patients with squamous NSCLC in the EMPHASIS trial;[34] however EMPHASIS only reported findings based on serum protein status (poor or good) as defined by the VeriStrat test and not for all patients treated with docetaxel. In that trial OS ranged from 4.4 months (poor classification) to 7.8 months (good classification) for patients treated with docetaxel. These OS data compare well with the OS estimate of 6.0 months (95% CI 5.3 to 7.4) observed at the time of the [redacted] data-cut in the CheckMate 017 trial. The ERG is not aware of any other trial

evidence that has reported median OS for patients who have squamous NSCLC and been treated with second-line docetaxel.

It should be noted that although treatment crossover was not originally permitted in the CheckMate 017 trial, patients did receive subsequent lines of therapy following disease progression. At the time of the December 2014 data-cut, 48 (36%) patients in the nivolumab arm and 33 (24%) patients in the docetaxel arm received subsequent chemotherapy and five (4%) patients treated with nivolumab and eight (6%) patients treated with docetaxel received subsequent erlotinib. Of those receiving chemotherapy, most (39 [81%]) of the patients in the nivolumab arm received a subsequent taxane but only seven (21%) of those in the docetaxel arm received subsequent taxane therapy. Although 32 (24%) patients treated with nivolumab received subsequent docetaxel this is not considered crossover because the therapy received was in accordance with current treatment pathways and current standards of care. Following the analysis of OS at the December 2014 data-cut, the protocol was modified to allow patients initially treated with docetaxel to crossover to receive nivolumab; at the time of the most recent data-cut ([redacted]), only [redacted] patients had initiated nivolumab in this extension phase. Sensitivity analyses taking subsequent treatment into consideration were not reported in the CS but were reported in the EPAR.[1] The ERG is unaware as to the company's methods for adjusting for subsequent treatment (since these are not pre-specified in the protocol) but the results suggest a consistent effect in favour of nivolumab (HR=0.50, 95% CI: 0.35 to 0.71).

system, are directly due to the immunologic mode of action of nivolumab and are based on the types of AEs observed across all nivolumab studies (where they are also sometimes referred to as AEs of special interest [AESIs]). The company notes that there are treatment algorithms for each Select AE category to guide management of these types of AE.[2] Typically treatment requires systemic corticosteroids.

Overall, the proportions of Select AEs were similar in both arms (Table 10); the incidence and severity of drug-related Select AEs are reported in Table 11. Skin and gastrointestinal AEs were the most common Select AEs with nivolumab (9% and 8% respectively). However, the ERG notes the same proportion of skin AEs was reported for patients treated with docetaxel and nivolumab (9%) but the proportion of gastrointestinal AEs with use of docetaxel (20%) was more than double that reported with use of nivolumab (8%). The majority of Select AEs were of low severity. There were only three Grade 3 drug-related Select AEs reported with treatment with nivolumab: a case of tubulointerstitial nephritis, a case of colitis and a case of pneumonitis. No Grade 4 or Grade 5 Select AEs were reported in the nivolumab arm.

Table 10 Summary of Select AEs in CheckMate 017

Type of Select AE	Proportion of patients (%)	
	Nivolumab (n=131)	Docetaxel (n=129)
All cause Select AE		
Drug-related Select AE		
Median time to onset of drug-related Select AEs, weeks	0.3 to 17.6	1.0 to 17.7
Median time to resolution of drug-related Select AEs, weeks	0.3 to 0.5	0.7 to 5.6

Source: CS, adapted from Table 27 and page 92

In summary, the ERG agrees with the company that the overall safety profiles of both nivolumab and docetaxel were consistent with expectations based on prior data with respect to the type, frequency, and severity of AEs. Further information on AEs from previous nivolumab studies is reported in the Appendices to this ERG report (Section 11.5.3) and the results of a pooled analysis of AEs from the EPAR[1] are also summarised in the Appendices to this ERG report (Section 11.6).

