NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for previously treated locally advanced or metastatic non-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 non-squamous non-small-cell lung cancer [ID900]

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 non-squamous non-small-cell lung cancer [ID900]

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.

Please note that this document does not include the results calculated using patient access schemes.

Key issues for consideration

- The company has not provided comparisons with all comparators listed in the scope. The ERG agrees that the data were not available to allow for these comparisons to be made. Is the committee satisfied that the comparators included in the submission (docetaxel, nintedanib plus docetaxel, best supportive care) reflect established clinical practice in the NHS?
- Are the results of CheckMate 057 generalisable for people with non-squamous NSCLC in clinical practice in England?

- Hazard ratios for death and progression were provided within the submission although the company states that the conditions for proportional hazards were violated. The ERG considers that HRs should therefore be interpreted with caution. Median statistics are provided as an alternative. What is the committee's view on the clinical effectiveness of nivolumab vs docetaxel based on CheckMate057?
- What is the committee's view on the methods, baseline characteristics of included populations, and the results of the company's indirect comparisons with nintedanib plus docetaxel and best supportive care?
- The ERG uses an exponential projection of overall survival which results in a 58% decrease in overall survival for nivolumab compared with docetaxel. The corresponding effect on the ICER is an increase of over £40,000 to just under £144,000 per QALY gained (company base case ICER £103,589 per QALY gained). Compared to nintedanib plus docetaxel, the impact on the ICER of this change is much greater (an increase of just under £122,000 to just under £249,000 per QALY gained). Does the committee agree with the ERG's justification for using an exponential approach to projecting overall survival?
- The company used time to treatment discontinuation data to model progression-free survival, whereas the ERG preferred method was to use progression-free survival data from CheckMate057 and only using time to treatment discontinuation data for modelling costs and adverse events associated with nivolumab treatment. The corresponding effect on the ICER is a decrease of £20,000 to £83,600 per QALY gained (company base case ICER £103,589 per QALY gained). Compared to nintedanib plus docetaxel, the impact on the ICER of this change is much greater (an increase of £40,000 to £87,400 per QALY gained). What is the committee's preferred approach to modelling progression-free survival?
- The company used utility values based on EQ-5D results from CheckMate057 in the model, whereas the ERG used combined utility values based on CheckMate57 and a study by van den Hout et al. What is the committee's preferred approach?
- Can the supplementary advice to the committee regarding the end-of-life criteria be applied?

1 Remit and decision problems

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
Pop.	People with previously treated non-squamous locally advanced or metastatic NSCLC	Adults with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	This patient population is in line with the expected marketing authorisation of nivolumab and the NICE decision problem; however, please note that it differs from the patient population (i.e. is a sub-group of the scoped population) outlined in the final scope issued by NICE.	In line with expected marketing authorisation.
Int.	nivolumab		-	-
Com.	**Non-squamous Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation positive tumours:** • After one prior therapy: - Platinum therapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane) - Single agent	Base-case economic analysis in a previously treated setting is nivolumab versus: • Docetaxel monotherapy • Nintedanib in combination with docetaxel	The comparators listed in the final scope are representative of the standard treatments used in the NHS. However, not all are relevant comparators to nivolumab. **Non-squamous EGFR mutation-positive tumours:** Data were not available in this population, owing to the small number of patients with EGFR mutation-positive tumours in the CheckMate 057 study. Further,	Base case economic analysis in a previously treated setting is limited to nivolumab compared with: • Docetaxel monotherapy • Nintedanib in combination with docetaxel **EGFR positive** Platinum based therapy - patients in trial had already received this therapy

	gemcitabine and vinorelbine (for people for whom platinum therapy is not appropriate) - Afatinib, erlotinib or gefitinib (if no previous EGFR-TKI therapy received due to delayed confirmation of mutation status; erlotinib and gefitinib subject to ongoing NICE appraisal) • After two prior therapies (an EGFR-TKI and one other therapy): - Docetaxel monotherapy - Erlotinib - Nintedanib in combination with docetaxel - Best supportive care		patients had to have received prior therapy (specifically a platinum-based chemotherapy) in order to be recruited into the nivolumab clinical study. This renders platinum-based chemotherapy inappropriate as a comparator to nivolumab. Single-agent gemcitabine and vinorelbine may be considered where platinum-based chemotherapy is not appropriate. Considering the lack of available data and as all patients in the nivolumab clinical studies have received prior platinum-based chemotherapy, these agents are inappropriate comparators for nivolumab. It is standard for afatinib, erlotinib or gefitinib therapies to be used first-line in patients who are EGFR mutation-positive, meaning there are insufficient data to allow comparisons with these targeted therapies in the second-line setting in this population. Further, gefitinib is not recommend by NICE for the second-line treatment of patients who are EGFR mutation-positive.	so this is not a valid comparator Gemcitabine or vinorelbine - no available data Erlotinib, afatinib - limited data Gefitinib - not recommended for second-line

	Non-squamous EGFR-TK mutation negative or unknown tumours: • After one prior therapy: - Docetaxel monotherapy - Erlotinib (subject to ongoing NICE appraisal) - Nintedanib in combination with docetaxel - Crizotinib (only for patients with anaplastic lymphoma kinase [ALK] positive mutation status) - Ceritinib (only for patients with ALK positive mutation status; subject to ongoing NICE appraisal) - Best supportive care • After two prior therapies: - Docetaxel monotherapy		**Non-squamous EGFR mutation-negative/unknown tumours:** Erlotinib has been recommended by NICE in patients with unknown EGFR mutation status only, which is a small sub-group. No nivolumab data were available to allow for comparisons in this submission. **Non-squamous ALK mutation-positive tumours:** The ALK mutation is only seen in approximately 5% of patients with NSCLC. The resulting small sample size in the CheckMate 057 study was not powered for this sub-group and thus did not allow robust comparison. Therefore, crizotinib is not deemed an appropriate comparator for nivolumab. Ceritinib is being appraised by NICE for use in ALK-positive NSCLC after crizotinib; however, the current appraisal consultation document does not recommend its use, and it is not standard of care. Further, the small sample size in the Checkmate 057 study was not powered for this sub-group and thus did not allow	**EGFR negative/unknown** Erlotinib - no data from trial available ALK mutation positive - too few patients in trial to allow for subgroup analysis Ceritinib - at the time of CS not recommended by NICE – currently the appraisal has been suspended BSC - lack of data available for comparison

	- Erlotinib (if not received previously; subject to ongoing NICE appraisal) - Best supportive care		robust comparison. Therefore, ceritinib is also not considered an appropriate comparator for nivolumab. Although BSC is a potential comparator for this submission, there is a paucity of data available for use of BSC alone in previously treated patients with locally advanced or metastatic non-squamous NSCLC (Shepherd et al., 2000), which precludes any comparison of nivolumab vs. BSC.	
Out	• overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life		-	-

2 The technology and the treatment pathway

2.1 Nivolumab (Opdivo, 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). This receptor is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. Nivolumab has a marketing authorisation for treating 'locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults'. In February, 2016 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for an extended indication to include both squamous and non-squamous NSCLC after prior chemotherapy in adults. The new proposed indication says nivolumab 'is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults'. Nivolumab for non-squamous NSCLC has been available through the Early Access to Medicines Scheme (EAMS) from the UK Medicines and Healthcare products Regulatory Agency (MHRA) since 5th February, 2016. It is administered by intravenous infusion over 60 minutes, at a dose of 3 mg/kg every 2 weeks.

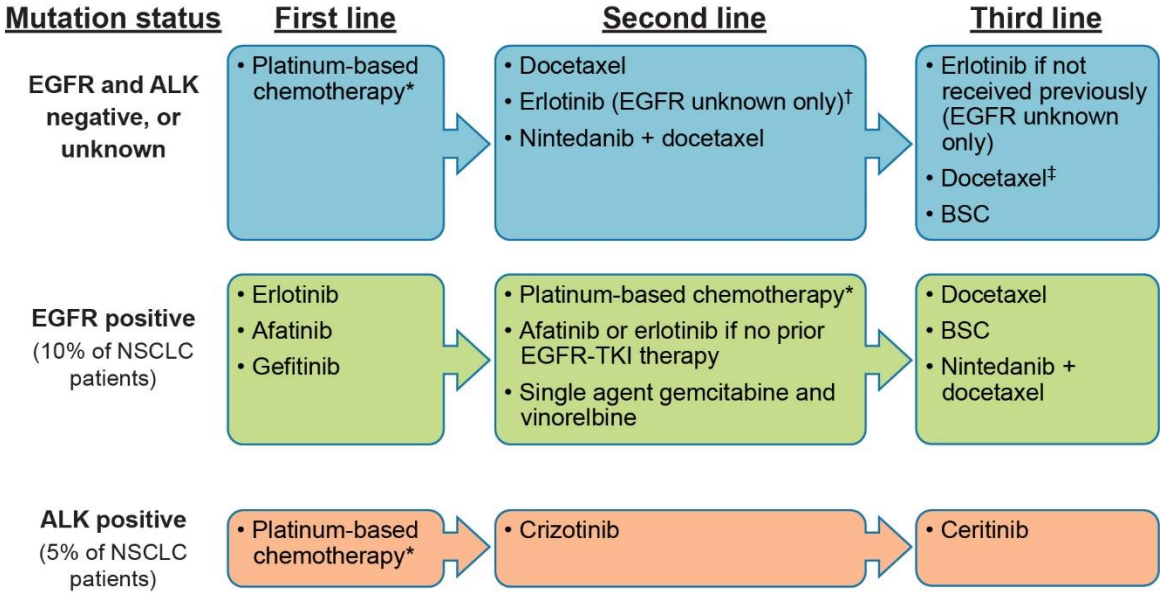
2.2 Nivolumab has also been granted a marketing authorisation for the treatment of advanced (unresectable or metastatic) melanoma in adults (for which it has received positive guidance in NICE technology appraisal 384, published in February 2016). It is also being appraised by NICE for squamous NSCLC (anticipated publication: May 2016 [ID811]), for untreated, advanced, unresectable, metastatic melanoma in combination with ipilimumab (anticipated publication: September 2016 [ID848]) and for previously treated metastatic renal cell carcinoma (anticipated publication: October 2016 [ID853]).

2.3 Non-squamous NSCLC accounts for about 64% of all NSCLC. Most lung cancers are diagnosed at an advanced stage, when the cancer is in locally advanced or metastatic stage. The treatment pathway can be seen

in Figure 1. NICE clinical guideline 121 (CG121) recommends platinum based chemotherapy (carboplatin on cisplatin, in combination with docetaxel, gemcitabine, paclitaxel or vinorelbine) for people with advanced NSCLC and a good performance status. For patients with EGFR positive NSCLC an EGFR-TKI is recommended (afatinib, erlotinib or gefitinib). Pemetrexed in combination with cisplatin is also recommended as an option for locally advanced or metastatic NSCLC with adenocarcinoma histology. Nintedanib (given in combination with docetaxel) is recommended in NICE guidance (TA347) in line with its marketing authorisation, that is, after disease progression of locally advanced, metastatic or locally recurrent NSCLC with adenocarcinoma histology. For NSCLC with delayed or unknown EGFR mutation status after the disease has progressed after non-targeted chemotherapy, erlotinib is recommended as an option (TA258). For ALK mutation positive NSCLC after chemotherapy, NICE TA296 does not recommend crizotinib, however it is available via the Cancer Drugs Fund (CDF). Ceritinib for ALK –positive NSCLC after crizotinib is currently being appraised by NICE (ID729), however the draft appraisal consultation document does not recommend it. Docetaxel monotherapy is also recommended as second-line treatment for locally advanced or metastatic NSCLC after the disease has progressed after previous chemotherapy. People with NSCLC that has progressed after chemotherapy may also be offered best supportive care. The company in its submission considered that nivolumab would be offered as second- or third line treatment for non-squamous NSCLC, however they deemed that only docetaxel and nintedanib plus docetaxel would be relevant comparators.

2.4 The ERG considered the company appropriately summarised the health problem and treatment pathway. It noted that the company estimated the number of patients eligible for nivolumab in second line setting would be 1,413, which might be an underestimate. The ERG agreed with the company that the current standard of care for non-squamous NSCLC is docetaxel monotherapy and nintedanib plus docetaxel.

Figure 1 The treatment pathway for non-squamous non-small-cell lung cancer



Abbreviations: ALK=anaplastic lymphoma kinase; BSC=best supportive care; EGFR=Epidermal Growth Factor Receptor; NSCLC=non-small cell lung cancer; TKI= tyrosine kinase inhibitor; UK=United Kingdom

* Platinum-based chemotherapy + gemcitabine, vinorelbine, pemetrexed or a taxane

† Until recently, erlotinib was recommended second-line in patients with EGFR mutation-negative/unknown status; however, recent NICE guidance recommends erlotinib only in patients with EGFR unknown mutation status, which is a very small subgroup of patients

‡ As erlotinib is no longer recommended in second-line for patients with EGFR mutation-negative status, docetaxel (as monotherapy or in combination with nintedanib) is the only second-line option and, as a result, will no longer be used in third-line

Sources: Company submission, Figure 1 and ERG report, Figure 1

Table 2 The technologies

	Nivolumab	**Docetaxel monotherapy**	**Nintedanib in combination with docetaxel**
Marketing authorisation	Nivolumab (Opdivo, BMS) is indicated for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults. Nivolumab is expected to gain marketing	Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.	Nintedanib (Vargatef, Boehringer Ingelheim) is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma

	authorisation for locally advanced or metastatic non-squamous NSCLC [redacted]. It received CHMP positive opinion in February, 2016.		tumour histology after first-line chemotherapy.
Administration method	Intravenous infusion. Recommended dose is 3 mg/kg over 60 minutes every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.	Intravenous infusion. Recommended dose is 75 mg/m², as a one-hour infusion every three weeks.	Orally Recommended is 200 mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21 day docetaxel treatment cycle.
Cost (Sources: Company's submission and BNF, February 2016)	£439.00 per 40-mg vial Price per dose: £2,538.25* (intravenous infusion 3mg/kg over 60 minutes) Price per course of treatment: £31,960 (assumes a mean dose number of 12.6**) Price per year: £68,995	140-mg vial: £900 (A A H Pharmaceuticals, Actavis) 140-mg vial: £720 (Medac) Price per dose*** : £900; £720 Price per year: £15,600; £12,480	100mg capsules x 120 = £2151.10 150mg capsules x 60 = £2151.10 Price per dose: £35.85 Price per year: £26,171.72 There is a simple discount PAS available for nintedanib.
Abbreviations: NSCLC, non-small cell lung cancer; CHMP, Committee for Medicinal Products for Human Use; BNF, British National Formulary * From company submission, based on list price and the weight and BSA calculator provided by the ERG during the appraisal of the nivolumab in squamous NSCLC model. ** From company submission, based on CheckMate 057 ***Assuming a body surface area of 1.82m^2 for a person weighing 73kg See summary of product characteristics for details on adverse reactions and contraindications.			

3 Comments from consultees

Comments were received from the patient organisation, Roy Castle Lung Cancer Foundation, and from 7 professional groups (Royal College of Pathologists, British thoracic Society, Royal College of Physicians, Royal College of Radiologists, Association of Cancer Physicians, British Thoracic Oncology Group and National Cancer Research Institute).

3.1 Consultees noted that the treatment options for non-squamous NSCLC that has progressed after prior chemotherapy differ based on the presence of genetic mutations, such as EGFR or ALK mutation. If these mutations are present, then targeted treatments are offered. EGFR mutation positive NSCLC occurs in approximately 5-10% of patients with the disease. The treatment options are EGFR-TKIs, such as erlotinib, gefitinib or afatinib, first line. In the case of a relapse, platinum doublet chemotherapy and as third line treatment a second line of chemotherapy is offered. ALK mutation occurs in approximately 4-6% of patients with NSCLC. These patients are offered a platinum doublet first line, then crizotinib (available via CDF) as second line, then docetaxel monotherapy could be considered for third line treatment. If patients are negative for these mutations, then docetaxel monotherapy, nintedanib plus docetaxel, erlotinib or best supportive care are offered. Nivolumab would likely to be offered as third line treatment for EGFR or ALK positive patients and as second line treatment for EGFR or ALK negative patients. The relevant comparators would therefore be nintedanib plus docetaxel, docetaxel monotherapy or erlotinib.

3.2 Nivolumab could be delivered through the specialist oncology/chemotherapy units, however compared to docetaxel or nintedanib plus docetaxel it would require additional capacity, since it is administered more frequently than docetaxel and intravenously, whereas nintedanib is administered orally at home.

3.3 Consultees noted that the side effect profile for nivolumab is different to standard chemotherapy, but generally better. However clinical experts noted that additional training might be necessary to support clinicians and nurses to identify and manage the side effects of nivolumab.

3.4 Clinical experts noted that evidence suggests that patients with PD-L1 mutation expression may have a better response to treatment with nivolumab and that there is a complementary diagnostic test available to test for the presence of PD-L1 mutation. Testing is not considered necessary for eligibility for nivolumab treatment, however if it was a requirement, training would be needed and the costs of the test would need to be taken into account.

3.5 The patient group emphasised that there is a high unmet need for this patient group since current treatment options are limited and many patients are unable to tolerate the side effects of current treatments. Relapsed non-squamous NSCLC has debilitating and distressing symptoms, therefore improving quality of life and even a small extension to life would be considered as a significant benefit by both patients and their families.

4 Clinical-effectiveness evidence

Overview of the clinical trial

4.1 The company's systematic literature review identified 1 randomised controlled trial (RCT), the CheckMate 057. This was an international, open-label, phase III RCT, which compared nivolumab with docetaxel in an adult population with non-squamous NSCLC, whose disease has progressed during or after one prior combination chemotherapy. Patients were randomised to receive nivolumab (at a dose of 3mg/kg every 2 weeks, n=292), or docetaxel (at a dose of 75mg/m^2 every 3 weeks, n=290), discontinuation due to toxicity or withdrawal of consent. The company stated that the patient characteristics were balanced between

the two arms. The primary endpoint was overall survival. Secondary outcomes were progression-free survival, objective response rate, duration of response, time to response, level of PD-L1 expression, health related quality of life (HRQoL), safety and tolerability. Results were presented based on a planned interim analysis at 12 months (after which the study was stopped, because the primary endpoint had been reached), and on the basis of an additional follow-up at 18 months. No cross-over was allowed before the 12 months interim analysis. For further information see section 4.3.1 of company submission.