Table 11 Summary of drug-related Select adverse events in CheckMate 017

Type of AE	Patients with each type of AE, n (%)			
	Nivolumab (n=131)		Docetaxel (n=129)	
	All Grade	Grade 3 to 5	All Grade	Grade 3 to 5
Endocrine	5 (4)	0	0	0
• Hypothyroidism	5 (4)	0	0	0
Gastrointestinal	11 (8)	1 (1)	26 (20)	3 (2)
• Diarrhoea	10 (8)	0	26 (20)	3 (2)
• Colitis	1 (1)	1 (1)	0	0
Hepatic	2 (2)	0	2 (2)	1 (1)
• Alanine aminotransferase increased	2 (2)	0	1 (1)	1 (1)
• Aspartate aminotransferase increased	2 (2)	0	1 (1)	1 (1)
• Blood bilirubin increased	0	0	1 (1)	0
Pulmonary	7 (5)	1 (1)	1 (1) †	1 (1) †
• Pneumonitis	6 (5)	1 (1)	0	0
• Lung infiltration	1 (1)	0	0	0
• Interstitial lung disease	0	0	1 (1) †	1 (1) †
Renal	4 (3)	1 (1)	3 (2)	0
• Blood creatinine increased	4 (3)	0	2 (2)	0
• Tubulointerstitial nephritis	1 (1)	1 (1)	0	0
• Renal failure acute	0	0	1 (1)	0
Skin	12 (9)	0	11 (9)	2 (2)
• Rash	5 (4)	0	8 (6)	2 (2)
• Pruritus	3 (2)	0	0	0
• Erythema	1 (1)	0	2 (2)	0
• Rash maculopapular	1 (1)	0	0	0
• Skin exfoliation	1 (1)	0	2 (2)	0
• Urticaria	1 (1)	0	0	0
• Palmar-Plantar erythrodysaesthesia syndrome	0	0	1 (1)	0
Hypersensitivity/infusion reaction	1 (1)	0	3 (2)	1 (1)
• Infusion-related reaction	1 (1)	0	1 (1)	0
• Hypersensitivity	0	0	2 (2)	1 (1)

AE=adverse event
NOTE: a patient may be recorded as having more than one adverse event within a category
† Grade 5 AE; there were no Grade 5 AEs (i.e. deaths) in the nivolumab arm
Source: adapted from CS, Table 29