Table 3 Patient characteristics in CheckMate 057

	Nivolumab (n=292)	**Docetaxel (n=290)**
Median age, years (range)	61 (37 to 84)	64 (21 to 85)
Sex, n (%) male	151 (52%)	168 (58%)
Race, n (%) white	267 (91%)	266 (92%)
ECOG PS, n (%)		
0	84 (29%)	95 (33%)
1	208 (71%)	193 (67%)
Not reported	0	1 (< 1%)
Smoking status, n (%)		
Current/Former	231 (79%)	227 (78%)
Never smoked	58 (20%)	60 (21%)
Unknown	3 (1%)	3 (1%)
Disease stage, n (%)		
IIIb	20 (7%)	24 (8%)
IV	272 (93%)	266 (92%)
CNS metastases, n (%) Yes	34 (12%)	34 (12%)
PD-L1 expression level n (%)		
< 1%	108 (46.8%)	101 (45.1%)
< 5%	136 (58.9%)	138 (61.6%)
< 10%	145 (62.8%)	145 (64.7%)
≥ 10%	86 (37.2%)	79 (35.3%)
Not quantifiable at baseline	61 (20.9%)	66 (22.8%)
Type of prior systemic cancer therapy, n (%)		
Prior platinum-based therapy	292 (100%)	290 (100%)
Prior ALK inhibitor	1 (0.3%)	2 (0.7%)
Prior EGFR-TKI	29 (9.9%)	24 (8.3%)

Other – chemotherapy	292 (100%)	290 (100%)
Other – experimental drugs	23 (7.9%)	18 (6.2%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD-L1, programmed cell death 1 ligand, CNS, central nervous system; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase

Source: Table 14, Company submission

ERG comments

4.2 The ERG considered the company's literature search to be appropriate. It was not aware of any additional relevant studies which should have been included.

4.3 The ERG considered that CheckMate 057 was a well conducted study and it captured all relevant outcomes and these were also pre-specified in the trial protocol. It noted that there was a greater percentage of males on the docetaxel arm, which might favour nivolumab and a smaller percentage of people with Eastern Cooperative Oncology Group (ECOG) performance status 0 on the nivolumab arm, which might favour docetaxel. Overall the ERG considered that the characteristics of the patient population in CheckMate 057 was representative of the population who would be eligible for nivolumab treatment in England.

Clinical trial results

4.4 The analyses were based on an intention-to-treat population (n=582), Interim analysis was conducted after a minimum duration of follow up of 13.2 months (company refers to this interim analysis as the '12 months analysis'). The company also presented results from an additional follow-up analysis, with a minimum duration of follow up of 17.1 month (the company refers to this as the '18 months analysis').

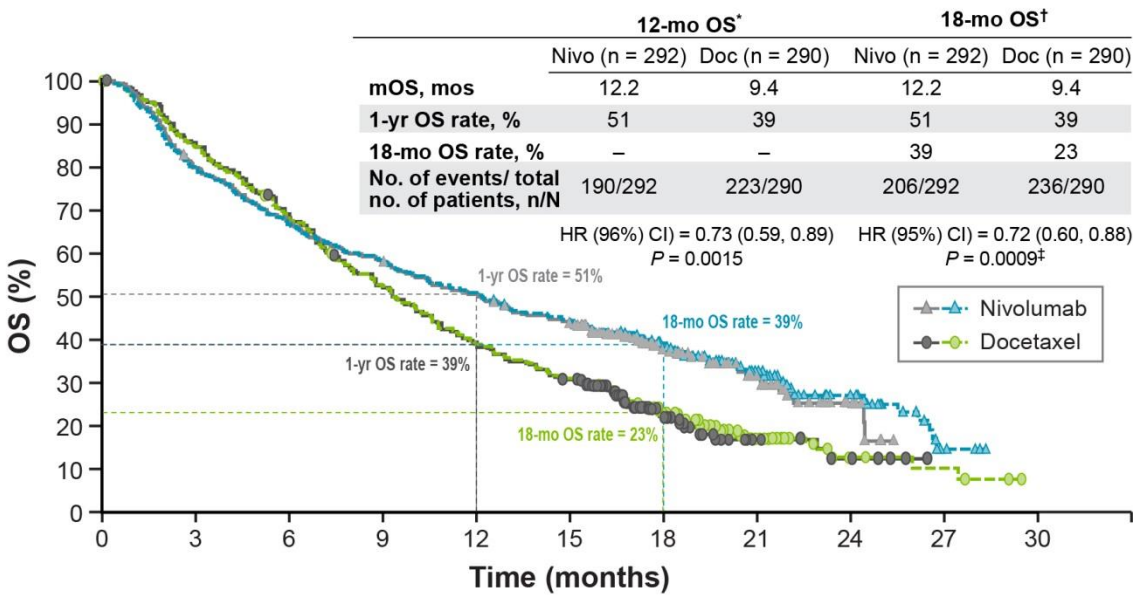
4.5 Nivolumab was associated with a statistically significant improvement in overall survival, both in the 12 month and the 18 month analyses and in overall response rates (see Table 4 and Figure 2). In progression-free survival the median results did not favour nivolumab, although the 12

months progression-free survival rate was higher for nivolumab than for docetaxel (Table 4). The company stated that pseudo-progression might had an effect on the results. Pseudo-progression occurs in the case of immune-oncology treatments, when an initial effect of the treatment is that the tumour appears to be larger before positive clinical outcomes can be observed. Treatment beyond progression was allowed in the case of 71 (24.3%) patients in the nivolumab group.

Table 4 Clinical trial outcomes of CheckMate 057 (12 months and 18 months analyses)

Outcome	nivolumab (n=292)	Docetaxel (n=290)
Overall survival		
Median, months (95% CI)	12.2 (9.7 to 15.0)	9.4 (8.1 to 10.7)
Overall survival rate at 12 months (95% CI)	50.5 (44.6 to 56.1)	39.0 (33.3 to 44.6)
HR (95% CI) at 12 months	0.73 (0.59 to 0.89) (p=0.002)	
Overall survival rate at 18 months (95% CI)	39 (34 to 45)	23 (19 to 28)
HR (95% CI) at 18 months	0.72 (0.60 to 0.88) (p=0.001)	
Progression-free survival		
Median, months (95% CI)	2.3 (2.2 to 3.3)	4.2 (3.5 to 4.9)
Progression-free survival rate at 12 months (95% CI)	18.5 (14.1 to 23.4)	8.1 (5.1 to 12.0)
HR (95% CI) at 12 months	0.92 (0.77 to 1.11) (p=0.3932)	
Progression-free survival rate at 18 months (95% CI)		
HR (95% CI) at 18 months	0.91 (0.76 to 1.09) p value was not presented	
Response rate		
Objective response rate: % of patients (95% CI)	19 (15 to 24)	12 (9 to 17)
Odds ratio (95% CI)	1.7 (1.1 to 2.6) (p=0.02)	
Time to response: median months (range)	2.1 (1.2 to 8.6)	2.6 (1.4 to 6.3)
Duration of response: median months (range)	17.2 (1.8 to 22.6*)	5.6 (1.2* to 15.2*)
Abbreviations: CI, confidence interval; HR, hazard ratio * censored values Sources: company submission, Tables 16, 17, 18 and Figure 12		

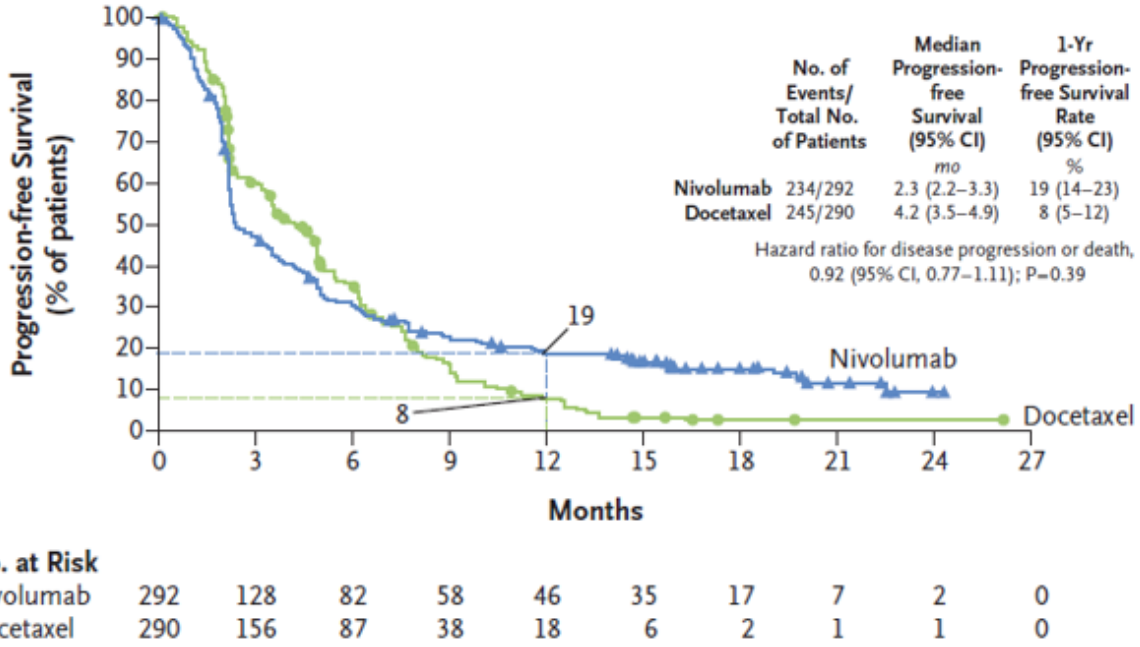
Figure 2 Overall survival in CheckMate 057 (12 months and 18 months analyses)



No. of patients at risk (12-mo OS)*											
Nivolumab	292	232	194	169	146	123	62	32	9	0	0
Docetaxel	290	244	194	150	111	88	34	10	5	0	0
No. of patients at risk (18-mo OS)†											
Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

Abbreviations: CI, Confidence Interval; Doc, Docetaxel; HR, Hazard Ratio; mOS, Median Overall Survival; Mo, Months; Nivo, Nivolumab; OS, Overall Survival
* Based on 12 months analysis.
† Based on 18 months analysis
Source: Company submission, Figure 12

Figure 3 Progression-free survival in CheckMate 057 (12 months analysis)



Abbreviations: CI = Confidence Interval; OS = Overall Survival
Note: The analysis included all the patients who underwent randomisation. Symbols indicate censored observations, and horizontal lines the rates of OS at 1 year.
Source: company submission, Figure 13

4.6 Health related quality of life (HRQoL) was measured in Checkmate 057 using the Lung Cancer Symptom Scale Average Symptom Burden Index (LCSS ASBI) and the EuroQol EQ-5D plus the EQ-5D Visual Analogue Scale. The results of the EQ-5D visual analogue scale (VAS) showed improvement for both patient groups while on treatment and returned to baseline values after discontinuation of treatment (baseline values range: 60.6-66.4; see section 4.7.1 of company submission).

4.7 Subgroup analyses of pre-specified demographic subgroups showed overall survival and progression-free survival benefit for nivolumab compared with docetaxel for most of the subgroups. The subgroup analysis, which was based on EGFR mutation status showed overall survival benefit for nivolumab compared with docetaxel for patients with EGFR negative or unknown mutation status (see section 4.8.2 of company submission and Table 5). For progression-free survival, no

statistically significant differences were observed between the different subgroups based on EGFR mutation status.

The results of the subgroup analysis, based on PD-L1 expression level showed that nivolumab had longer overall survival, progression-free survival and higher objective response rate compared to docetaxel, for patients with PD-L1 expression at baseline, in both the 12 months and 18 months analyses. The magnitude of these benefits were higher than what was observed in the case of the entire study population, however the company noted that CheckMate 057 was not powered to measure it (see section 4.8.3 of company submission and Table 6).

Table 5 Median overall survival by EGFR mutation status, CheckMate 057

	Nivolumab (N = 292)	Docetaxel (N = 290)
12 month analysis		
EGFR Positive, months (95% CI)	9.2 (5.2 to 13.1)	11.5 (5.8 to 17.8)
HR (95% CI)	1.18 (0.69 to 2.00)	
EGFR Not detected/not reported, months (95% CI)	12.8 (10.0 to 15.7)	9.30 (8.0 to 10.6)
HR (95% CI)	0.69 (0.56 to 0.85)	
18 month analysis		
EGFR Not detected/not reported, months (95% CI)	12.8 (10.0 to 15.7)	9.3 (8.0 to 10.6)
HR (95% CI)	0.68 (0.55 to 0.83)	
Abbreviations: CI, Confidence Interval; HR, hazard ratio Source: company submission, Table 20		

Table 6 Median overall survival by PD-L1 expression level at baseline, CheckMate 057

	Nivolumab (N = 292)	Docetaxel (N = 290)
12 month analysis		
PD-L1 ≥ 1%, months	17.2	9.0
HR (95% CI)	0.59 (0.43 to 0.82) p=0.06	
PD-L1 ≥ 5%, months	18.2	8.1
HR (95% CI)	0.43 (0.30 to 0.63) p<0.001	
PD-L1 ≥ 10%, months	19.4	8.0
HR (95% CI)	0.40 (0.26 to 0.59) p<0.001	
Abbreviations: PD-L1, Programmed death-ligand 1; HR, hazard ratio; CI, confidence interval Source: company submission, Section 4.8.3 and Figure 19		

ERG comments

4.8 The ERG noted that the results of CheckMate 057 showed that nivolumab had superior clinical effectiveness compared with docetaxel in the case of both primary and secondary endpoints. However these results were only statistically significant in the case of overall survival and response rates, but not for progression-free survival.

4.9 The ERG noted that the use of hazard ratios in the analyses cannot be considered reliable, because the proportional hazards assumption was violated for both overall survival and progression-free survival.

4.10 The ERG noted the company's statement that the overall survival results, observed on the docetaxel arm are an overestimation, however this statement was not supported by other clinical trials results.

4.11 The ERG noted the company's statement, that pseudo-progression might had an effect on the overall survival results, however it was not convinced that this statement was supported by the data presented.

4.12 The ERG noted the results of subgroup analyses, which showed that that nivolumab had statistically significantly greater treatment effect for

- patients treated second-line, than for patients treated third-line with nivolumab,
- patients from the US/Canada and Europe, than for patients from the rest of the world
- and for patients who are smoking, than for patients who never smoked.

The results also showed that nivolumab is statistically significantly more effective in patients with PD-L1 mutation, however it is not clear whether patients should be tested for it.

4.13 The ERG considered that crossover was allowed for a small number of patients (n=2) on the docetaxel arm after the trial was stopped in April 2015, after it had reached the primary endpoint in March 2015.

4.14 The ERG also highlighted that considering the more mature 18 month results, which are consistent with the 12 month results; stopping the trial early did not appear to have a biased effect on the efficacy results.

Non-randomised trials

The company presented the results of 2 non-randomised controlled trials in section 4.11 of the company submission.

CheckMate 153

4.15 CheckMate 153 was phase IIIb/IV, open-label study, which enrolled people with both non-squamous and squamous NSCLC, who had previously been treated with at least one conventional systemic therapy. The percentage of non-squamous NSCLC was 46.8%. The ORR was 12% and 44% of patients had stable disease. For the non-squamous subgroup, the ORR was 11% and 42% of patients had stable disease.

CheckMate 003

4.16 CheckMate 003 was a single-arm, dose-escalation study, which enrolled people with advanced or recurrent malignancies (including: melanoma, NSCLC, renal cell carcinoma, castration-resistant prostate cancer or colorectal cancer, who had received at least one prior systemic therapy,

including a platinum-based or taxane-based chemotherapy (although most patients had multiple previous cycles of chemotherapy). The percentage of people with NSCLC was 42.2%. For the subgroup of patients who were treated with the licensed dose of nivolumab (3mg/kg every two weeks; n=19, 14.7%) and had non-squamous NSCLC, the ORR was 26.3% (95% CI 9.1 to 51.2). Stable disease was observed in [redacted] for the same subgroup. The median overall survival for all NSCLC patients, who received the licensed dose of nivolumab, was 14.9 months (95% CI 7.3 to 30.3). Overall survival results for the non-squamous NSCLC subgroup were not reported.

Indirect treatment comparison

4.17 Because direct comparisons with nintedanib plus docetaxel and best supportive care were not available, the company carried out an indirect treatment comparison for these comparisons. Separate analyses were conducted for the full population of non-squamous NSCLC (referred to as the 'all comers population' in the submission) and for the population with EGFR negative/unknown mutation status. The systematic review identified 33 studies, out of which 5 were included in the analyses:

- LUME-Lung 1: docetaxel vs. nintedanib plus docetaxel
- ISTANA: docetaxel vs. gefitinib
- ISEL: best supportive care vs. gefitinib plus best supportive care
- CheckMate 057: nivolumab vs. docetaxel
- V-15-32: docetaxel vs. gefitinib.

4.18 For the 'all comers' population all the 5 studies were included in the analysis. The company stated that there were differences between the studies in terms of the design and population included. Apart from CheckMate 057 all studies included people with both squamous and non-squamous NSCLC, however subgroup data was available for the non-squamous populations. Besides, 4 out of the 5 studies included people whose disease did not respond to previous platinum-based

chemotherapy, whereas LUME-Lung 1 study included people whose disease did not respond to one line of chemotherapy. There were also differences in the performance status of the patients included in the different studies. The company stated that it was not possible to control for this heterogeneity. The results suggested a reduction in the risk of death for nivolumab compared with nintedanib plus docetaxel, however this benefit was not statistically significant (HR: [redacted]; 95% CI [redacted]; p=[redacted]). When nivolumab was compared with best supportive care, the reduction in the risk of death was statistically significant (HR: [redacted]; 95% CI [redacted]; p=[redacted]). Progression-free survival was higher for nivolumab than for nintedanib plus docetaxel, however the results were not statistically significant (HR: [redacted], 95% CI [redacted], p=[redacted]). Progression-free survival was not reported for the comparison of nivolumab with best supportive care. Objective response rate was higher for the nivolumab population, than for the population treated with nintedanib plus docetaxel, however these results were not statistically significant (Relative Risk [RR]: [redacted]; 95% CI [redacted]; p=[redacted]). Objective response rate was not reported for the comparison of nivolumab with best supportive care. For further details see section 4.10.5 of the company submission and Table 7.

4.19 The company noted that the validity of the hazard ratios is dependent on the proportional hazard assumption, which was violated and therefore the hazard ratio analysis results should be interpreted with caution. It also presented results in terms of differences in restricted mean survival time (RMST). The results showed that that nivolumab increased the life expectancy by [redacted] months compared with nintedanib plus docetaxel, however the results were not statistically significant (RMST difference: [redacted]). When nivolumab was compared with best supportive care, the RMST results showed that nivolumab statistically significantly increased the life expectancy by [redacted] months compared with best supportive care (RMST difference: [redacted]). For progression-free survival the RMST method showed worse results for nivolumab than for nintedanib

plus docetaxel, however this result was not statistically significant (RMST difference: [redacted]). The progression-free survival results were not presented for the comparison of nivolumab with best supportive care. For further details see section 4.10 of company submission.

4.20 For the population with non-squamous NSCLC with EGFR negative/unknown mutation status, 4 studies were included in the analysis (LUME-Lung 1, ISTANA, ISEL, CheckMate 057). The company stated that the same differences existed between the studies than in the case of the 'all comers' population and that it was not possible to control for these heterogeneity. The results showed reduction in the risk of death when nivolumab was compared with nintedanib plus docetaxel, however this benefit was not statistically significant (HR: [redacted]; 95% CI [redacted]; p=[redacted]). When nivolumab was compared with best supportive care, the reduction in the risk of death was also not statistically significant (HR: [redacted]; 95% CI [redacted]; p=[redacted]). Progression-free survival was higher for nivolumab when it was compared with nintedanib plus best supportive care, however the results were not statistically significant (HR: [redacted], 95% CI [redacted], p=[redacted]). Progression-free survival was not reported for the comparison of nivolumab with best supportive care. Objective response rate was higher for the nivolumab population, than for the population treated with nintedanib plus docetaxel, however these results were not statistically significant (RR: [redacted]; 95% CI [redacted]; p=[redacted]). Objective response rate was not reported for the comparison of nivolumab with best supportive care. For further details see section 4.10.5 of the company submission and Table 7.

4.21 The results of the RMST difference analysis for the EGFR negative/unknown population showed that nivolumab increased the life expectancy compared with nintedanib plus docetaxel, however this was not statistically significant (RMST difference: [redacted]). When nivolumab was compared

with best supportive care, the results showed increased life expectancy with nivolumab, however this was not statistically significant difference (RMST difference: [redacted]). For progression-free survival the RMST method showed no difference between nivolumab and nintedanib plus docetaxel, however this result was not statistically significant (RMST difference: [redacted]). The progression-free survival results were not presented for the comparison of nivolumab with best supportive care. For further details see section 4.10 of company submission.

Table 7 Results of the indirect comparison

Outcome	Nivolumab vs. nintedanib plus docetaxel	Nivolumab vs. BSC
'All-comers' non-squamous NSCLC		
OS HR (95% CI) p value	[redacted]	[redacted]
PFS HR (95% CI) p value	[redacted]	-
ORR (RR [95% CI]; p value)	[redacted]	-
Any adverse event (RR [95% CI]; p value)	[redacted]	-
Any grade 3/4 adverse event (RR [95% CI]; p value)	[redacted]	-
OS RMST difference (95% CI) p value	[redacted]	[redacted]
PFS RMST difference (95% CI) p value	[redacted]	
EGFR mutation-negative/unknown non-squamous NSCLC		
OS HR (95% CI) p value	[redacted]	[redacted]
PFS HR (95% CI) p value	[redacted]	-
ORR (RR [95% CI]; p value)	[redacted]	-
OS RMST difference (95% CI) p value	[redacted]	[redacted]
PFS RMST difference (95% CI) p value	[redacted]	

Abbreviations: OS, overall survival; PFS, progression-free survival; BSC, best supportive care; RMST, restricted mean survival time

Source: Table 28 of company submission

ERG comments

4.22 The ERG considered that all relevant studies were included in the indirect treatment comparison. It also considered that the company's modelling approach was appropriate. It noted the company's statement that the

proportional hazard assumption did not hold and it advised that the hazard ratio results are invalid. It advised that only the RMST analysis results should be considered, however it noted that these analyses were sometimes based on reasonably short follow-up periods.

4.23 The ERG noted that it is not possible to assess whether the patient populations of the trials included in the EGFR negative/unknown analyses was different, therefore it was unable to estimate the validity of those results.

Adverse effects of treatment

4.24 The company presented detailed adverse event data from CheckMate 057, 153 and 003 in section 4.12 of the submission and in response to clarification question B5. The company stated that nivolumab was generally well tolerated. Based on the results of CheckMate 057, the company stated that nivolumab had a more favourable safety profile than docetaxel and was associated with fewer grade 3–4 treatment related adverse events. It also stated that similar results were seen in CheckMate 153 and 003.

4.25 The company identified a group of immune-related select adverse events, which require more frequent monitoring or intervention with immune suppression. These are caused by the mechanism of action of nivolumab. The company stated that these are usually manageable and reversible with dose reduction or interruption of treatment with nivolumab. The most common select adverse events associated with nivolumab in CheckMate 057 were rash, pruritus, diarrhoea and hypothyroidism. The company stated that most of the select adverse events were manageable with the recommended algorithm, specified in the Summary of Product Characteristics.

Table 8 Summary of adverse events in CheckMate 057

	Nivolumab, n (%) (N = 287)	**Docetaxel, n (%) (N = 268)**

Patients with 1 or more AE	280 (98%)	265 (99%)
Grade 3–4 AE	132 (46%)	180 (67%)
Select AEs	27 (9.4%)	1 (0.4%)
SAEs	134 (46.7%)	111 (41.4%)
AEs leading to discontinuation	48 (16.7%)	58 (21.6%)
Deaths Deaths related to study drug toxicity	1 (0.35%)	1 (0.37%)
Treatment-related AEs Patients with 1 or more AE	199 (69%)	236 (88%)
Select AEs	132 (46%)	105 (39.3%)
SAEs	21 (7%)	53 (20%)
AEs leading to discontinuation	14 (5%)	40 (14.9%)

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 table 32

ERG comments

4.26 The ERG considered that nivolumab was better tolerated than docetaxel in CheckMate 057 and it was also well tolerated in the other non-randomised trials presented by the company.

5 Cost-effectiveness evidence

Model structure

5.1 The company presented an economic model with 3 states: progression-free, progressed disease and death. In the base case, the company compared nivolumab with docetaxel and with nintedanib plus docetaxel. The model used a time horizon of 20 years (lifetime) and a cycle length of 1 week. Half-cycle correction was applied. The model perspective was the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.

ERG comments

5.2 The ERG noted that the patient population in the model is a subgroup of the population defined in the scope, however it also noted that it is in line with the population in CheckMate057 trial; adults, with locally advanced or metastatic non-squamous NSCLC, who have been previously treated with chemotherapy.

5.3 The ERG also noted that only docetaxel and nintedanib plus docetaxel were included as comparators in the economic analysis and that the company did not conduct a comparison with best supportive care, although this comparator was included in the indirect treatment comparison (see sections 4.17–4.21).

5.4 The ERG noted that although it is stated in the company submission that costs were considered from NHS and Personal Social Services perspective, Personal Social Services costs were not included in the model.

5.5 The ERG was satisfied with the company's literature search and confirmed that no important studies were missed out. It also considered the model to be appropriately structured and in line with previous economic analyses for advanced NSCLC.

Model details

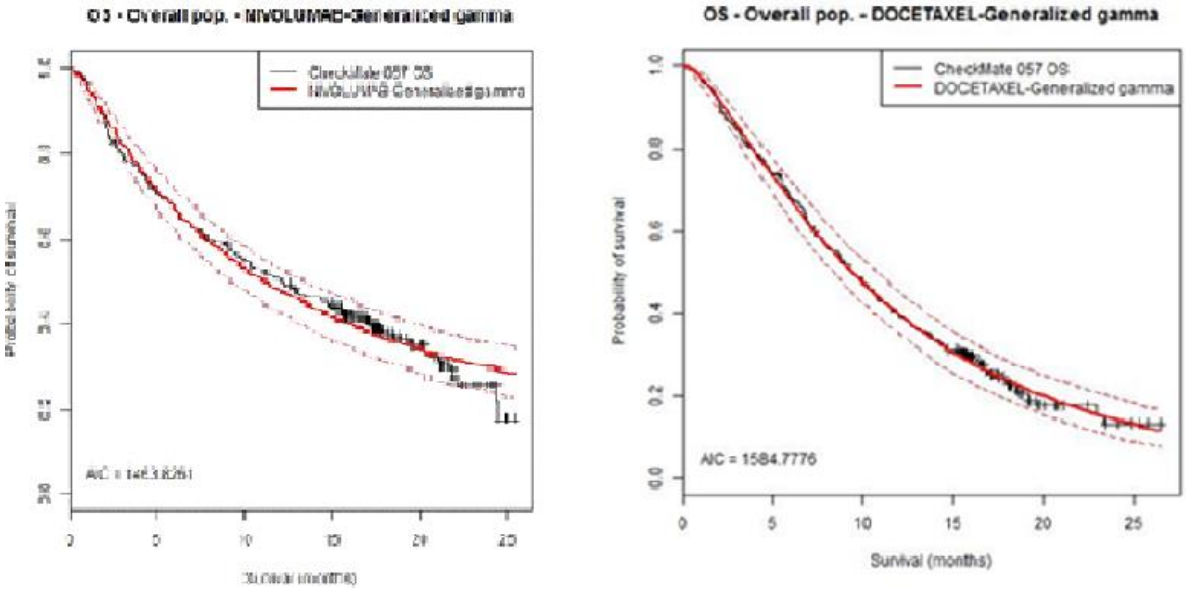
5.6 Patients entered the model in the progression-free state, in which they had treatment with nivolumab or docetaxel until their disease progressed and they moved to either the progressed disease or death' states The proportion of people in each health state in each cycle was based on estimates of overall survival and time to treatment discontinuation (as opposed to progression-free survival) using a partitioned-survival (also known as area under the curve) approach.

5.7 For the comparison between nivolumab and docetaxel the company used short-term clinical trial data from CheckMate 057 (12 months analysis)

and extrapolated it for 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 against CheckMate 003 and real world data. Overall survival was extrapolated using a generalised gamma distribution on both arms of the model and time to treatment discontinuation was also extrapolated using a generalised gamma distribution on both arms of the model (Figure 4). Alternative models were explored in scenario analyses (see sections 5.3.1-5.3.6 of company submission).

5.8 For the comparison between nivolumab and nintedanib plus docetaxel, instead of using the results of the indirect treatment comparison (see section 4.18), the company digitised Kaplan-Meier graphs for the adenocarcinoma population from a publication of the LUME-Lung 1 study. The company considered that there was no difference between the Kaplan-Meier curves for docetaxel and nintedanib plus docetaxel for the first six months, and therefore it assumed a HR of 1 until 6 months for overall survival and after 6 months a HR of 0.75 (95% CI 0.60 to 0.93) was assumed. For time to treatment discontinuation a HR of 1 was assumed until 2 months and after 2 months a HR of 0.98 (95% CI 0.73 to 1.33) was assumed. For further details see section 5.7 of company submission.

Figure 4 Extrapolation of overall survival for nivolumab and docetaxel, company base case



Source: Figure 29 and Figure 30 of company submission

Figure 5 Extrapolation of time to treatment discontinuation for nivolumab and docetaxel, company base case

[redacted]

Source: Figure 35 and Figure 36 of company submission

5.9 Health-related quality of life was incorporated into the model by applying utility values to each health state. The utility values were derived from EQ-

5D results collected in CheckMate 057, before and after disease progression, valued using the UK value set (see section 4.6). The utility values in the progression-free and progressed disease health states were 0.739 and 0.688 respectively (see section 5.4.1 of company submission). Quality of life was also affected by adverse events, by applying utility decrements for each event with a severity grade of 3–4 and an incidence of at least 2% in either arm of CheckMate 057, because no all-cause grade 3–4 adverse events for nivolumab had an incidence of at least 5% (see table 53 of company submission). The utility decrements ranged from 0.00 to 0.09 (see table 57 of company submission) for nivolumab and docetaxel. For nintedanib plus docetaxel adverse events incidence data from LUME-Lung 1 study were used (see Table 75 of company submission).

5.10 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 and the weight and body surface area calculator (provided by the ERG during the squamous appraisal, ID811), monitoring, and disease management; the progressed disease state included costs associated with 1 subsequent line of lung cancer therapy for an average duration of [redacted] (based on treatments used in CheckMate 057) and disease management. The model also included costs for end of life care and management of adverse events (events with a severity grade of 3–4 and an incidence of at least 2% in either arm of CheckMate 057). The costs were informed by estimates in the ongoing appraisal of erlotinib and gefinitib (ID620), the appraisal of nintedanib (TA347), clinical expert opinion, Personal Social Services Unit costs and NHS reference costs.

ERG comments

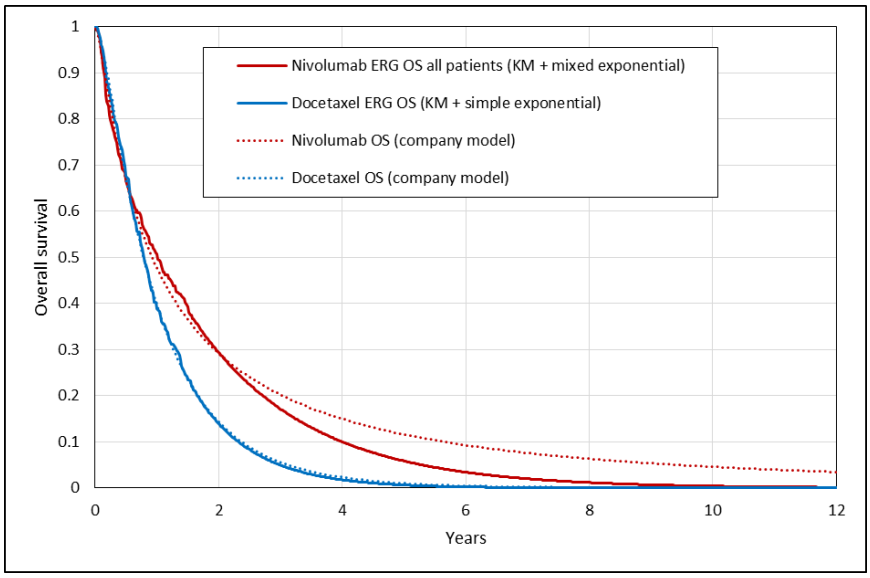
Comparison of nivolumab with docetaxel

5.11 For the comparison of nivolumab with docetaxel, the ERG considered that the company's approach for modelling overall survival, progression-free survival and post-progression survival were flawed for both nivolumab and docetaxel. It did not agree with the company's method of using time to treatment discontinuation data for modelling progression-free survival, because in CheckMate 057 25% of patients (n=72) were permitted to continue treatment with nivolumab after progression. It also noted that this led to clinically implausible results and that there was a significant difference in terms of survival gain between the subgroup of patients who received treatment after progression and those who did not. The subgroup of patients who received treatment after progression had a much higher probability for post-progression survival than patients who did not continue treatment with nivolumab after progression.

5.12 The ERG also considered that using the generalised gamma model for extrapolating overall survival for nivolumab and docetaxel was inappropriate, because it underestimated part of the Kaplan-Meier overall survival data, which lead to over-estimation of overall survival in the long term. It also noted that the Kaplan-Meier data of CheckMate 003 which was used for validating the results of extrapolation, suggested a different survival profile to that of CheckMate 057. Furthermore the ERG suggested that it would have been more appropriate to use the more mature 18 month data, instead of the 12 month data and also to consider the two subgroups on the nivolumab arm (those who have been treated after progression and those who were not) separately. To investigate alternative methods of extrapolating the data, the ERG found that a simple exponential distribution could be justified for modelling survival from around 8 months for the group that received treatment after progression and from around 12 months for the group that did not receive treatment after progression. The ERG stated that long-term hazards in the

nivolumab subgroups are very similar and much of the difference in survival occurs before 10 months. On finding that exponential models fit well to the overall survival Kaplan Meier data, the ERG developed a mixed exponential model based on 25% of patients receiving nivolumab after progression. This was then appended to the Kaplan Meier data for the full nivolumab cohort. Overall survival for docetaxel was modelled using the Kaplan Meier data followed by a simple exponential projection. For more details see section 5.5.5, page 95 of the ERG report.

Figure 6 The extrapolation of overall survival by the company and the ERG for nivolumab and docetaxel



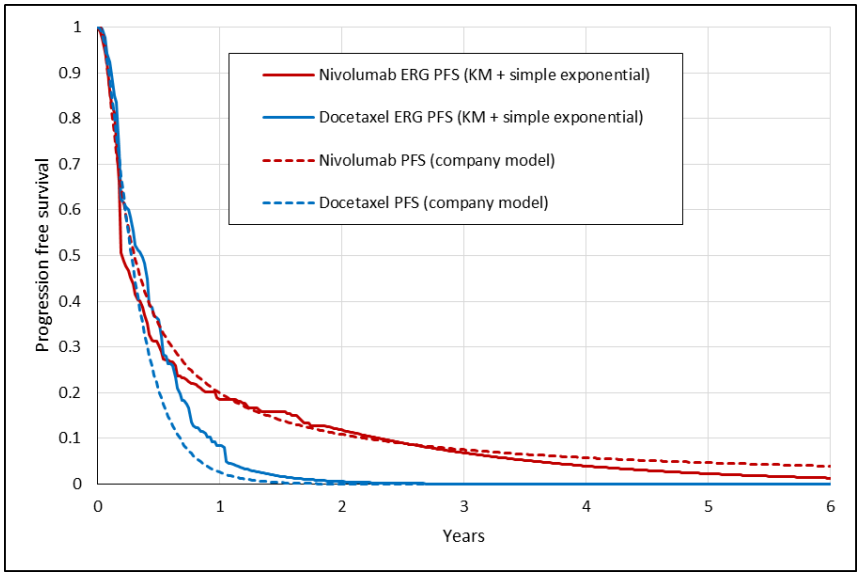
Source: Figure 19 of ERG report; company model; response to clarification question B1a

5.13 The ERG considered that using time to treatment discontinuation data for modelling progression-free survival resulted in clinically implausible results (85% of patients who were still alive at year 20, remained progression-free and were receiving nivolumab treatment). It advised that instead, progression-free survival data should have been used. It also considered that the generalised gamma model was inappropriate, because it poorly fitted the Kaplan-Meier data and overestimated the time on treatment in the early part of the model for patients in both trial arms. Using generalised gamma model also overestimated the progression-free

survival for nivolumab and underestimated it for docetaxel. The ERG suggested that instead an exponential model should have been fitted on the progression-free survival Kaplan-Meier data of the 18 month analysis.

5.14 The ERG noted that for calculating costs and adverse events associated with nivolumab treatment it would be appropriate to use time to treatment discontinuation data, because treatment after progression was permitted for some patients in the clinical trial. It suggested however that instead of the generalised gamma model, no extrapolation would have been needed for docetaxel, because all patients finished treatment by the end of the 18 month period. For nivolumab, it suggested that an exponential model would have fitted the Kaplan-Meier data better. (N.B In the case of the squamous indication (ID811) the ERG made the same observation and this rationale was accepted by the committee).

Figure 7 The extrapolation of progression-free survival by the company and the ERG for nivolumab and docetaxel



Source: Figure 25 of ERG report; company submission, Response to clarification question B1b; ERG calculations

Comparison of nivolumab with nintedanib plus docetaxel

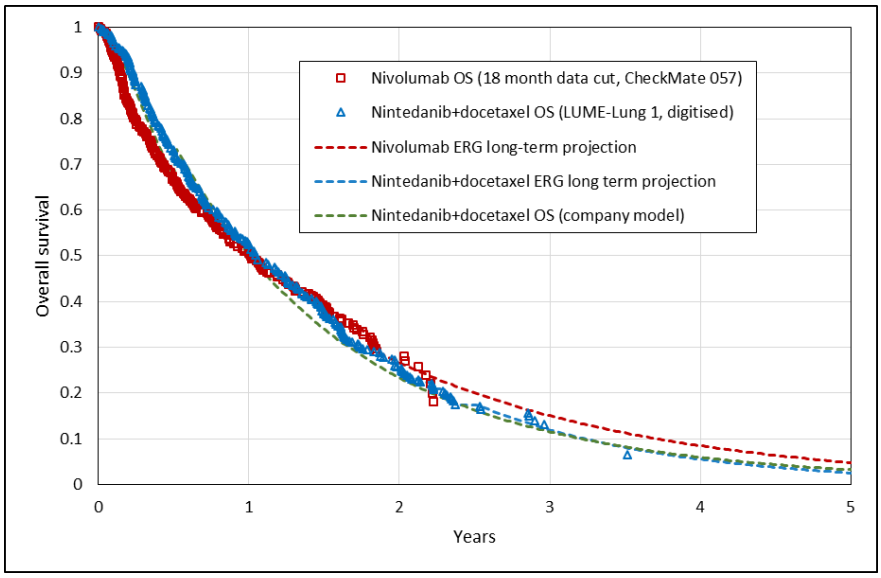
5.15 For the comparison of nivolumab with nintedanib plus docetaxel, the ERG considered that the company's approach for modelling overall survival,

progression-free survival and post-progression survival were flawed for both nivolumab and nintedanib plus docetaxel. It noted that the proportional hazard assumption was violated and because of this, the company's comparison of nivolumab with nintedanib plus docetaxel was invalid.