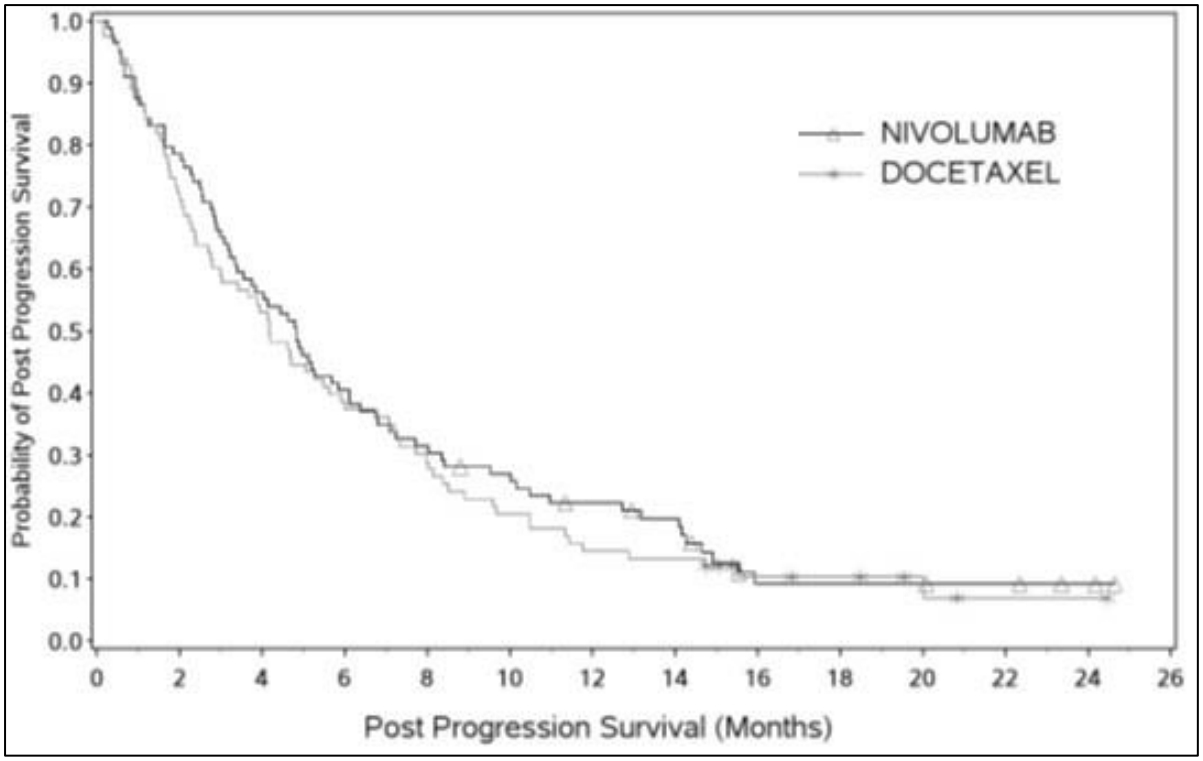

Figure 7 Post-progression survival in the CheckMate 017 trial

At first sight these data may suggest that none of the 9.2 months post-progression survival (PPS) gain generated by the company model (**Error! Reference source not found.**) is upported by the trial evidence. However, some differential PPS can arise if there is a difference in the proportion of patients who die prior to overt disease progression, and who would therefore not feature in the PPS analysis. Information in the CSR for the CheckMate 017 trial (CSR, Table S.5.13) indicates that [redacted] such deaths occurred in the nivolumab arm than in the docetaxel arm. Using a 2-phase exponential function to represent accurately the joint PPS trial data (Figure 8), the difference in pre-progression deaths leads to a notional mean gain in PPS of 1.15 months rather than 9.2 months in the company base case (Table 36), and a corresponding reduction in OS gain from 15.7 months to 7.65 months. This modification to the company model would be expected to increase substantially the size of the estimated ICER per QALY gained for nivolumab versus docetaxel.

5.4.11 Restricted use of docetaxel

In the UK, the use of docetaxel chemotherapy in second-line NSCLC is restricted to a maximum of four cycles, due to the risk of AEs (especially febrile neutropenia). Applying this restriction on docetaxel use in the model and assuming that this affects only the cost of treatment (i.e. has no impact on outcomes), this change reduces the cost of docetaxel treatment and thereby increases the incremental cost of using nivolumab so that the estimated ICER for nivolumab compared to docetaxel increases by £4,213 per QALY gained.

5.4.12 Timing of chemotherapy

Treatment costs (acquisition and administration) are estimated in the company model by applying a unit cost to the average number of patients on treatment across each cycle. However, both the intervention and the comparator treatments are given on the first day of each cycle and should be costed accordingly. When this correction is applied the cost per patient increases in both arms, and the size of the estimated ICER increases by £704 per QALY gained.

5.4.13 Health state utility

Although EQ-5D data were collected in the CheckMate 017 trial, the response rates were poor and patchy. Only [redacted] of randomised patients completed the baseline EQ-5D assessment, and participation (relative to the number of patients still progression-free) fell to [redacted] at [redacted], [redacted] at [redacted] and [redacted] at [redacted]. Inevitably, the decision to continue responding to the EQ-5D questionnaire will have been influenced by a variety of factors, but it must be of concern that those who continued to participate will have been self-selecting and are unlikely to be typical of the initial cohort. The ERG therefore considers that claims to improvements in mean utility scores over time, or significant differences between arms attributable to the randomised treatment are unreliable; the ERG's detailed reasons are provided in Addendum 2.

In the company model, it is assumed that patients with stable disease or showing a response to treatment experience a mean utility score of 0.75, whereas those who have suffered disease progression have a mean utility score of 0.592. These values were derived from the CheckMate 017 trial EQ-5D data. The ERG has tested the effect of substituting alternative values (based on the study by Nafees *et al* 2008[60]) previously used for patients treated with second-line chemotherapy in a systematic review and economic evaluation of first-line chemotherapy for NSCLC;[68] 0.65 for the PF state and 0.43 for the PD state. Though these values were obtained from a Standard Gamble exercise with members of the general public,

they are broadly similar to randomised trial data from lung cancer patients (see Addendum 2).

These changes reduce the incremental QALYs gained per patient by 19%, and increase the size of the estimated ICER by 23%.

5.4.14 Adverse event utility decrements

The effects of AEs on health-related utility are represented in the company model by six selected AEs. The associated disutility estimates are derived from three sources: the Nafees study[60] for asthenia, fatigue, neutropenia and febrile neutropenia, a study by Marti[61] for pneumonia, and a study by Doyle and Walker[59] for dyspnoea. The Marti *et al* study is a standard gamble exercise involving South and Central American parents of hospitalised children aged 3 to 36 months, considering the disutility of a 7 day stay followed by recovery to full health. Clearly this cannot be considered relevant to elderly patients with metastatic lung cancer undergoing second-line chemotherapy. The Doyle and Walker study[59] was less sophisticated than the Nafees *et al* study,[60] including only three symptoms and omitting PD. It is therefore inappropriate to select a single estimated parameter value from the Doyle and Walker model[59] and combine it with the Nafees *et al* model parameters.[60]

The method of applying the disutility effects of AEs in the company model is unsatisfactory. It involves multiplying the Grade 3 to 5 incidence rates of the selected AEs with the corresponding disutility values and summing them to a single disutility quantum, which is applied only to week 1 of the model. This involves two strong assumptions:

- that any patient experiencing a specific AE only suffers a single episode (because the incidence rate per person is used instead of the event rate)
- that, on average, all AE events and their sequelae last for no more than one week.

As a consequence, the estimated disutility effect of AEs in the model is necessarily understated to an unknown extent. The ERG is not able to assess the potential size of this problem due to lack of data, but considers it is unlikely to be large relative to the other issues previously highlighted.

5.5 Summary of ERG's review of the company model

For the comparison of nivolumab versus docetaxel, the ERG has made revisions in all three areas of interest: clinical outcomes, especially in survival analysis; cost estimation and implementation for drug treatments; and the selection of appropriate health-related utility values. In particular, the ERG considers that estimation of OS gain in the company's model is flawed and that this is the primary issue of concern in this appraisal. The company's

estimation of PFS, the use of PFS rather than TTD data to estimate drug costs, and the choice of AE utility values are also of particular concern to the ERG.

11 APPENDICES

11.1 Trials included in the company's systematic review

Fourteen trials were included in the company's systematic review. All of the RCT publications reported analyses of outcome data from patients with pre-treated squamous NSCLC (CS, Figure 6 and Table 8). The characteristics of the 14 included studies are summarised here in Table 40. Three trials (CheckMate 017, LUX-Lung 8[16] and EMPHASIS[34]) included only patients with squamous NSCLC. All of the other studies included a minority (20% to 43%) of patients with squamous NSCLC. The numbers of patients with squamous NSCLC varied widely (n=19 to 795) across the included studies. The company notes that only one study (CheckMate 017) included nivolumab as an intervention; in this study nivolumab was compared with docetaxel.

Two of the included studies[38,42] included a comparison of pemetrexed with pemetrexed + carboplatin or gefitinib. Pemetrexed, pemetrexed + carboplatin and gefitinib are not relevant comparators to nivolumab. However, as the company planned to conduct ITCs, the inclusion of these trials was appropriate, as they may have been required to complete the evidence network. A description and critique of the company's ITCs is provided by the ERG in Section 4.3.

Table 40: Characteristics of trials included in the company's systematic review

Trial		Intervention and Comparators (n at baseline)		Squamous NSCLC (%)	Squamous NSCLC (n)
CheckMate 017[8]	Open-label, active-controlled Phase III study Multicentre: 95 sites in 21 countries	Nivolumab (n=135) Docetaxel (n=137)	Stage IIIB or IV NSCLC Recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease	100.0	272
TAILOR[31]	Open-label, active-controlled Phase III study Multicentre: 105 sites in Italy	Docetaxel (n=110) Erlotinib (n=109)	Locally advanced or metastatic NSCLC Recurrence or progression after platinum-based chemotherapy	34.7	76
BR.21[32]	Double-blind, placebo-controlled Phase III study Multicentre: 15 countries	Erlotinib (n=488) Placebo (BSC) (n=243)	Stage IIIB or IV NSCLC One or two prior chemotherapy	30.5	223
HORG[37]	Open-label, active-controlled Phase III study Multicentre: 9 sites in Greece	Pemetrexed (n=166) Erlotinib (n=166)	Stage IIIB or IV NSCLC Progression after one or two chemotherapy lines	22.5	75
JMID[42]	Open-label, active-controlled Phase III study Multicentre: 7 sites in China	Pemetrexed (n=104) Docetaxel (n=107)	Stage IIIB or IV NSCLC Second-line treatment (after chemotherapy)	24.6	52
Li 2012[39]	Active-controlled study Multicentre: 13 sites in China	Pemetrexed (n=102) Docetaxel (n=106)	Stage IIIB or IV NSCLC Only one prior chemotherapy regimen for advanced disease	21.2	44
LUME-LUNG 1[40]	Open-label, active-controlled Phase III study Multicentre: 211 sites in 27 countries	Nintedanib+docetaxel (n=655) Docetaxel (n=659)	Stage IIIB or IV recurrent NSCLC Relapse of failure of one previous first-line chemotherapy	42.2	555
Kim 2015[38]	Open-label, active-controlled Phase II study Single-centre in Korea	Pemetrexed (n=47) Gefitinib (n=48)	Stage IIIB or IV NSCLC Progression after 1st or 2nd line chemotherapy	20.0	19
NVALT-7[41]	Active-controlled Phase II and pharmacogenetic study Sites nor location not reported	Pemetrexed (n=121) Carboplatin+pemetrexed (n=119)	NSCLC Progression after cytotoxic therapy, which included a platinum compound, with the last cycle administered ≥3 months before entry	25.0	60