5.16 In an exploratory analysis the ERG independently digitised published data from the appraisal of nintedanib (TA347), which contained more mature overall survival and progression-free survival data from the LUME-Lung 1 clinical trial. Based on these data it tested whether the proportional hazards assumptions held after six months. It found that that the proportional hazards assumptions were violated, therefore it tested alternative ways. It compared digitised Kaplan-Meier overall survival data for the adenocarcinoma population in the docetaxel plus placebo arm of the LUME-Lung 1 trial with overall survival data from the docetaxel arm of the CheckMate 057 trial to investigate whether the overall survival results were statistically significantly different. It concluded that the two trials could be treated as equal and therefore an exponential model could be used for extrapolation. However it also added that there may be unexplored differences in baseline characteristics in the two trials.

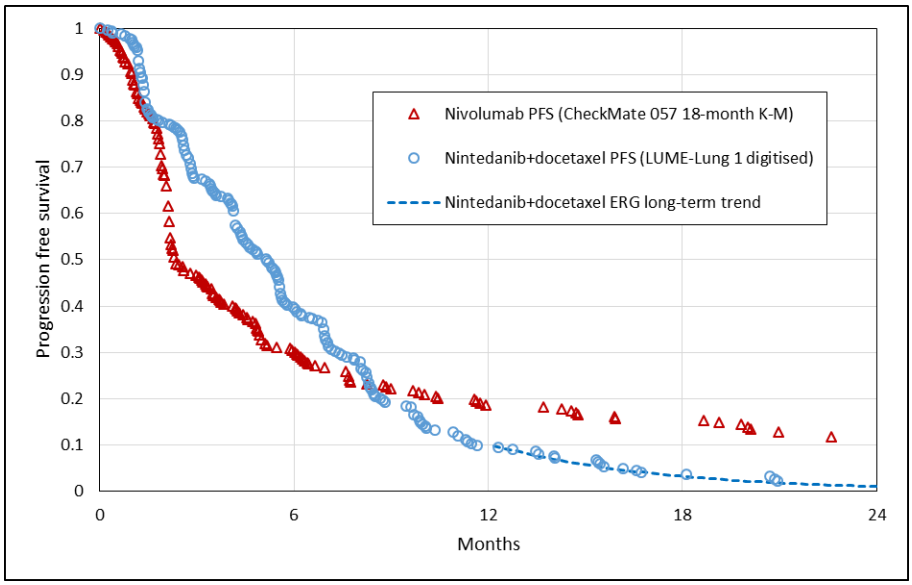
5.17 Regarding the use of time to treatment discontinuation data for modelling progression-free survival, the ERG expressed the same concerns as in the comparison with docetaxel.

Figure 8 Nivolumab and nintedanib plus docetaxel overall survival Kaplan-Meier data plus ERG projections



Source: Figure 31 of ERG report; Response to clarification question B1a; ERG calculations; TA347

Figure 9 Nivolumab and nintedanib plus docetaxel progression-free survival Kaplan-Meier data plus ERG projections



Source: Figure 34 of ERG report; TA347; Response to clarification B1b, ERG calculations

ERG comments on other assumptions in the cost-effectiveness model

5.18 The ERG considered the company's approach to ensure that disease specific mortality rates never fell below all-cause mortality rates led to clinically invalid results. After 18.4 years, the progression-free survival curve for nivolumab fell below the all-cause mortality rate. The company made the assumption that patients who were in the progression-free health state at that point in time would never progress and were cured of the disease. The ERG considered this to be a very strong assumption, which was not supported by clinical evidence.

5.19 The ERG noted that the completion rates for filling out the EQ-5D questionnaires declined rapidly over time. It considered that this might have influenced the utility values in the model. It therefore tested the use of alternative utility values in its analyses. Using data from a study published by van den Hout et al., the ERG calculated the utility value of the progressed disease health state to be 0.545 for both arms of the model. It then applied a disutility value associated with terminal care,

which resulted in a final utility value of 0.476 for the progressed disease health state. For the progression-free health state, the ERG used early EQ-5D results (i.e. during the first 12 weeks after randomisation) for European patients alone. This resulted in a utility value of 0.713 for the progression-free health state. N.B. In the squamous appraisal (ID811) the committee's preferred utility values were 0.693 (progression-free state) and 0.509 (progressed-disease state). For further details see section 5.5.12 or ERG report.

5.20 The ERG considered the company's approach for calculating disutilities inconsistent because the company used data from various different sources for the different disutilities. It also noted that applying adverse event disutilities only to the first cycle of the model lacks validity and instead of the incidence rate, event rates should have been considered. It also considered that applying disutilities separately may lead to double counting. However it did not expect these issues to have a major impact on the ICER.

5.21 The ERG noted that the company made two mistakes in the cost calculations. Firstly, it overestimated the cost per dose of nivolumab and secondly it calculated administration costs at the middle of each cycle, whereas it should be calculated in the beginning of the cycle. The ERG has corrected these errors in its analyses.

Company's base-case results and sensitivity analysis

5.22 In the base case, nivolumab was associated with additional costs of £75,452 and 0.73 additional quality-adjusted life years (QALYs), compared with docetaxel, giving an incremental cost effectiveness ratio (ICER) of £103,589 per QALY gained (Table 8). When compared with nintedanib plus docetaxel, nivolumab was associated with additional costs of £62,598 and 0.49 additional QALYs, giving an ICER or £126,861 per QALY gained (Table 9).

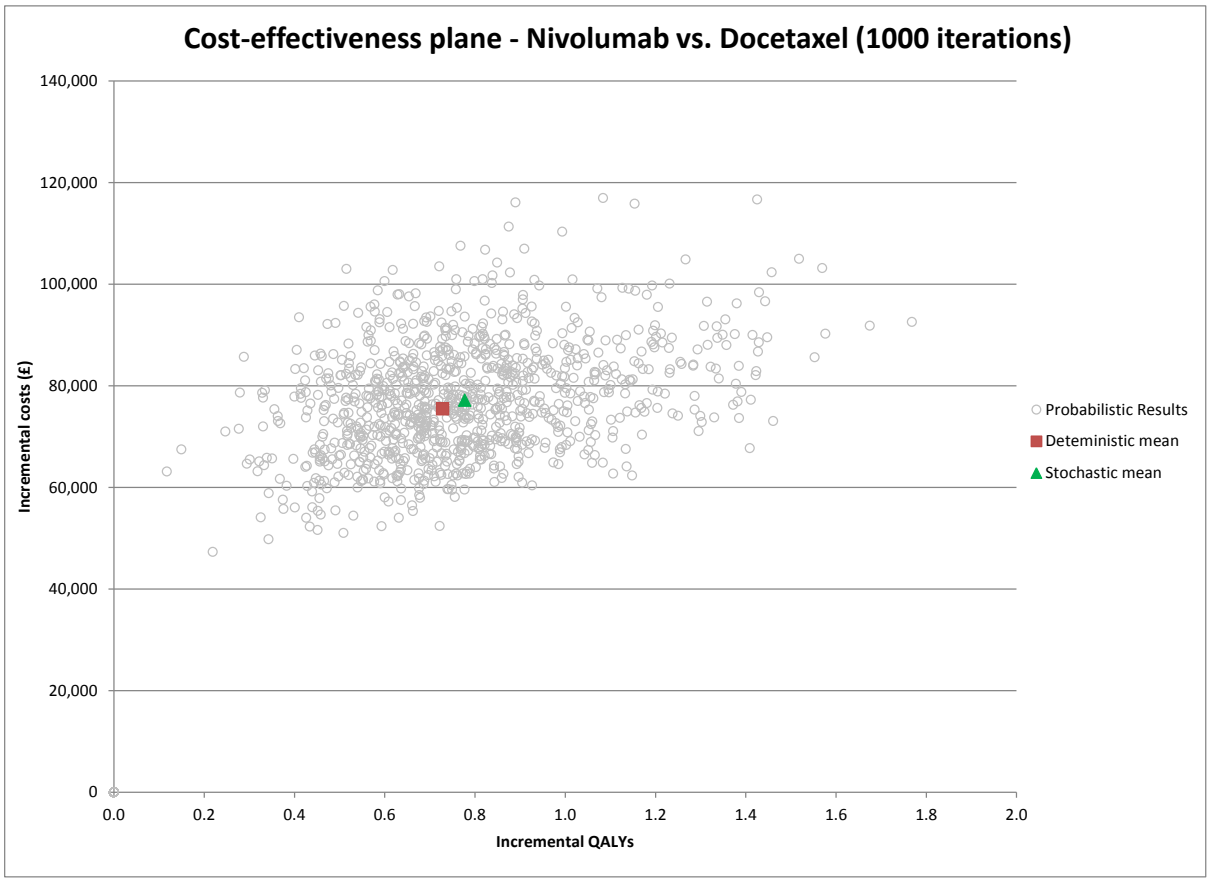
5.23 The company presented both deterministic and probabilistic sensitivity analyses. The deterministic sensitivity analysis showed that when nivolumab was compared with docetaxel, the model results were most sensitive to average body weight, the discount rates and the utility values in the progression-free and progressed disease health states (see the tornado diagram Figure 46 of the company submission). When nivolumab was compared with nintedanib plus docetaxel, the deterministic sensitivity analysis showed that the model results were most sensitive to the hazard ratio for overall survival associated with nintedanib plus docetaxel, average body weight, the discount rates and the hazard ratio associated for progression-free survival associated with nintedanib plus docetaxel. The results of the probabilistic sensitivity analysis showed that the probability that nivolumab was cost-effective compared with docetaxel or with nintedanib plus docetaxel, at a maximum acceptable ICER of 50,000 per QALY gained was 0%.

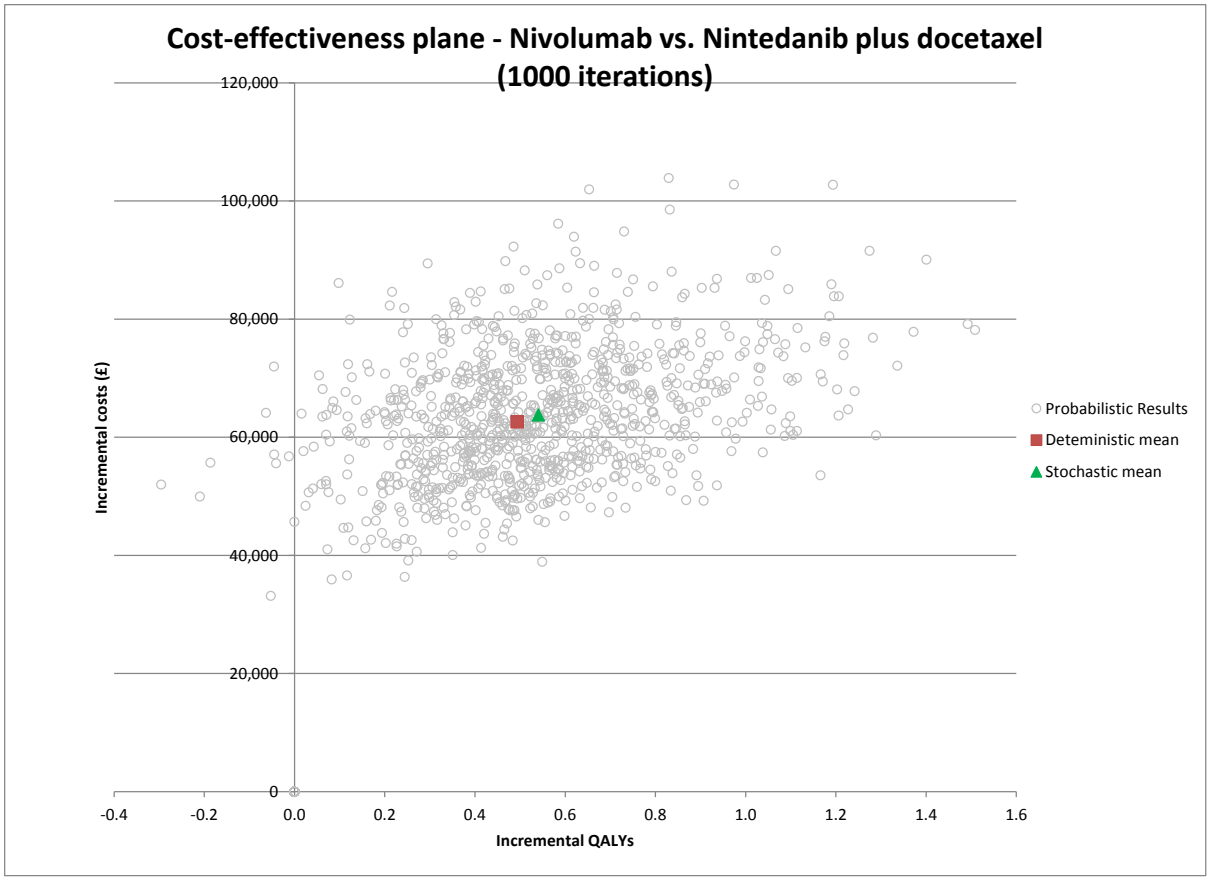
Table 9 Company's base case results

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Deterministic analysis					
Nivolumab	93,306	1.42	-	-	-
Docetaxel	17,854	0.70	75,452	0.73	103,589
Nintedanib plus docetaxel	30,708	0.93	62,598	0.49	126,861
Probabilistic analysis					
Nivolumab	94,83	1.50	-	-	-
Docetaxel	17,666	0.72	77,166	0.78	99,291
Nintedanib plus docetaxel	31,070	0.96	63,761	0.54	117,934
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio Source: Table 76 and 102 of company submission					

Source: Table 76 and 102 of company submission

Figure 10 CE planes of the probabilistic analyses





Source: Figure 43 and 44 of company submission

Company scenarios

5.24 The company presented scenario analyses for the following scenarios:

- Using different OS distributions for nivolumab and docetaxel. The generalised gamma model, which was used in the base case, was replaced by 2-knot spline hazards model for nivolumab and gamma distribution for docetaxel.
- Using different TTD distributions for nivolumab and docetaxel. The generalised gamma model, which was used in the base case, was replaced by 1-knot spline hazards model for nivolumab and gamma distribution for docetaxel.
- Using a 1 year stopping rule for nivolumab treatment, but maintaining the clinical benefit, based on the results of CheckMate 003.
- Using a 2 year stopping rule for nivolumab treatment, but maintaining the clinical benefit, based on the results of CheckMate 003.

Table 10 Results of the scenario analyses

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Scenario 1 (Different OS distributions: 2-knot spline hazards model for nivolumab and gamma distribution for docetaxel)					
Nivolumab	89,553	1.16	-	-	-
Docetaxel	17,375	0.66	72,178	0.50	144,594
Nintedanib plus docetaxel	29,612	0.85	59,941	0.31	195,348
Scenario 2 (Different TTD distributions: 1-knot spline hazards model for nivolumab and gamma distribution for docetaxel)					
Nivolumab	112,380	1.48	-	-	-
Docetaxel	17,858	0.70	94,522	0.78	120,773
Nintedanib plus docetaxel	30,709	0.93	81,671	0.55	149,112
Scenario 3 (1 year stopping rule for nivolumab)					
Nivolumab	51,986	1.42	-	-	-
Docetaxel	17,854	0.70	34,132	0.73	46,860
Nintedanib plus docetaxel	30,708	0.93	21,278	0.49	43,122
Scenario 4 (2 year stopping rule for nivolumab)					
Nivolumab	62,252	1.42	-	-	-
Docetaxel	17,854	0.70	44,398	0.73	60,955
Nintedanib plus docetaxel	30,708	0.93	31,544	0.49	63,928

Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio

Source: Table 108, Table 111, Table 114 and Table 117.

5.25 The company also presented the results of subgroup analyses in Appendix 16 of the company submission for 2 subgroups; for patients with not detected or not recorded EGFR mutation status and for people with ≥1% PD-L1 expression. The results of the subgroup analysis are also considered commercial in confidence information by the company.

ERG comments

5.26 Regarding the company's scenario analyses of 1 and 2 year stopping rules the ERG noted that there is a lack of data available which describes the clinical effect of stopping treatment before progression.

ERG exploratory analyses

5.27 The ERG's revised base case analysis for comparing nivolumab with docetaxel (Scenario B) incorporated the following changes to the model:

- Used the ERG's preferred method for modelling overall survival (used 18 months data and a mixed exponential model based on 25% of patients receiving nivolumab after progression on the nivolumab arm; and simple exponential model for extrapolation on the docetaxel arm.)
- Used progression-free survival for modelling health state costs and QALYs (based on 18 months data and used exponential model for extrapolation). Used time to treatment discontinuation data for modelling costs and AEs associated with treatment and exponential model for extrapolation on the nivolumab arm.
- Corrected for the mistake in calculating the dose for nivolumab
- Calculated treatment administration costs at the start of each cycle
- Used the ERG's preferred utility values

It resulted in ICER of £165,234 per QALY gained for nivolumab compared with docetaxel, which is £61,644 per QALY gained higher than the company's base case ICER (see Table 11).

5.28 The ERG's revised base case analysis for comparing nivolumab with nintedanib plus docetaxel (Scenario C) incorporated the following changes to the model:

- Used the ERG's preferred method for modelling overall survival (used 18 months data on the nivolumab arm, more mature data from the LUME-Lung 1 trial and exponential model for extrapolation)
- Used progression-free survival for modelling health state costs and QALYs for nivolumab and used time to treatment discontinuation data for modelling costs and AEs associated with nivolumab treatment. Used the ERG's preferred method for modelling progression free survival for nintedanib plus docetaxel (used more mature data from LUME-Lung 1 trial).

- Corrected for the mistake in calculating the dose of nivolumab
- Calculated treatment administration costs at the start of each cycle
- Used the ERG's preferred utility values

It resulted in ICER of £293,232 per QALY gained for nivolumab versus nintedanib plus docetaxel, which is £166,370 per QALY gained higher than the company's original ICER (see Table 12).