Trial		Intervention and Comparators (n at baseline)		Squamous NSCLC (%)	Squamous NSCLC (n)
NVALT-10[35]	Open-label, active-controlled Phase II study Multicentre: 14 sites in Netherlands	Erlotinib (n=115) Erlotinib+docetaxel or pemetrexed (n=116)*	Locally advanced or metastatic NSCLC Progressed on first-line platinum-based chemotherapy	32.0	74
Juan *et al* 2014[43]	Double-blind, placebo-controlled Phase III study Multicentre: 7 sites in Spain	Docetaxel+erlotinib (n=33) Erlotinib (n=35)	Stage IIIB or IV NSCLC PD with previous chemotherapy	43.0	29
EMPHASIS[34]	Active-controlled Phase III study Multicentre: 12 countries (Europe and Israel)	Erlotinib † Docetaxel †	Advanced NSCLC patients Progression after standard platinum-based chemotherapy doublet	100.0	80 †
TITAN[36]	Open-label, active-controlled Phase III study Multicentre: 77 sites in 24 countries	Erlotinib (n=221) Docetaxel/Pemetrexed (n=203)	Advanced NSCLC Progression after standard platinum-based chemotherapy doublet	36.3	154
LUX-Lung 8[33]	Active-controlled Phase III study Multicentre: 23 countries	Afatinib (n=398) Erlotinib (n=397)	Stage IIIB or IV NSCLC Failure of platinum-based chemotherapy	100.0	795

CNS=Central Nervous System; CT=Computerised Tomography; ECOG=European Cooperative Oncology Group; EGFR=Epidermal Growth Factor Receptor; KPS=Karnofsky Performance Status; MRI=Magnetic Resonance Imaging; ECOG PS=Performance Status; NSCLC=Non-Small Cell Lung Cancer; PD=Progressive Disease; RCT=randomised controlled trial; RECIST= Response Evaluation Criteria in Solid Tumors; TKI=Tyrosine-Kinase Inhibitor

* In the comparator arm of NVALT-10, all patients with squamous NSCLC received erlotinib + docetaxel and all patients with non-squamous NSCLC received erlotinib + pemetrexed

† EMPHASIS aimed to recruit 500 patients but was closed prematurely due to low accrual. To date, results have been presented based on 80 patients with serum protein status defined as good or poor based on the VeriStrat test. Results have been presented for patients with erlotinib good or poor status and docetaxel good or poor status and not for all patients treated with erlotinib or all patients treated with docetaxel

Source: CS, adapted from Table 8, Table 12, Table 13 and Table 14 of Appendices to CS (of Appendix 7.12 and Appendix 7.13 respectively)

Table 47 Drug related Select AEs taken from pooled analysis of CheckMate 017 (n=272) and CheckMate 063 (n=248) reported in EPAR

Type of Select AE			Resolution of AEs		
Endocrinopathies (Endocrine AEs)	12 (4.8%)	1 (0.4%) †	6 (50.0%)	3	1 †
• Thyroid disorders (including hypothyroidism or thyroiditis)	11 (4.4%)	0	5 (45.5%)	3	0
• Adrenal insufficiency	1 (0.4%)	1 (0.4%) †	1 (100.0%)	0	1 †
• Hypophysitis	0	0	NA	NA	NA
• Diabetes mellitus	0	0	NA	NA	NA
• Diabetic ketoacidosis	0	0	NA	NA	NA
Diarrhoea/colitis (Gastrointestinal AEs)	23 (9.3%)	NR	19 (82.6%)	3	1
• Diarrhoea	NR	5 (2.0%)	NR	NR	1
• Colitis	NR	4 (1.6%)	NR	NR	0
Hepatitis (Hepatic AEs)	3 (1.2%)	0	2 (66.7%)	0	1 §
Pneumonitis, including interstitial lung disease (Pulmonary AEs)	13 (5.2%)	4 (1.6%) ¥	13 (100.0%)	11	8 ¥
Nephritis (Renal AEs)	8 (3.2%)	1 (0.4%) †	5 (71.4%)	2 †	0
Rash (Skin AEs)	30 (12.1%)	2 (0.8%) ‡	24 (83.0%)	0	2 ‡
Hypersensitivity/infusion reactions	4 (1.6%)	2 (0.8%) ‡	4 (100.0%)	2	2 ‡

NA=not applicable; NR=not reported; AE=adverse event
Note: With the exception of one patient with Grade 4 hypersensitivity/infusion reactions AEs, the highest severity of AE was Grade 3 in either study
* Corticosteroids at least 40mg prednisone equivalents or permanent discontinuation
† all Grade 3 AEs required corticoids
§ due to Grade 2 increases in transaminases
¥ all Grade 3 to 5 AEs required permanent discontinuation of treatment
‡ one patient with Grade 3 AE required permanent discontinuation of treatment
Source: pooled analysis of Select AEs reported in the text of pages 89 to 91 of EPAR

APPENDIX E1

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated locally advanced or metastatic squamous non-small cell lung cancer [ID811]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/05

Completed 9 November 2015

CONTAINS ACADEMIC IN CONFIDENCE DATA

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A MEMBER OF THE RUSSELL GROUP

Erlotinib (list price) as comparator to nivolumab (list price)

In Appendix 11.9 to the ERG main report (page 136), it was observed that:

> "… the proposed evidence network is effectively 'broken' for both OS and PFS by the mixed population of the TAILOR trial, and also for PFS by the lack of any subgroup analysis of BR.21 for PFS."