Table 11 ERG exploratory analyses comparing nivolumab with docetaxel

Scenario	Inc. cost (£)	Inc. QALY	ICER (£)	ICER Change (£)
A. Company's base case	+75,452	+0.728	103,589	-
R1) ERG OS	+72,207	+0.501	143,984	+40,395
R2) ERG PFS*	+57,328	+0.708	80,940	-22,649
R3) ERG TTD*	+58,577	+0.719	81,513	-22,077
R4) ERG PFS for disease costs and QALYs, ERG TTD for treatment costs and AEs	+59,208	+0.708	83,594	-19,996
R7) Nivolumab dosing calculations	+74,100	+0.728	101,734	-1,855
R8) Treatment administration costed at start of cycle	+74,587	+0.728	102,403	-1,187
R9) ERG utility values (Van den Hout + CheckMate 057)	+75,452	+0.654	115,443	+11,853
R10) Utility values from study by Nafees	+75,452	+0.599	125,936	+22,347
B. ERG revised base case A+R1, R4, R7:R9	**+53,343**	**+0.323**	**165,234**	**+61,644**

Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; OS, overall survival

Source Table 46 of ERG report

* Revisions R2 and R3 are superseded by R4

Table 12 ERG exploratory analyses comparing nivolumab with nintedanib plus docetaxel

Scenario	Inc. cost (£)	Inc. QALY	ICER (£)	ICER Change (£)
A. Company base case	+62,598	+0.493	126,861	-
R1) ERG OS	+59,164	+0.238	248,838	+121,977
R2) ERG PFS*	+41,069	+0.471	87,202	-39,660
R5) ERG TTD for nivolumab treatment costs and AEs, ERG PFS for nintedanib+docetaxel disease costs and QALYs*	+41,593	+0.472	88,147	-38,714
R6) ERG PFS for nivolumab disease costs and QALYs, ERG TTD for nivolumab treatment costs and AEs; ERG PFS for nintedanib+docetaxel disease costs and QALYs	+41,149	+0.471	87,371	-39,491
R7) Nivolumab dosing calculations	+61,247	+0.493	124,123	-2,738
R8) Treatment administration costed at start of cycle	+62,611	+0.493	126,887	+26
R9) ERG utility values (Van den Hout66 + CheckMate 057)	+62,598	+0.486	128,916	+2,055
R10) Utility values from Nafees59	+62,598	+0.446	140,399	+13,537
C. ERG revised base case A+R1, R6:R9	**+35,116**	**+0.120**	**293,232**	**+166,370**

Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; OS, overall survival

Source Table 47 of ERG report

*Revisions R2 and R5 (shaded rows) are superseded by R6

Innovation

5.29 The company considered nivolumab to be innovative and represents a 'step-change' in the management of locally advanced or metastatic squamous NSCLC (section 2.5 of company submission):

- Nivolumab is one of the fist immune-oncology treatments that become available for the treatment of non-squamous NSCLC.
- It was designated a 'Promising Innovative Medicine' by the MHRA, and was approved through the Early Access to Medicines Scheme (EAMS).
- The treatment options are limited for people with non-squamous NSCLC which is not EGFR or ALK mutation positive. The current standard of care is docetaxel, which has limited efficacy and poorly tolerated by patients. Nintedanib plus docetaxel has also been recommended by NICE TA347 for locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first‑line chemotherapy, however it is still associated with high level of toxicity and contraindicated for several conditions.
- It provides statistically significant survival benefit (HR: 0.73; 95% CI 0.59 to 0.89; p=0.002) compared with docetaxel. It also provides high survival benefit compared with nintedanib plus docetaxel (HR: 0.80; 95% CI 0.60 to 1.05; p=0.11).

5.30 Consultees also considered nivolumab to be innovative, noting that it is likely to replace docetaxel in the treatment pathway and that it is the first immunotherapy agent to be licenced for NSCLC.

6 End-of-life considerations

Table 13 End-of-life considerations

<table>
<tr><th>Criterion</th><th>Data available</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>The company stated that patients with advanced or metastatic NSCLC have a short life expectancy of less than 24 months (Table 40 of company submission).
In CheckMate 057 the median overall survival for patients on the docetaxel arm was 9.4 months (see Table 4)
Median survival for stage III NSCLC is 9.6 months.
Median survival for stage IV NSCLC is 3.3 months.</td></tr>
<tr><td>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</td><td>Please see the mean and median OS results in the table below.
The results of the company’s model showed that nivolumab gave a mean 13.7 months extension to life when compared with docetaxel. When compared with nintedanib plus docetaxel it gave a mean 9.6 months extension to life.

Using the ERGs preferred assumptions, nivolumab gave an mean 8.8 and 4.1 months extension to life when compared with docetaxel or nintedanib plus docetaxel, respectively.

The median OS results from CheckMate 057 showed that nivolumab gives a 2.83 months extension to life when compared with docetaxel. When the results were compared with the median OS from LUME-Lung 1 for nintedanib plus docetaxel, nivolumab gave a median 0.41 months extension to life.

<table>
<tr><td></td><td colspan="2">Clinical trials (CheckMate 057 for nivolumab and docetaxel; LUME-Lung 1 for nintedanib plus docetaxel)</td></tr>
<tr><td></td><td>Median OS</td><td>Diff.</td></tr>
<tr><td>Nivolumab</td><td>12.2</td><td>-</td></tr>
<tr><td>Docetaxel</td><td>9.4</td><td>2.8</td></tr>
<tr><td>Nintedanib + docetaxel</td><td>12.6</td><td>0.4</td></tr>
<tr><td></td><td colspan="2">Company’s model</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td></td><td>Mean OS</td><td>Diff.</td><td>Median OS</td><td>Diff.</td></tr>
<tr><td>Nivolumab</td><td>26.8</td><td>-</td><td>11.1</td><td>-</td></tr>
<tr><td>Docetaxel</td><td>13.1</td><td>13.7</td><td>9.2</td><td>1.8</td></tr>
<tr><td>Nintedanib + docetaxel</td><td>17.2</td><td>9.6</td><td>12.1</td><td>-1.0</td></tr>
<tr><td></td><td colspan="4">ERG’s preferred assumptions</td></tr>
<tr><td></td><td>Mean OS</td><td>Diff.</td><td>Median OS</td><td>Diff.</td></tr>
<tr><td>Nivolumab</td><td>21.6</td><td>-</td><td>12.1</td><td>-</td></tr>
<tr><td>Docetaxel</td><td>12.8</td><td>8.8</td><td>9.2</td><td>2.9</td></tr>
<tr><td>Nintedanib + docetaxel</td><td>17.4</td><td>4.1</td><td>12.5</td><td>-0.4</td></tr>
<tr><td colspan="5">Abbreviations: OS, overall survival; Diff., OS difference compared with nivolumab</td></tr>
</table>
</td></tr>
<tr><td>The treatment is licensed or otherwise indicated for small patient populations</td><td>The company estimated that 1413 patients with non-squamous NSCLC would be eligible for nivolumab in England and Wales.
(19,138 diagnosed with locally advanced or metastatic NSCLC in 2013. 64% of them have non-squamous histology and 23% of non-squamous stage IIIb/IV NSCLC would be treated with fist line treatment. 50% of these fail to respond, therefore 1,413 patients would be eligible for nivolumab).
In addition, the population size for the melanoma indication is estimated to be 2200 and for the squamous indication is 853. The total population size is therefore in the region of 4500.</td></tr>
</table>

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 submission.

8 Authors

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Technical Lead

Joanne Holden

Technical Adviser

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

European Medicines Agency. Opdivo. Available from:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab for previously treated locally advanced or metastatic non-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].

The aims of therapy are to prolong survival and improve quality of life. Treatment choices may be influenced by the presence of biological markers (such as activating mutations in the epidermal growth factor receptor [EGFR]), histology (squamous or non-squamous) and previous treatment experience. For people with locally advanced or metastatic NSCLC whose disease has progressed after previous treatment with chemotherapy, NICE recommends docetaxel monotherapy, erlotinib, afatinib and nintedanib as options in certain circumstances (CG121, technology appraisal 162 [subject to ongoing NICE appraisal], technology appraisal 310 and technology appraisal 347 respectively). Crizotinib is not recommended by NICE (technology appraisal 296), however it is available via the Cancer Drugs Fund. Best supportive care may be considered for some people for whom chemotherapy is unsuitable or may not be tolerated.

The technology

Nivolumab (Nivolumab BMS, Bristol-Myers Squibb UK) 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-squamous non-small cell lung cancer. It has been studied in one randomised, open-label clinical trial compared with docetaxel, in adults with non-squamous non-small-cell lung cancer, which has progressed after platinum-based chemotherapy.

Intervention(s)	Nivolumab
Population(s)	People with previously treated locally advanced or metastatic non-squamous non-small cell lung cancer
Comparators	**Non-squamous EGFR-TK mutation positive tumours:** • After one prior therapy: – Platinum therapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane) – Single agent gemcitabine and vinorelbine (for people for whom platinum therapy is not appropriate) – Afatinib, erlotinib or gefitinib (if no previous EGFR-TKI therapy received due to delayed confirmation of mutation status; erlotinib and gefitinib subject to ongoing NICE appraisal) • After two prior therapies (an EGFR-TKI and one other therapy): – Docetaxel monotherapy – Erlotinib – Nintedanib in combination with docetaxel – Best supportive care **Non-squamous EGFR-TK mutation negative or unknown tumours:** • After one prior therapy: – Docetaxel monotherapy

	– Erlotinib (subject to ongoing NICE appraisal) – Nintedanib in combination with docetaxel – Crizotinib (only for patients with ALK positive mutation status) – Ceritinib (only for patients with ALK positive mutation status; subject to ongoing NICE appraisal) – Best supportive care • After two prior therapies: – Docetaxel monotherapy – Erlotinib (if not received previously; subject to ongoing NICE appraisal) – 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 will 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. 310, Mar 2014, 'Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer'. Review Proposal Date Apr 2017. Technology Appraisal No. 296, September 2013, 'Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene'. Review Proposal Date May 2016. Technology Appraisal No. 175, Jul 2009, 'Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer (terminated appraisal)'. Review in progress. Technology Appraisal No. 162, Nov 2008, 'Erlotinib for the treatment of non-small-cell lung cancer'. Review in progress. Technology Appraisal No. 124, Nov 2007, 'Pemetrexed for the treatment of non-small-cell lung cancer'. Static list. Technology Appraisal No. 347, July 2015, 'Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer'. 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. Technology Appraisal in preparation, 'Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer'. Expected date of publication May 2016. Technology Appraisal in preparation, 'Ceritinib for previously treated anaplastic lymphoma kinase-positive non-small-cell lung cancer' [ID729]. Expected date of publication January 2016.

	Related Guidelines: Clinical Guideline No. 121, Apr 2011, 'The diagnosis and treatment of lung cancer'. Review date March 2016 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

References

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 non-squamous non-small-cell lung cancer

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Bristol-Myers Squibb (nivolumab) Patient/carer groups • Black Health Agency • British Lung Foundation • Cancer Black Care • Cancer Equality • 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 Cancer Care • 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 • Royal College of General Practitioners • Royal College of Nursing	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, carboplatin, cisplatin, gemcitabine) • Actavis UK (docetaxel, gemcitabine, vinorelbine) • AstraZeneca (gefitinib) • Boehringer Ingelheim (afatinib, nintedanib) • Dr Reddy's Laboratories (docetaxel) • Eli Lilly and Company (gemcitabine, pemetrexed) • Hospira UK (docetaxel, carboplatin, cisplatin, gemcitabine) • Medac UK (docetaxel, gemcitabine, vinorelbine) • Novartis (ceritinib)

Consultees	**Commentators (no right to submit or appeal)**
• 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 Eastbourne, Hailsham and Seaford CCG • NHS England • NHS Hartlepool and Stockton-on-Tees CCG • Welsh Government	• Pierre Fabre (vinorelbine) • Pfizer (crizotinib) • Roche Products (erlotinib) • Sandoz (cisplatin) • Sanofi (docetaxel) • Sun Pharmaceuticals UK (carboplatin, gemcitabine) <u>Relevant research groups</u> • Cochrane Lung Cancer Group • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research <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 non-squamous non-small-cell lung cancer [ID900]

Company evidence submission

Submitted by Bristol-Myers Squibb Pharmaceuticals Ltd

January 2016

File name	Version	Contains confidential information	Date
ID900 BMS Nivolumab NSQ NSCLC final STA submission ACIC	3.0	Yes	23 December 2015

Contents

Tables

Figures

Abbreviations

Term	Definition
ACD	Appraisal consultation document
ADA	Adenosine deaminase
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ASBI	Average Symptom Burden Index
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BMS	Bristol-Myers Squibb
BNF	British National Formulary
BOR	Best objective response
BSA	Body surface area
BSC	Best supportive care
CE	Cost-effective
CENTRAL	Cochrane® Central Register of Controlled Trials
CI	Confidence interval
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
CUA	Cost-utility analysis
DMC	Data monitoring committee
DOR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-VAS	EQ-5D Visual Analogue Scale
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GP	General practitioner
HR	Hazard ratio
HRG	Healthcare Resource Group

Term	Definition
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFNγ	Interferon gamma
IFNγR	Interferon gamma receptor
IgG4	Immunoglobulin G4
irAE	Immune-related adverse event
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
IV	Intravenous
KM	Kaplan-Meier
LCSS	Lung Cancer Symptom Scale
LRiG	Liverpool Reviews and Implementation Group
LYG	Life-year gained
MET	Mesenchymal epithelial transition
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare Products Regulatory Agency
MID	Minimally important difference
mOS	Median overall survival
mPFS	Median progression-free survival
MTA	Multiple technology appraisal
MVH	Measurement and Valuation of Health
NA	Not available
N/A	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NFκB	Nuclear transcription factor-κB
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit
NR	Not reported
NSCLC	Non-small cell lung cancer
NSQ	Non-squamous
ORR	Objective response rate
OS	Overall survival
PbR	Payment by results
PD	Progressive disease
PD-1	Programmed death-1

Term	Definition
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PIM	Promising innovative medicine
PK	Pharmacokinetics
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PRO	Patient-reported outcome
PS	Performance status
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RWD	Real-world data
RWE	Real-world evidence
SAE	Serious adverse event
SD	Stable disease
SE	Standard error
SEER	Surveillance, Epidemiology and End Results Program
Shp-2	Src homology 2 domain-containing protein tyrosine phosphatase 2
SmPC	Summary of product characteristics
SQ	Squamous
STA	Single technology appraisal
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
TTR	Time to response
UK	United Kingdom
US	United States
VAT	Value added tax
VEGF	Vascular endothelial growth factor
WCLC	World Conference on Lung Cancer
WHO	World Health Organization
WTP	Willingness to pay

1 Executive summary

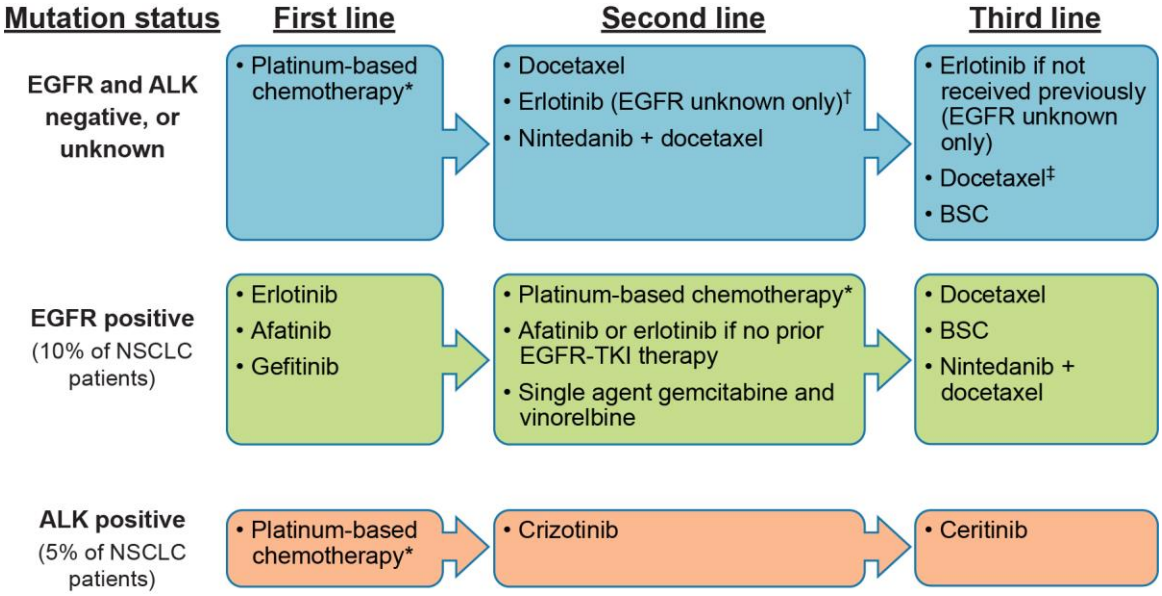
1.1 Lung cancer and non-small cell lung cancer

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 (Office for National Statistics, 2012; Office for National Statistics, 2013). 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) (Health and Social Care Information Centre, 2014), and a large proportion of patients experience increasingly severe morbidity as their disease progresses (Section 3.1) (Schrump et al., 2011). However, younger patients also are affected by lung cancer, with more than 10% of patients being younger than 60 years at diagnosis (Health and Social Care Information Centre, 2015). 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, 2014), of these 19,138 had a diagnosis of stage IIIb or IV NSCLC. The median survival for stage III and stage IV NSCLC in England was 9.6 months and 3.3 months from presentation in secondary care, respectively, in 2013 (Health and Social Care Information Centre, 2014). Non-small cell lung cancer can be divided further by histology into squamous and non-squamous NSCLC—non-squamous NSCLC is the focus of this dossier.

1.2 Treatment of non-squamous non-small cell lung cancer

Patients with a certain type of NSCLC (i.e. non-squamous NSCLC) can have specific mutations in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes that are drivers of the disease. These patients generally have more treatment options and a better prognosis. Notably, the highest unmet medical need is in patients who do not have EGFR or ALK mutations (termed “EGFR-negative” or “ALK-negative,” which represent most of the non-squamous NSCLC population), as these patients will not benefit from available EGFR- and ALK-targeted agents such as erlotinib, afatinib, gefitinib, crizotinib or ceritinib. Figure 1 summarises the current treatment pathway.

Figure 1: Overview of treatments in the UK for unresectable locally advanced or metastatic non-squamous NSCLC



Abbreviations: ALK = Anaplastic Lymphoma Kinase; BSC = Best Supportive Care; EGFR = Epidermal Growth Factor Receptor; NSCLC = Non-Small Cell Lung Cancer; TKI = Tyrosine Kinase Inhibitor; UK = United Kingdom

* Platinum-based chemotherapy + gemcitabine, vinorelbine, pemetrexed or a taxane.

† Until recently, erlotinib was recommended second-line in patients with EGFR mutation-negative/unknown status; however, recent NICE guidance recommends erlotinib only in patients with EGFR unknown mutation status, which is a very small sub-group of patients.

‡ As erlotinib is no longer recommended in second-line for patients with EGFR mutation-negative status, docetaxel (as monotherapy or in combination with nintedanib) is the only second-line option and, as a result, will no longer be used in third-line.

Despite recent advances in treatments, the prognosis in terms of survival in NSCLC has not substantially improved in the last 30 years. In a recent RCT, the current standard of care, docetaxel, resulted in a 1-year OS of 24% (95% CI: 17, 31) and a median OS of 6.0 months (95% CI: 5.1, 7.3) (Brahmer et al., 2015). Thus, there remains an unmet medical need for effective treatments for previously treated patients with advanced non-squamous NSCLC.

In England, patients with unresectable non-squamous NSCLC are currently treated first-line with platinum-based chemotherapy; however, beyond first-line, there is a limited range of treatments available. In England, approximately 23% of patients with non-squamous stage IIIb/IV NSCLC are treated with a first-line therapy (approximately 2,832 patients) (NICE, 2010d; Sculier and Moro-Sibilot, 2009). This therapy usually fails in 50% of these patients (approximately 1,413 individuals) (Sculier and Moro-Sibilot, 2009), and these are the patients who are potentially eligible for second-line treatment with nivolumab. For further detail, please refer to Section 3.1.

1.3 Nivolumab for the treatment of non-small cell lung cancer

Nivolumab is a new treatment option for previously treated adults with locally advanced or metastatic non-squamous NSCLC. It is a programmed death-1 (PD-1) receptor inhibitor that demonstrated a significant improvement in OS compared with docetaxel in patients with advanced non-squamous NSCLC (interim data,[1] CheckMate 057):

[1] Results from the interim analysis are based on a minimum follow-up of 13.2 months; however, this analysis is sometimes termed the “12-month interim analysis” for simplicity.

- 1-year OS rate: 51% (95% CI: 45, 56) versus 39% (95% CI: 33, 45) for docetaxel
- 27% reduction in risk of death with nivolumab (hazard ratio [HR]: 0.73; 95% confidence interval [CI]: 0.59, 0.89; p = 0.002)
- Median OS: 12.2 months (95% CI: 9.7, 15.0) versus 9.4 months for docetaxel (95% CI: 8.1, 10.7)

With additional follow-up, the OS rate at 18 months was 39% (95% CI: 34, 45) with nivolumab versus 23% (95% CI: 19, 28) with docetaxel, and there was a 28% reduction in risk of death (HR: 0.72; 95% CI: 0.60, 0.88; p = 0.0009).[2]

The study demonstrated statistically significant superiority of nivolumab over docetaxel for objective response rate (ORR):

- ORR: 19% (95% CI: 14.8, 24.2) for nivolumab and 12% (95% CI: 8.8, 16.8) for docetaxel (p = 0.02)

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.

[2] Updated efficacy results with additional follow-up are based on a minimum follow-up of 17.1 months; however, this analysis is sometimes termed the “18-month updated analysis” for simplicity.

1.4 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 non-squamous NSCLC	Adults with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	This patient population is in line with the expected marketing authorisation of nivolumab and the NICE decision problem; however, please note that it differs from the patient population (i.e. is a sub-group of the scoped population) outlined in the final scope issued by NICE.
Intervention	Nivolumab	As per scope	—
Comparator (s)	**Non-squamous EGFR mutation-negative/unknown tumours:** After one prior therapy: • Docetaxel monotherapy • Erlotinib • Nintedanib in combination with docetaxel • Crizotinib (only for patients with ALK-positive mutation status) • Ceritinib (only for patients with ALK-positive mutation status; subject to ongoing NICE appraisal) • BSC After two prior therapies: • Docetaxel monotherapy • Erlotinib (if not received previously) • BSC	Base-case economic analysis in a previously treated setting is nivolumab versus: • Docetaxel monotherapy • Nintedanib in combination with docetaxel	The comparators listed in the final scope are representative of the standard treatments used in the NHS. However, not all are relevant comparators to nivolumab, as discussed below and illustrated in Figure 2. **Non-squamous EGFR mutation-negative/unknown tumours:** Erlotinib has been recommended by NICE in patients with unknown EGFR mutation status only, which is a small sub-group. No nivolumab data were available to allow for comparisons in this submission. **Non-squamous ALK mutation-positive tumours:** The ALK mutation is only seen in approximately 5% of patients with NSCLC. The resulting small sample size in the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Non-squamous EGFR mutation-positive tumours: After one prior therapy: • Platinum-based chemotherapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane) • Single-agent gemcitabine and vinorelbine (for people for whom platinum-based chemotherapy is not appropriate) • Afatinib, erlotinib or gefitinib (if no previous EGFR-TKI therapy received due to delayed confirmation of mutation status; erlotinib and gefitinib subject to ongoing NICE appraisal) After two prior therapies (an EGFR-TKI and one other therapy): • Docetaxel monotherapy • Erlotinib • Nintedanib in combination with docetaxel • BSC		CheckMate 057 study was not powered for this sub-group and thus did not allow robust comparison. Therefore, crizotinib is not deemed an appropriate comparator for nivolumab. Ceritinib is under review by NICE for use in ALK-positive NSCLC after crizotinib; however, the current appraisal consultation document does not recommend its use, and it is not standard of care. Further, the small sample size in the Checkmate 057 study was not powered for this sub-group and thus did not allow robust comparison. Therefore, ceritinib is also not considered an appropriate comparator for nivolumab. Although BSC is a potential comparator for this submission, there is a paucity of data available for use of BSC alone in previously treated patients with locally advanced or metastatic non-squamous NSCLC (Shepherd et al., 2000), which precludes any comparison of nivolumab vs. BSC. N**on-squamous EGFR mutation-positive tumours:** Data were not available in this population, owing to the small number of patients with EGFR mutation-positive tumours in the CheckMate 057 study. Further, patients had to have received prior therapy (specifically a platinum-based chemotherapy) in order to be recruited into the nivolumab clinical study. This renders

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			platinum-based chemotherapy inappropriate as a comparator to nivolumab. Single-agent gemcitabine and vinorelbine may be considered in patients for whom platinum-based chemotherapy is not appropriate. Considering the lack of available data and as all patients in the nivolumab clinical studies have received prior platinum-based chemotherapy, these agents are rendered inappropriate comparators for nivolumab. It is standard for afatinib, erlotinib or gefitinib therapies to be used first-line in patients who are EGFR mutation-positive, meaning there are insufficient data to allow comparisons with these targeted therapies in the second-line setting in this population. Further, gefitinib is not recommend by NICE for the second-line treatment of patients who are EGFR mutation-positive.
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope	—

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE 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	—

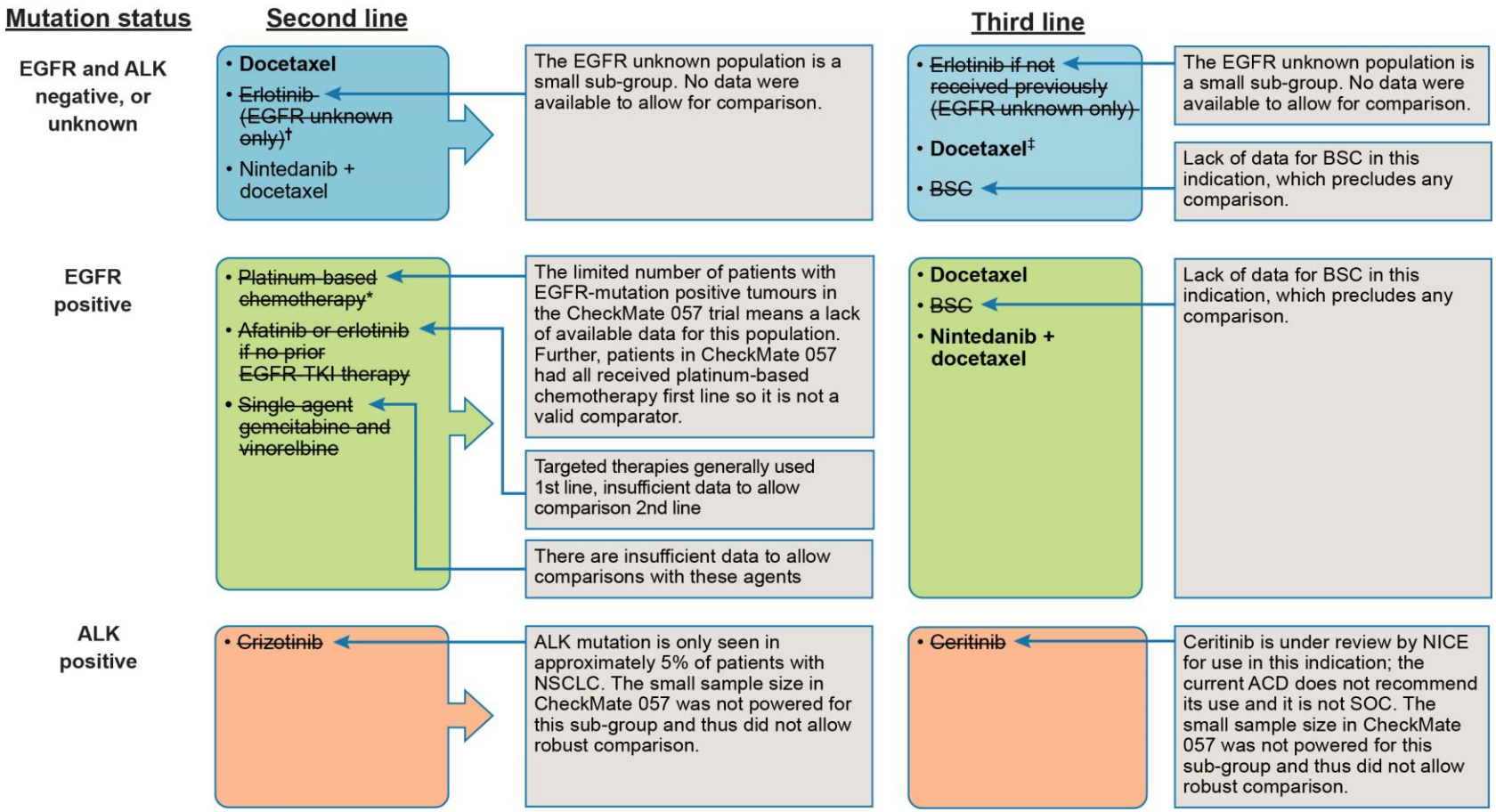
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Other considerations	If the evidence allows, consideration will be given to sub-groups based on biological markers. If appropriate, the appraisal should include consideration 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	—

Source: NICE (2015h)

Abbreviations: ALK = Anaplastic Lymphoma Kinase; BSC = Best Supportive Care; EGFR = Epidermal Growth Factor Receptor; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NSCLC = Non-Small Cell Lung Cancer; PD-L1 = Programmed Death-Ligand 1; TKI = Tyrosine Kinase Inhibitor; UK = United Kingdom

Although some of the above comparisons with treatments stated in the National Institute for Health and Care Excellence (NICE) final scope are justified by the anticipated nivolumab label, they are not possible due to the small number of patients suitable for comparison in CheckMate 057, particularly in EGFR- and ALK-positive groups (Figure 2). The comparators included in our analyses are also in line with those specified in the recent draft scope for pembrolizumab in NSCLC (NICE, In progress). Notably, CheckMate 057 principally represents the largest and most clinically significant group—patients who are EGFR mutation-negative/unknown.

Figure 2: Assessment of appropriate comparators for nivolumab in previously treated unresectable locally advanced or metastatic non-squamous NSCLC based on NICE guidance and clinical practice



Abbreviations: ACD = Appraisal Consultation Document; ALK = Anaplastic Lymphoma Kinase; BSC = Best Supportive Care; EGFR = Epidermal Growth Factor Receptor; NICE = National Institute for Health and Care Excellence; NSCLC = Non-Small Cell Lung Cancer; SOC = Standard of Care; TKI = Tyrosine Kinase Inhibitor

* Platinum-based chemotherapy + gemcitabine, vinorelbine, pemetrexed or a taxane.

† Until recently, erlotinib was recommended second-line in patients with EGFR mutation-negative/unknown status; however, recent NICE guidance means that erlotinib is only recommended in patients with EGFR unknown mutation status, which is a very small sub-group of patients.

‡ As erlotinib is no longer recommended in second-line for patients with EGFR mutation-negative status, docetaxel (as monotherapy or in combination with nintedanib) is the only second-line option and, as a result, will imminently no longer be used in third-line.

1.5 Description of the technology being appraised

Nivolumab, an immuno-oncology treatment, is a PD-1 receptor inhibitor and the "first-in-class" for NSCLC in the UK. It is a fully human immunoglobulin G4 (IgG4) monoclonal antibody and is indicated for the treatment of locally advanced or metastatic NSCLC in previously treated adults after prior chemotherapy (in both squamous and non-squamous indications), as well as the treatment of advanced (unresectable or metastatic) melanoma in adults. The MHRA has designated nivolumab as a PIM in the treatment of locally advanced or metastatic NSCLC (Table 2).

Table 2: Technology being appraised

UK approved name and brand name	Nivolumab (Opdivo®)
Marketing authorisation/CE-mark status	Nivolumab holds marketing authorisation for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults and for the treatment of advanced (unresectable or metastatic) melanoma in adults. Nivolumab is expected to gain marketing authorisation for locally advanced or metastatic non-squamous NSCLC in April 2016.
Indications and any restriction(s) as described in the summary of product characteristics	Nivolumab is indicated for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults and for the treatment of advanced (unresectable or metastatic) melanoma in adults. It is anticipated that nivolumab will be indicated for the treatment of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy in adults.
Method of administration and dosage	Intravenous infusion 3 mg/kg over 60 minutes every 2 weeks

Source: Bristol-Myers Squibb (2015c)

Abbreviations: NSCLC = Non-Small Cell Lung Cancer

There are a number of factors that determine the treatment of patients with non-squamous NSCLC. A key factor is the presence of specific mutations (in the EGFR and ALK genes), as these are drivers of the disease. Patients with driver mutations generally have more treatment options and a better prognosis; therefore, the highest unmet medical need is in patients who do not have EGFR or ALK mutations (representing most of the non-squamous NSCLC population), who will not benefit from available targeted agents.

Docetaxel, the current standard of care for patients with locally advanced or metastatic non-squamous NSCLC previously treated with chemotherapy, is poorly tolerated and has moderate efficacy with limited effect on OS.

Nintedanib in combination with docetaxel is recommended by NICE in patients with adenocarcinoma, but market research currently suggests that use is currently low in the UK (Figure 3); it showed a reduction in the risk of progression or death of 21% versus docetaxel in its pivotal study (HR: 0.79; 95% CI: 0.68, 0.92; p = 0.0019) (European Medicines Agency, 2015). However, although the safety profile of nintedanib is acceptable, the combination treatment still harbours the toxicity of docetaxel. Further, many patients are not eligible for its use owing to its numerous contraindications (European Medicines Agency, 2015).

Erlotinib is also a second-line treatment option in patients who are EGFR- unknown 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 (Figure 3).

Figure 3. Stage IIIb/IV non-squamous NSCLC market in the moving annual total (second-line)

Source: Bristol-Myers Squibb (2015d)

Note: Based on percentage of patients on each treatment in a sample of 399 anonymous patients over a 12-month period.

Although best supportive care (BSC) is a potential comparator for this submission, there is a paucity of data available for its use in previously treated patients with locally advanced or metastatic non-squamous NSCLC, which precludes any comparison of nivolumab versus BSC. Therefore, there is a high unmet medical need for treatments for patients with stage IIIb/IV non-squamous NSCLC.

1.6 Summary of the clinical effectiveness analysis

- The Phase III CheckMate 057 study demonstrated superior survival and a favourable tolerability profile with nivolumab over docetaxel in patients with locally advanced or metastatic previously treated non-squamous NSCLC.
- CheckMate 057 was stopped early, as the assessment conducted by the independent data monitoring committee (DMC) concluded that nivolumab had met its endpoint demonstrating superior OS in patients treated with nivolumab compared with patients treated with docetaxel.

- CheckMate 057 met its primary objective, demonstrating a significant improvement in OS with nivolumab versus docetaxel in patients with advanced non-squamous NSCLC, at the interim analysis based on 413 reported deaths.[3]
  - 1-year OS: 51% (95% CI: 45, 56) versus 39% (95% CI: 33, 45) for docetaxel[4]
  - 27% reduction in risk of death with nivolumab (HR: 0.73; 95% CI: 0.59, 0.89; p = 0.002)
  - Median OS: 12.2 months (95% CI: 9.7, 15.0) versus 9.4 months for docetaxel (95% CI: 8.1, 10.7)
- With additional follow-up[5], the OS rate at 18 months was 39% (95% CI: 34, 45) with nivolumab versus 23% (95% CI: 19, 28) with docetaxel, and there was a 28% reduction in risk of death (HR: 0.72; 95% CI: 0.60, 0.88; p = 0.0009).
- The study demonstrated statistically significant superiority of nivolumab over docetaxel for objective response rate (ORR):
  - ORR: 19% (95% CI: 14.8, 24.2) for nivolumab and 12% (95% CI: 8.8, 16.8) for docetaxel (p = 0.02)

- One-year progression-free survival (PFS) was higher for nivolumab (19%) than for docetaxel (8%). Although median PFS did not favour nivolumab (2.3 months [95% CI: 2.2, 3.3] versus 4.2 months [95% CI: 3.5, 4.9] for docetaxel), the nivolumab and docetaxel Kaplan-Meier (KM) curves showed markedly different profiles (Figure 13), and the overall HR for PFS or death favoured nivolumab (HR: 0.92; 95% CI: 0.77, 1.11; p = 0.39).
- In high programmed death-ligand 1 (PD-L1) expressors, superior efficacy with nivolumab was observed for all endpoints (OS, PFS, ORR) regardless of expression level (≥ 1%, ≥ 5% or ≥ 10%—the values representing the number of cells in a tissue section of 100 or more tumour cells staining for PD-L1, irrespective of staining level). In low expressors, clinical efficacy for nivolumab was similar to that for docetaxel, and tolerability was favourable, regardless of expression level (< 1%, < 5% or < 10%).

[3] Results from the interim analysis are based on a minimum follow-up of 13.2 months; however, this analysis is sometimes termed the "12-month interim analysis" for simplicity.

[4] The 1-year OS for docetaxel is higher in this study than in other studies (e.g. Checkmate 017) (Brahmer et al., 2015).

[5] Updated efficacy results with additional follow-up are based on a minimum follow-up of 17.1 months; however, this analysis is sometimes termed the "18-month updated analysis" for simplicity.

- The OS benefit observed for nivolumab compared with docetaxel in the whole study population was observed when a sub-group analysis examined patients known to have EGFR mutation-negative/unknown status. No meaningful differences in median PFS were observed across the pre-defined EGFR mutation status sub-groups. A statistically significant benefit was not observed in patients with EGFR mutation-positive status; however, the CIs in this sub-group were wide due to its small size, and the study was not powered to identify significant differences in this sub-group. Further, it is not anticipated that nivolumab would be widely used in this population in clinical practice owing to the availability of effective alternatives.
- Further evidence for nivolumab is provided from two uncontrolled studies, CheckMate 153 and CheckMate 003:
    - CheckMate 153 – a Phase IIIb/IV, open-label study in previously treated patients with locally advanced or metastatic non-squamous and squamous NSCLC and PS 0-2.
    - CheckMate 003 – a dose-escalation expansion cohort Phase Ib study in a heavily pre-treated patient population.
    - Results from these two uncontrolled studies demonstrated that the efficacy and safety of nivolumab was consistent with that observed in the pivotal study (CheckMate 057). CheckMate 153 also included data for patients with a performance status of 2 (PS2).
- The current standard of care in the UK for second-line non-squamous NSCLC is docetaxel, and this was used as the comparator in the pivotal CheckMate 057 study. Docetaxel is associated with limited efficacy and poor tolerability; hence, there is a significant unmet medical need for treatments for this group of patients. Nintedanib in combination with docetaxel is recommended by NICE in patients with adenocarcinoma, but market research suggests that use is currently low in the UK. Although the safety profile of nintedanib is acceptable, the combination treatment still harbours the toxicity of docetaxel. Further, many patients are not eligible for treatment owing to its numerous contraindications (European Medicines Agency, 2015).
- Indirect treatment comparisons (ITCs) were undertaken to allow comparisons of nivolumab versus (1) nintedanib in combination with docetaxel and (2) BSC. Because of the paucity of available evidence and heterogeneity among the studies, the following results should be interpreted with caution.
- When all non-squamous patients were considered, the results suggested an OS benefit for nivolumab over nintedanib, although this did not reach statistical significance (HR: [redacted]; 95% CI[redacted]; p = [redacted]). No significant differences were observed in PFS between nivolumab and nintedanib in combination with docetaxel in the all-comers population (HR: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted]). Similar results were seen in the sub-group of patients who were EGFR mutation-negative/unknown.
- Statistically significant benefit in OS with nivolumab was observed against BSC in the entire population group, suggesting a [redacted]% reduction in the risk of death (HR: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted]). Similar results were seen in the sub-group of patients who were EGFR mutation-negative/unknown.