On this basis, the Evidence Review Group (ERG) concluded that a viable indirect comparison between nivolumab and either erlotinib or best supportive care (BSC) is not possible, due primarily to the absence of results from the TAILOR trial differentiated by histology, which are needed to allow overall survival (OS) and progression-free survival (PFS) results from the squamous subgroup of the trial to be incorporated into the network.

Prior to submission of the ERG report to NICE, the ERG submitted a request to the corresponding author of the TAILOR trial in Italy, requesting a subgroup survival analysis for squamous patients in the hope of resolving this problem. On 29th October 2015, the ERG received the requested information and have now been able to assess the implications of the new data for the assessment of cost-effectiveness for comparators to nivolumab other than docetaxel.

The squamous subgroup of the TAILOR trial comprised 54 patients, 25% of the 219 patients randomised. Despite histology not being a randomisation factor in the design of the trial, the trial population was balanced across treatment arms with respect to histology (chi-squared = 1.67, p = 0.20). It is not possible to validate comparability of other baseline characteristics in this subgroup.

Comparing the docetaxel arms of the CheckMate 017 trial and the squamous subgroup of the TAILOR trial indicates [redacted].

On this basis the ERG conclude that the docetaxel arms of the CheckMate 017 trial and the TAILOR trial [redacted] for the purpose of carrying out an exploratory cost-effectiveness analysis including erlotinib. This compares the nivolumab arm of the CheckMate 017 and the erlotinib arm of the TAILOR trial squamous subgroup directly for both PFS and OS. However, the absence of equivalent squamous subgroup data for PFS in the BR.21 trial remains an obstacle to including BSC in the cost-effectiveness analysis.

The TAILOR squamous subgroup results, including ERG projective modelling of PFS and OS have been incorporated into the company model and additional cost-effectiveness estimates generated for the comparison of nivolumab and erlotinib in the following table.

Given the similarity of the main outcome variables, the only substantive differences between nivolumab and erlotinib occur in the relative cost of treatment and adverse events, and the incremental QALYs generated due to the different adverse event profiles.

Table E1: Cost effectiveness results (nivolumab list price vs erlotinib list price) - ERG revisions to company base case comparison

Model scenario ERG revision	**Nivolumab 3mg/kg Q2W**			**Erlotinib 150mg QD**			**Incremental**			**ICER**	**ICER**
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change**
A. Company's base case	**£86,599**	**1.299**	**2.261**	**£16,901**	**0.488**	**0.814**	**+ £69,698**	**+ 0.812**	**+ 1.446**	**£85,862**	**-**
R1) ERG PFS estimates	£71,172	1.265	2.261	£17,593	0.494	0.814	+ £53,579	+ 0.771	+ 1.446	£69,489	*- £16,372*
R2) ERG OS estimates	£79,923	0.894	1.343	£16,414	0.458	0.743	+ £63,509	+ 0.437	+ 0.600	£145,451	*+ £59,589*
R3) Revised costs of 2nd line drugs	£85,597	1.299	2.261	£16,783	0.488	0.814	+ £68,814	+ 0.812	+ 1.446	£84,772	*+ £1,089*
R4) Revised costs of 3rd line drugs	£86,089	1.299	2.261	£16,206	0.488	0.814	+ £69,883	+ 0.812	+ 1.446	£86,089	*+ £228*
R5) Common administration cost	£84,332	1.299	2.261	£16,901	0.488	0.814	+ £67,432	+ 0.812	+ 1.446	£83,070	*- £2,792*
R7) Timing of chemotherapy: drugs given at the start of each cycle	£87,311	1.299	2.261	£16,901	0.488	0.814	+ £70,410	+ 0.812	+ 1.446	£86,739	*+ £877*
R8) Drug costs based on time to treatment discontinuation data	£69,196	1.299	2.261	£16,901	0.488	0.814	+ £52,295	+ 0.812	+ 1.446	£64,423	*- £21,439*
R9) Use utilities from Nafees *et al* publication	£86,599	1.031	2.261	£16,901	0.373	0.814	+ £69,698	+ 0.657	+ 1.446	£106,052	*+ £20,191*
B. ERG revised base case A+R1 to R5, R8, R9	**£60,292**	**0.689**	**1.343**	**£16,282**	**0.361**	**0.743**	**+ £44,010**	**+ 0.328**	**+ 0.600**	**£134,171**	***+ £48,309***

Costs and QALYs discounted; life years undiscounted; ERG=Evidence Review Group; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years

ADDENDUM 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated locally advanced or metastatic squamous non-small cell lung cancer [ID811]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/05

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UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Health state utility

Following the company's factual error check of the original ERG report, the following has been produced by the ERG as an appendix to add clarity to its reasoning in Section 5.4.13.

Although EQ-5D data were collected in the CheckMate 017 trial, the response rates were poor and patchy. Only [redacted] of randomised patients completed the baseline EQ-5D assessment, and participation (relative to the number of patients still progression-free) fell to [redacted] at [redacted], [redacted] at [redacted] and [redacted] at [redacted]. Inevitably, the decision to continue responding to the EQ-5D questionnaire will have been influenced by a variety of factors, but it must be of concern that those who continued to participate will have been self-selecting and are unlikely to be typical of the initial cohort. Figure 15 illustrates the difficulty in interpreting these EQ-5D results.

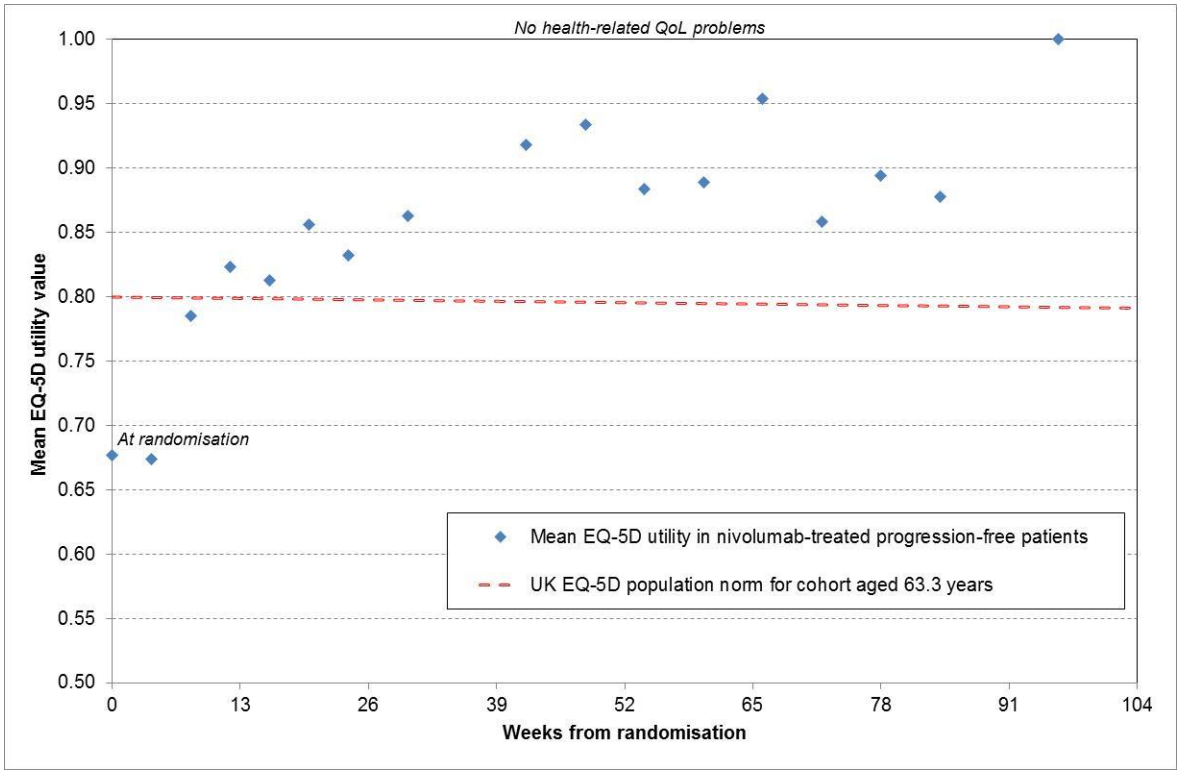

Figure 15 Mean EQ-5D utility estimates for progression-free patients in the nivolumab arm of the CheckMate 017 clinical trial