In the treatment of patients with locally advanced or metastatic non-squamous NSCLC previously treated with chemotherapy, we believe that nivolumab will fulfil NICE's end-of-life criteria:

- Patients with advanced or metastatic non-squamous NSCLC have a short life expectancy of less than 24 months (Health and Social Care Information Centre, 2014).
- The mean survival estimated in the cost-effectiveness model (with a 20-year time horizon) was 26.8 months for nivolumab and 13.09 months for docetaxel, resulting in an increase of more than 3 months of survival benefit.
- The licensed population potentially eligible for nivolumab treatment in this indication is expected to be small (estimated 1,413 patients in England).

1.7 Summary of the cost-effectiveness analysis

A *de novo* cost-utility analysis was undertaken to assess the cost-effectiveness of nivolumab in previously treated patients with locally advanced or metastatic non-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 [PF] disease,[6] progressed disease [PD] 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 CheckMate 057, where docetaxel was the comparator treatment. The analysis was also performed comparing nivolumab to nintedanib in combination with docetaxel using an indirect treatment comparison (ITC).

Resource use, costs and utilities were estimated based on information from CheckMate 057, previous technology appraisals, published sources and clinical experts. As recommended by 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 time to treatment discontinuation (TTD). In the base-case analysis, both OS and TTD were modelled using the generalised gamma survival model for both docetaxel and nivolumab, as these allowed the use of a single survival function while providing the optimal balance between statistical fit within the study period where patient-level data existed and long-term clinical plausibility based on real-world data (RWD) reported from the National Lung Cancer Audit (NLCA). The results from the base-case analysis are summarised in Section 5.7.

[6] Note, time to treatment discontinuation (TTD) was used to estimate time spent in the PFS health state to ensure the impact of post-progression treatment was included.

Table 3. Base-case incremental cost-effectiveness results

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	93,306	2.24	1.42				
Docetaxel	17,854	1.09	0.70	75,452	1.15	0.73	103,589

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

In the base-case analysis, nivolumab resulted in an incremental cost of £103,589 per QALY gained compared with current standard of care, docetaxel.

There is uncertainty of the length of the long-term duration of therapy, and data on a 1-year stopping rule are anticipated during the course of this appraisal (see Section 4.14). Sensitivity analyses of treatment-stopping rules at 1 year and 2 years that limited the duration on treatment were therefore also undertaken, which resulted in ICERs of £46,860 and £60,955, respectively, versus docetaxel. This suggests that, as duration on treatment is reduced, the ICER reduces to within the cost-effective range.

Deterministic sensitivity analysis revealed that the model was most sensitive to the discount rates, average body weight and HR for OS applied in the comparison with nintedanib in combination with docetaxel. 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 one of the first PD-1 inhibitors to demonstrate a clinically significant survival benefit in locally advanced or metastatic previously treated non-squamous NSCLC. Nivolumab provides an unprecedented survival benefit (27% reduction in mortality compared with docetaxel standard of care) in patients in whom docetaxel is poorly tolerated and has poor efficacy. This represents a step-change in the management of locally advanced or metastatic previously treated non-squamous NSCLC.

2 The technology

2.1 Description of the technology

Brand name: Opdivo®

UK approved name: nivolumab

Therapeutic class: Antineoplastic agents, monoclonal antibodies

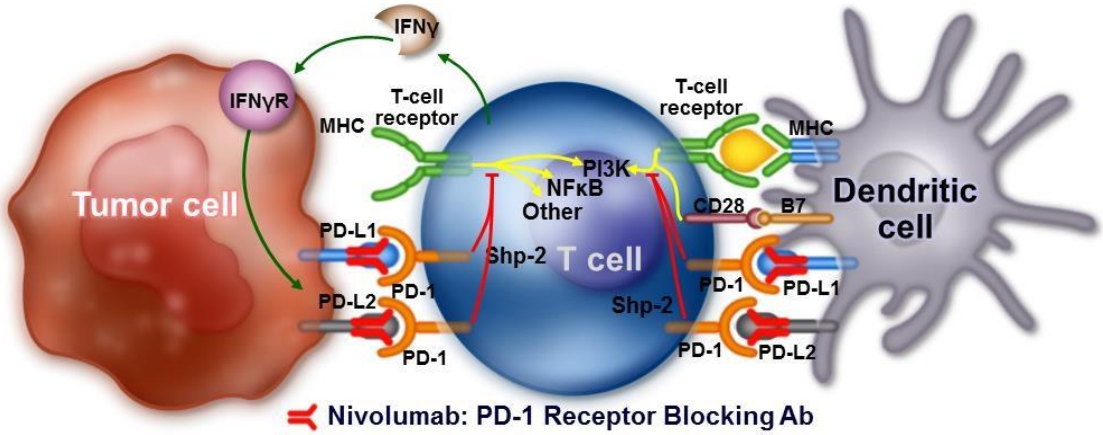
Brief overview of the mechanism of action:

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 NSCLC in particular, there are limited effective and well-tolerated treatment options beyond the first-line, especially in patients without a targetable driver mutation.

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 4). 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 et al., 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 4.

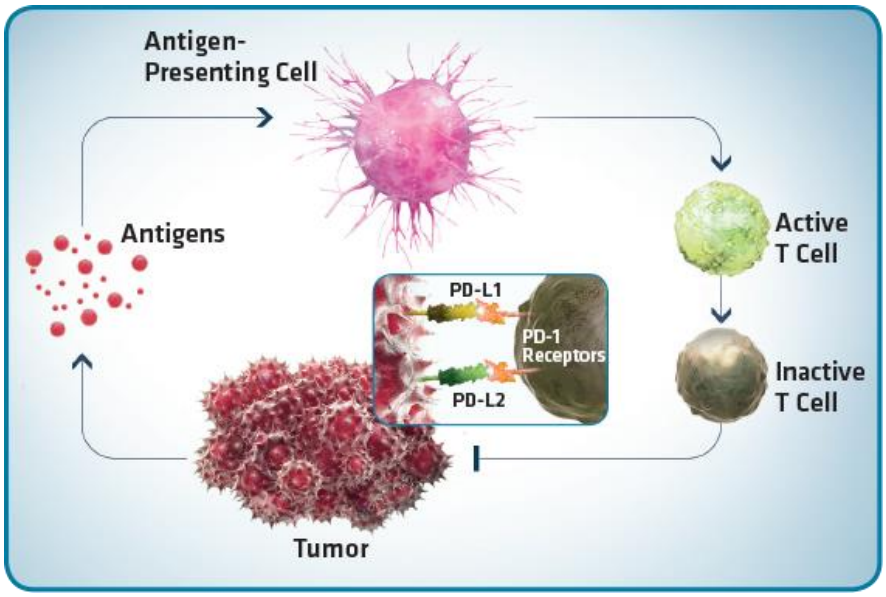
Figure 4: Regulation of the T-cell immune response



Abbreviations: 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 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 5) (Brahmer et al., 2010; Chen et al., 2012; Wang et al., 2014). PD-1 has also been shown to control the inhibition of T-cell response in human malignancies (Brahmer et al., 2010; Freeman et al., 2000; NICE, 2014a). In this submission, patients with PD-L1 expression are classified according to expression levels of ≥ 1%, ≥ 5% and ≥ 10% (high expressors); these are the values representing the number of cells in a tissue section of 100 or more tumour cells staining for PD-L1, irrespective of staining level; therefore, the test for PD-L1 expression does not give a clear binary outcome, but expression occurs on a continuum.

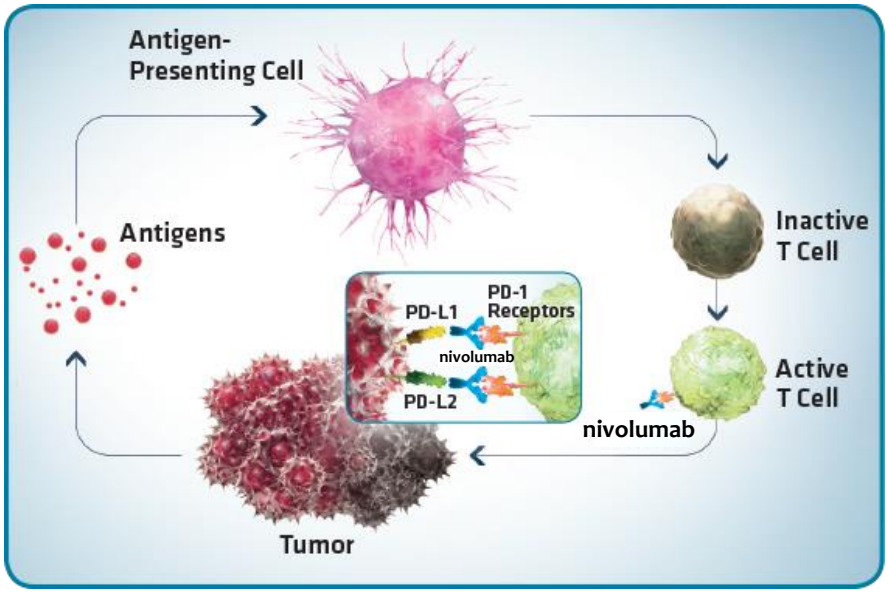
Figure 5: Tumour immune evasion



Abbreviation: PD-L1 = Programmed Death-Ligand 1

Nivolumab (Opdivo®) is the first licensed immuno-oncology treatment for NSCLC and is a human, monoclonal IgG4 antibody (IgG4 HuMAb) that acts as a PD-1 inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2 (Figure 6) (Chen et al., 2012; Wang et al., 2014). Nivolumab is anticipated to be one of the first highly-specific PD-1 inhibitors approved for locally advanced or metastatic previously treated non-squamous NSCLC and restores T-cell activity either by 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 6).

Figure 6: Nivolumab stimulation of immune-mediated destruction

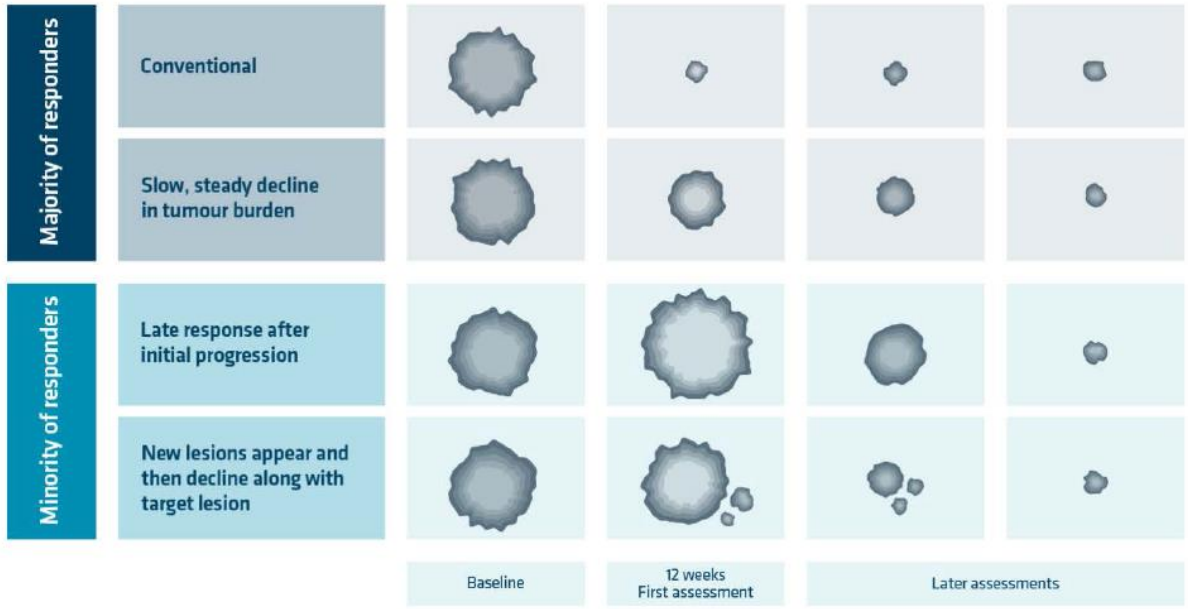


Abbreviations: PD-1 = Programmed Death- 1; PD-L1 = Programmed Death-Ligand 1

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 an 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 7.

Figure 7: Typical patterns of response observed with immuno-oncology



2.2 Marketing authorisation and health technology assessment

Nivolumab is currently under review by the Committee for Medicinal Products for Human Use (CHMP) with opinion anticipated in late February 2016, followed by marketing authorisation in late April 2016.

It is anticipated that nivolumab (brand name: Opdivo®) will be indicated for the treatment of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy in adults. The draft Summary of Product Characteristics (SmPC) is included in Appendix 1. The European Public Assessment Report (EPAR) has not yet been issued.

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 and for locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults.

At the time of submission, marketing authorisation regulatory approval was received in Switzerland for nivolumab in the treatment of locally advanced or metastatic NSCLC after prior chemotherapy. This includes both squamous and non-squamous histologies.

Regulatory approval for nivolumab was also received in the US for the treatment of metastatic NSCLC (both squamous and non-squamous histologies) with progression on or after platinum-based chemotherapy.

Nivolumab is also approved in Israel and Macau for the treatment of metastatic squamous NSCLC with progression on or after platinum-based chemotherapy and for the treatment of an advanced (unresectable or metastatic) melanoma indication in the US, Israel, Japan, Korea and Macau.

Nivolumab will be submitted to the Scottish Medicines Consortium (SMC) and the National Centre for Pharmacoeconomics (anticipated dates of submission: March 2016) 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 40-mg vial (BMS List Price)	BMS
Method of administration	Intravenous infusion	£167.34	NHS reference cost 2013-2014
Doses	3 mg/kg over 60 minutes	£2,538.25 (list price 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 (excluding administration costs)	£31,960	Treatment cost assumes a mean dose number of 12.6‡
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: BSA = Body Surface Area; NHS = National Health Service; SmPC = Summary of Product Characteristics; VAT = Value Added Tax

* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

† Based on list price and the weight and BSA calculator provided by the ERG during the review of the nivolumab in squamous NSCLC model.

‡ Based on CheckMate 057.

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.

2.4.1 Managing adverse events

Nivolumab is generally well tolerated by patients with NSCLC and has a favourable adverse event (AE) profile compared with 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 immune-based mechanism of action of nivolumab means many of its treatment-related AEs are immune-related adverse events (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 often 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 (Appendix 1), adequate evaluation 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. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month's duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

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.

2.4.2 Programmed death-ligand 1

Programmed death-ligand 1 (PD-L1) has been suggested as a potential predictive biomarker of non-squamous NSCLC. However, in CheckMate 057, where nivolumab demonstrated superior OS in previously treated metastatic non-squamous NSCLC compared with docetaxel, patients were enrolled regardless of PD-L1 expression. Half of the patients treated with nivolumab were alive at 1 year compared with 39% for docetaxel. The HR was 0.73 (95% CI: 0.60, 0.89; p = 0.0015), which translates to a 27% reduction in the risk of death with nivolumab compared with docetaxel, based on the pre-specified interim analysis and on 413 reported deaths (Horn et al., 2015). The median OS was 12.2 months in the nivolumab arm (95% CI: 9.7, 15.0) and 9.4 months in the docetaxel arm (95% CI: 8.1, 10.7). Thus, in a pre-specified exploratory analysis, nivolumab showed activity regardless of PD-L1 expression (Borghaei et al., 2015).

The effect of PD-L1 expression on outcomes was further investigated in CheckMate 057 as a pre-defined retrospective sub-group analysis. Although PD-L1 expression was predictive of an improved OS benefit with nivolumab in comparison to docetaxel when administered to patients with non-squamous NSCLC in a second-line clinical setting, the benefit/risk profile of nivolumab was favourable regardless of the level of PD-L1 expression, as follows:

- In patients with PD-L1 expression levels ≥ 1%, ≥ 5% and ≥ 10% (the values representing the number of cells in a tissue section of 100 or more tumour cells staining for PD-L1, irrespective of staining level), there was an OS benefit and a favourable safety profile.
- In patients with PD-L1 expression levels of < 1% (fewer than one cell staining positive in a tissue section of 100 or more tumour cells; known as "no PD-L1 expression" sub-group), there was no clinically relevant difference in OS relative to docetaxel and a favourable safety profile.
    - A proportion of the "no PD-L1 expression" sub-group experienced objective responses with nivolumab similar to that with docetaxel, and these responses were durable, with median duration of objective response (DOR) similar to that in tumours that expressed PD-L1.
- In patients who were classified as "PD-L1 non-quantifiable," because the quality of the testing did not allow accurate counting, there was no clinically relevant difference in OS relative to docetaxel and a favourable safety profile.

It should be emphasised that sub-group analyses by PD-L1 status should be interpreted with caution, as patients were not selected or stratified by PD-L1 expression status, and only 78% of the randomised population had quantifiable PD-L1 results. Additional limitations include the non-randomised nature, which may not account for imbalances for known or unknown prognostic factors within sub-groups; the small sample sizes for some sub-groups; and the lack of correction for multiple comparisons.

Because the results of the CheckMate 057 study indicate that durable responses do occur in nivolumab-treated patients with < 1% PD-L1 expression and because OS benefit in these patients is similar to the active comparator docetaxel (in conjunction with a favourable safety profile compared with docetaxel), PD-L1 expression is not an appropriate marker for restricting nivolumab treatment in patients with non-squamous NSCLC.

A biomarker test for tumour PD-L1 expression has potential value to inform oncologists' discussions with individual patients when setting expectations of clinical outcomes anticipated from treatment with nivolumab. For this purpose, a validated PD-L1 assay using the 28.8 antibody used in the BMS studies ("the DAKO IHC 28.8 PharmDx test") will be made available to practitioners through our diagnostic alliance partner Dako/Agilent. This in vitro diagnostic (IVD) test received a self-certified CE-mark on 1 December 2015 and is available for use in the European Union. Hence, IVD testing to inform treatment will be immediately available upon market authorisation of nivolumab.

BMS continues in its commitment to make this PD-L1 diagnostic test available for clinical use for the NHS at the point of nivolumab marketing authorisation. Centres providing this test will be appropriately trained and quality assured. The training and testing will be funded by BMS through the alliance partner.