At randomisation and after 4 weeks the estimated utility value is very similar, but subsequently increases sharply, reaching a plateau after 40 weeks of about 0.9. These values must be compared to the utility estimates obtained in the calibration of the EQ-5D instrument, and published as UK utility norms.[69] For an average cohort of UK residents on the same age and sex as the trial sample, the expected utility would be about 0.8, falling slowly over time. The implication of the data shown in Figure 15 is that lung cancer patients who have recently suffered disease progression on first line chemotherapy will achieve a rapid improvement in their health-related quality of life far above that experienced by the general population; the ERG considers this to be unlikely. Figure 16 illustrates an alternative interpretation based on the assumption that over time some patients who experience a generally poorer health-related quality of life will be increasing less inclined to continue completing the questionnaire, so that the group still available to provide new data will rely on a diminishing number of individuals with more favourable experience. By plotting the mean EQ-5D score at each time point against the corresponding number of responders reveals a strong inverse relationship which is sufficient to explain the anomalous trend seen in Figure 15. Without this effect, the mean utility value is likely to have remained fairly constant at the level seen at baseline until disease progression became apparent. This assumption is consistent with the structure of the company model (a single unchanging utility value for the progression-free health state), but not at the higher level assumed by the company and based on the compromised trial data.

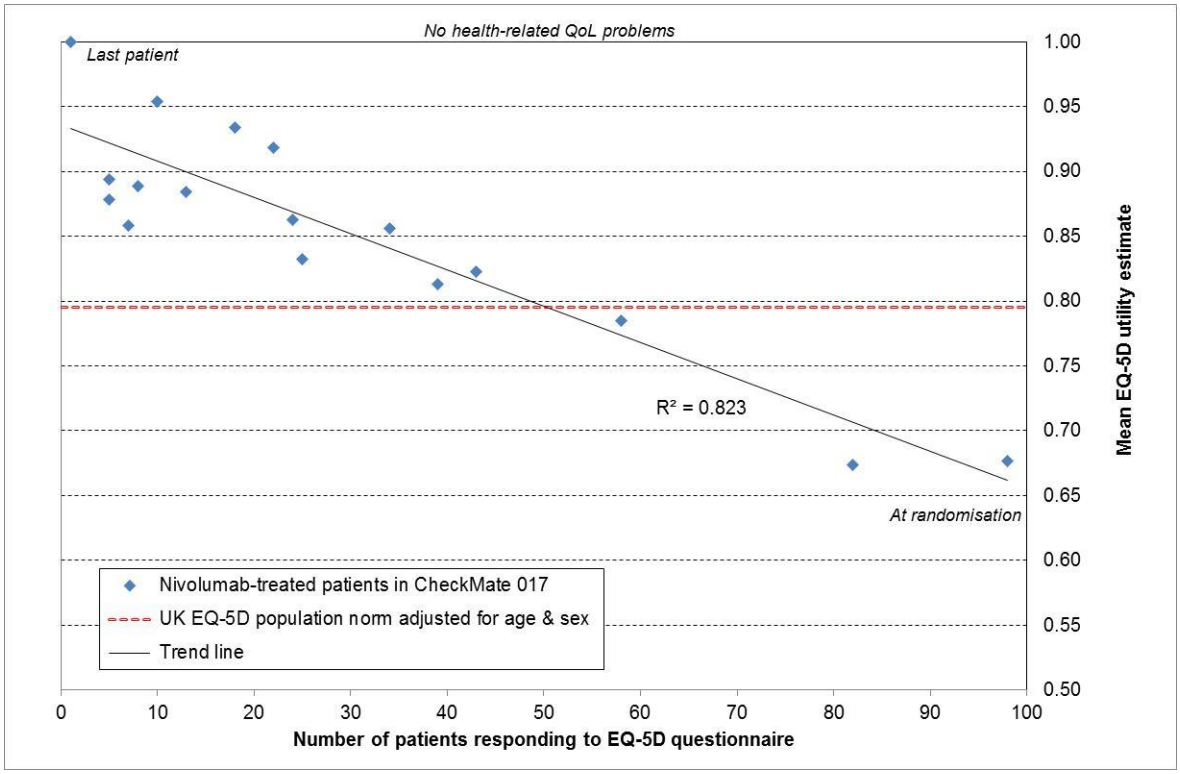

Figure 16 Mean EQ-5D utility estimates for progression-free patients in the nivolumab arm of the CheckMate 017 clinical trial analysed by the number of respondents at each time point

In particular, claims to improvements in mean utility scores over time, or significant differences attributable to the randomised treatment cannot be considered reliable.

In the company model, it is assumed that patients with stable disease or showing a response to treatment experience a mean utility score of 0.75, whereas those who have suffered disease progression have a mean utility score of 0.592. These values were derived from the CheckMate 017 trial EQ-5D data. The ERG has tested the effect of substituting alternative values (based on the study by Nafees *et al* 2008[60]) previously used for patients treated with second-line chemotherapy in a systematic review and economic evaluation of first-line chemotherapy for NSCLC;[68] 0.65 for the PF state and 0.43 for the PD state. Though these values were obtained from a Standard Gamble exercise with members of the general public, they are broadly similar to randomised trial data from lung cancer patients.[71]

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