2.5 Innovation

- Nivolumab is anticipated to be one of the first immuno-oncology treatments to receive marketing authorisation for locally advanced or metastatic previously treated non-squamous NSCLC in the UK.
- Nivolumab provides an unprecedented survival benefit (27% reduction in mortality compared with docetaxel standard of care) in patients with locally advanced or metastatic previously treated non-squamous NSCLC.
- The MHRA has designated nivolumab as a PIM in the treatment of locally advanced or metastatic NSCLC.
- Nivolumab represents a “step-change” in the treatment of NSCLC in an area of high unmet medical need.

There are limited effective treatment options for patients with non-squamous NSCLC. Treatment choice largely depends on the presence of specific mutations (in the EGFR and ALK genes), as these are drivers of the disease. As such, there is an unmet medical need that is particularly significant for patients who typically do not have EGFR or ALK mutations (representing most of the non-squamous NSCLC population) and hence will not benefit from available targeted agents.

Nivolumab is anticipated to be one of the first immuno-oncology treatments approved for locally advanced or metastatic previously treated non-squamous NSCLC in the UK that shows an OS benefit. Nivolumab offers a “step-change” in the treatment of NSCLC in terms of mechanism of action, degree of clinical benefit and addressing a significant unmet medical need. The MHRA awarded nivolumab a PIM designation in the treatment of locally advanced or metastatic NSCLC.

Nivolumab is anticipated to receive a marketing authorisation for all patients regardless of their PD-L1 status in the non-squamous previously treated setting. Thus, patients may benefit from the drug, regardless of their 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 and Weinberg, 2000).
- Nivolumab is the first approved therapy to effectively manipulate the immune system to allow tumour cells to be recognised and to improve outcomes, including survival, in locally advanced or metastatic NSCLC, as demonstrated in Phase III studies.
- For patients previously treated with chemotherapy, there are few effective treatment options available. Docetaxel, the current standard of care in this patient population, is poorly tolerated and has poor efficacy. Use of nintedanib in combination with docetaxel is likely to increase in patients with NSCLC following a positive NICE recommendation. However, although the safety profile of nintedanib is acceptable, the combination treatment still harbours the toxicity of docetaxel. Further, many patients are not eligible for its use owing to its numerous contraindications (European Medicines Agency, 2015).
- Nivolumab is anticipated to be one of the first PD-1 inhibitors licensed in locally advanced or metastatic previously treated non-squamous NSCLC in the UK.
- Nivolumab is one of the first PD-1 inhibitors to demonstrate a clinically significant survival benefit in locally advanced or metastatic previously treated non-squamous NSCLC.

- Nivolumab provides an unprecedented survival benefit (27% reduction in mortality compared with docetaxel standard of care) in patients in whom limited treatments are available and offers a step-change in the management of locally advanced or metastatic previously treated non-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 (Office for National Statistics, 2012; Office for National Statistics, 2013). 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 with a diagnosis of lung cancer were aged between 50 and 70 years (Health and Social Care Information Centre, 2014).

There are two major groups of lung cancer that differ based on histology: non-small cell lung cancer (NSCLC; 84%) and small cell lung cancer (11%) (Health and Social Care Information Centre, 2014). NSCLC can fall into two histological categories, squamous or non-squamous. In 2013, most patients with NSCLC had a histology that was non-squamous in origin (approximately 64%), and the remainder had squamous NSCLC (Health and Social Care Information Centre, 2014; Powell et al., 2013). In addition, two key genetic mutations have been identified, which are predominantly present in non-squamous NSCLC: EGFR and ALK (Ameratunga et al., 2014; Cancer Genome Atlas Research Network, 2012; Fiala et al., 2013a; Fiala et al., 2013b; Heist et al., 2012; Lindeman et al., 2013; United States National Library of Medicine, 2015a; United States National Library of Medicine, 2015b).

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 stage 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 resectable; 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 NSCLC in England, representing approximately 70% of all the 27,300 NSCLC cases (Health and Social Care Information Centre, 2014). The median survival for all lung cancer in England and Wales was 7.6 months, while the median survival for all patients with stage III NSCLC was 9.6 months (Health and Social Care Information Centre, 2014). In contrast, the median survival for patients with stage IV NSCLC was only 3.3 months (Health and Social Care Information Centre, 2014). On average, patients with lung cancer lose 15.2 years of life, as reported in the Surveillance, Epidemiology and End Results Program (SEER) Cancer Statistics Review (Howlader et al., 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 et al., 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 (Cella et al., 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 et al., 2015).

3.2 Clinical pathway of care

For most people with NSCLC with non-squamous histology, the aims of therapy are to prolong survival and improve HRQoL (NICE, 2015h). Treatment of patients with non-squamous NSCLC depends on a range of factors, including performance status (PS—patients' general well-being and activities of daily life), comorbidities, histology, presence of mutations, and personal choice.

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. Although there have been therapeutic advances to address this unmet medical need in some patients with specific mutations, the main systemic treatment for most patients with advanced lung cancer remains cytotoxic chemotherapy, in both treatment-naïve and previously treated patients.

Therefore, there is a significant unmet medical 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 non-squamous NSCLC, particularly in patients without EGFR and ALK mutations, and nivolumab meets this need.

An overview of treatments used in clinical practice in England was previously provided in Figure 1 and is described in more detail in sections 3.2.1 to 3.2.3.

3.2.1 EGFR- and ALK-negative or unknown tumours

First-line treatment: In England, patients with unresectable non-squamous NSCLC and good PS are currently initially treated with platinum-based chemotherapy (NICE, 2011); however, beyond first-line, there is a limited range of treatments available. In England, approximately 23% of patients with non-squamous stage IIIb/IV NSCLC are treated with a first-line therapy (approximately 2,832 patients) (NICE, 2010d), and this therapy usually fails in 50% of these patients (approximately 1,413 patients) (Sculier and Moro-Sibilot, 2009).

Second-line treatment: In the second-line setting, for patients who are EGFR mutation-negative/unknown, the current UK standard of care is docetaxel chemotherapy, although this has limited efficacy and high toxicity (Borghaei et al., 2015; Brahmer et al., 2015). Erlotinib (an EGFR-tyrosine kinase inhibitor [TKI]) offers an alternative treatment option in the second-line setting for EGFR-unknown patients only (ID620) (NICE, 2015g). However, there is limited use of erlotinib in UK clinical practice, and its use continues to decline (Figure 3) (Bristol-Myers Squibb, 2015d). For some patients with adenocarcinoma, which composes approximately 90% of non-squamous NSCLC, nintedanib in combination with docetaxel has been approved by NICE (NICE, 2015f). However, although the safety profile of nintedanib is acceptable, the combination treatment still harbours the toxicity of docetaxel. Further, many patients are not eligible for its use owing to its numerous contraindications (European Medicines Agency, 2015).

Third-line treatment: After two prior therapies, BSC can be used, although it is not recommended by NICE in the third-line setting. Docetaxel monotherapy could also be used in third-line patients; however, as erlotinib is no longer recommended in second-line treatment, docetaxel (as monotherapy or in combination with nintedanib) is now the only second-line option and, as a result, will imminently no longer be used in the third-line. Erlotinib may be used if not received previously in patients with EGFR-unknown mutation status (NICE, 2015g).

3.2.2 EGFR-positive tumours

Targeted agents are available for patients with EGFR mutations.

First-line treatment: NICE recommends the use of the EGFR inhibitors erlotinib, afatinib and gefitinib in this context (NICE, 2010c; NICE, 2012c; NICE, 2014b). However, approximately only 10% of patients with NSCLC have the activating EGFR mutation (Lung Cancer Profiles, 2015).

Second-line treatment: After one prior therapy, patients with EGFR-positive tumours may receive platinum-based chemotherapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane) (NICE, 2015h). If no previous EGFR-TKI therapy has been used because of delayed confirmation of mutation status, afatinib or erlotinib may be given second-line (NICE, 2015h). In patients for whom platinum-based chemotherapy is inappropriate, patients may receive single-agent gemcitabine or vinorelbine (NICE, 2015e).

Third-line treatment: Nintedanib in combination with docetaxel may be used in this patient population (NICE, 2015b). Following the use of an EGFR-TKI and one other therapy, docetaxel monotherapy and BSC may be used, although these are not recommended by NICE in the third-line setting.

3.2.3 ALK-positive tumours

The ALK mutation occurs in only 5% of patients with NSCLC (Lung Cancer Profiles, 2015)

First-line treatment: As with ALK-negative patients, those with ALK-positive tumours may receive platinum-based chemotherapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane) (NICE, 2015h).

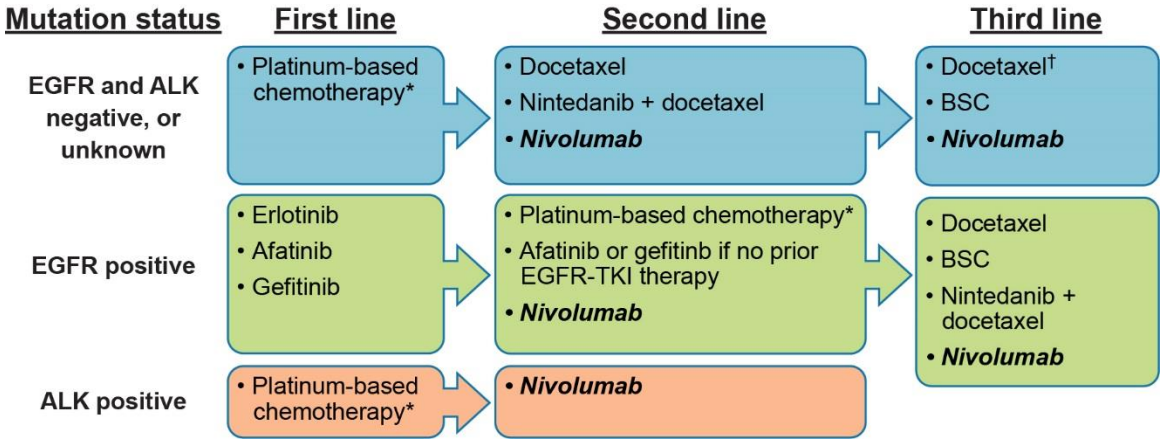
Second-line treatment: Crizotinib is currently available as a second-line treatment in ALK-positive patients through the Cancer Drugs Fund (currently set to continue until end of March 2016)(NICE, 2013b).

Third-line treatment: Ceritinib received a Food and Drug Administration (FDA) and conditional EMA approval for NSCLC treated with or intolerant to crizotinib (NICE, 2016, expected).

These treatments are representative of the standard clinical pathway of care in the NHS (and as listed in the final scope). However, not all are relevant comparators to nivolumab, as previously discussed in Table 1, Section 1.4 and illustrated in Figure 2.

To address the unmet need in this patient group, nivolumab will provide a treatment option for previously treated adults with locally advanced or metastatic non-squamous NSCLC (Figure 8).

Figure 8: Overview of treatments in the UK for unresectable locally advanced or metastatic non-squamous NSCLC with the introduction of nivolumab



Abbreviations: ALK = Anaplastic Lymphoma Kinase; BSC = Best Supportive Care; EGFR = Epidermal Growth Factor Receptor; NSCLC = Non-Small Cell Lung Cancer; TKI = Tyrosine Kinase Inhibitor; UK = United Kingdom

* Platinum-based chemotherapy + gemcitabine, vinorelbine, pemetrexed or a taxane.

† As erlotinib is no longer recommended in second-line for patients with EGFR mutation-negative status, docetaxel (as monotherapy or in combination with nintedanib) is the only second-line option and, as a result, will no longer be used in the third-line.

3.3 Life expectancy, prevalence and incidence of the disease

3.3.1 Population estimates

It is estimated that 27,300 patients will be diagnosed with NSCLC in 2016, of whom approximately 19,138 are expected to be diagnosed with locally advanced or metastatic NSCLC (Health and Social Care Information Centre, 2014). Most patients with NSCLC (approximately 64%) have a histology that is non-squamous in origin (Powell et al., 2013), and it is estimated that approximately 23% of patients with non-squamous stage IIIb/IV NSCLC are treated with a first-line therapy (approximately 2,817 patients) (NICE, 2010d). First-line therapy usually fails in 50% of these patients (approximately 1,413 individuals) (Sculier and Moro-Sibilot, 2009), and these are the patients who are potentially eligible for second-line treatment with nivolumab.

Taking the above considerations into account, alongside the anticipated market share of nivolumab, we estimate the likely number of patients in England and Wales with non-squamous NSCLC who may be eligible for second-line treatment with nivolumab to be approximately 1,413 in 2016.

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

3.3.2 Life expectancy

Patients with advanced or metastatic non-squamous NSCLC have limited life expectancy. Although data for English-only patients with non-squamous NSCLC are not available, in 2013 the median survival for all patients with stage III NSCLC in England and Wales was 9.6 months, whereas the median survival for patients with stage IV NSCLC was only 3.3zmonths (Health and Social Care Information Centre, 2014). 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, 2015).

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:

- NICE pathway: lung cancer. March 2012. http://pathways.nice.org.uk/pathways/lung-cancer (NICE, 2008)
- Lung cancer: diagnosis and management (Clinical Guideline CG121). April 2011. http://www.nice.org.uk/guidance/cg121 (NICE, 2011)
- Quality Standard No. 17. Quality standard for lung cancer. March 2012. http://www.nice.org.uk/guidance/qs17 (NICE, 2012d)
- Lung cancer (non-small cell, advanced, recurrent, PD-L1 positive) - pembrolizumab (after platinum chemotherapy) [ID840]. In progress (expected January 2017). https://www.nice.org.uk/guidance/indevelopment/gid-ta10010 (NICE, In progress)

Related NICE technology appraisals:

- TA124: Pemetrexed for the treatment of non-small-cell lung cancer. August 2007. http://www.nice.org.uk/guidance/ta124 (NICE, 2007)
- TA162: Erlotinib for the treatment of non-small-cell lung cancer. November 2008. http://www.nice.org.uk/guidance/ta162 (NICE, 2008)
- 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, 2010c)
- 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, 2014b)
- Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer. (ID438). July 2015. https://www.nice.org.uk/guidance/indevelopment/gid-tag449 (NICE, 2015f)
- Lung cancer (non-small cell) - erlotinib & gefitinib (post-chemotherapy) (rev TA162, TA175) (ID620). 2015. 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, 2015g)
- In development: Lung cancer (non-small-cell, anaplastic lymphoma kinase positive, previously treated) - ceritinib (ID729). Expected January 2016. https://www.nice.org.uk/guidance/indevelopment/gid-tag478 (NICE, 2016, expected)

3.5 Issues relating to current clinical practice

In the UK, NSCLC is often diagnosed late in the progression of the disease; the median age at diagnosis in the UK is 74 years (Health and Social Care Information Centre, 2014). As a consequence, by the time of their diagnosis, these patients have high levels of advanced disease with poor prognosis; they also often have a large number of comorbidities. As a result, many patients in the UK are unsuitable for systemic treatment.

Existing treatments (e.g. platinum-based chemotherapy in first-line) are associated with high toxicity and limited efficacy, meaning the mortality rate in such patients is high, and long-term survival, with a concomitant good HRQoL, is not considered achievable with current treatments.

All patients receive BSC to help control their symptoms, regardless of whether they receive systemic therapy. Best supportive care encompasses the range of treatment options and is provided based on individual need and may include analgesia, antiemetics and a range of other palliative interventions.

Current treatment pathways require the testing of driver mutation status to establish EGFR and ALK status. NICE (2013a) recommend five different tests for detecting EGFR status in NSCLC, based on biopsy or cytology samples, although the relative predictive accuracy of different tests could not reliably be established and the committee recognised that test accuracy is dependent on the quality of the tissue samples available.

Currently, turnaround times for EGFR mutation testing are from 3 to 7 days, being dependent on the test used and factors such as transportation of samples and laboratory set up (NICE, 2013a). Generally, laboratories perform ALK testing either in parallel with EGFR testing or in a sequential manner. While sequential testing is more cost-effective, parallel testing allows for more rapid turnaround of results (Khoo et al., 2015).

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 057 study evaluating the efficacy, safety and tolerability of nivolumab versus docetaxel in patients with advanced or metastatic previously treated non-squamous NSCLC.
- CheckMate 057 was stopped early, as the assessment conducted by the independent DMC concluded that nivolumab had met its endpoint demonstrating superior OS in patients treated with nivolumab compared with patients treated with docetaxel.
- CheckMate 057 met its primary objective, demonstrating a significant improvement in OS with nivolumab versus docetaxel in patients with advanced non-squamous NSCLC at the interim analysis, based on 413 reported deaths[7]:
  - 1-year OS: 51% (95% CI: 45, 56) versus 39% (95% CI: 33, 45) for docetaxel[8]
  - 27% reduction in risk of death with nivolumab (HR: 0.73; 95% CI: 0.59, 0.89; p = 0.002)
  - Median OS: 12.2 months (95% CI: 9.7, 15.0) versus 9.4 months for docetaxel (95% CI: 8.1, 10.7)
- With additional follow-up,[9] the OS rate at 18 months was 39% (95% CI: 34, 45) with nivolumab versus 23% (95% CI: 19, 28) with docetaxel, and there was a 28% reduction in risk of death (HR: 0.72; 95% CI: 0.60, 0.88; p = 0.0009).
- The study demonstrated statistically significant superiority of nivolumab over docetaxel for objective response rate (ORR):
  - ORR: 19% (95% CI: 14.8, 24.2) for nivolumab and 12% (95% CI: 8.8, 16.8) for docetaxel (p = 0.02)
- One-year PFS was higher for nivolumab (19%) than for docetaxel (8%). Although median PFS did not favour nivolumab (2.3 months [95% CI: 2.2, 3.3] vs. 4.2 months [95% CI: 3.5, 4.9] for docetaxel), the nivolumab and docetaxel KM curves showed markedly different profiles (Figure 13), and the overall HR for PFS or death favoured nivolumab (HR: 0.92; 95% CI: 0.77, 1.11; p = 0.39).
- In high PD-L1 expressors, superior efficacy with nivolumab was observed for all endpoints (OS, PFS, ORR) regardless of expression level (≥ 1%, ≥ 5% or ≥ 10%—the values representing the number of cells in a tissue section of 100 or more tumour cells staining for PD-L1, irrespective of staining level). In low expressors, clinical efficacy for nivolumab was similar to that for docetaxel, and tolerability was favourable, regardless of expression level (< 1%, < 5% or < 10%).
- Further, the OS benefit observed for nivolumab compared with docetaxel in the whole study population was observed when a sub-group analysis examined patients known to have EGFR mutation-negative/unknown status. No meaningful differences in median PFS were observed across the pre-defined EGFR mutation status sub-groups. A statistically significant benefit was not observed in patients

[7] Results from the interim analysis are based on a minimum follow-up of 13.2 months; however, this analysis is sometimes termed the "12-month interim analysis" for simplicity.

[8] The 1-year OS for docetaxel is higher in this study than in other studies (e.g. Checkmate 017) (Brahmer et al., 2015).

[9] Updated efficacy results with additional follow-up are based on a minimum follow-up of 17.1 months; however, this analysis is sometimes termed the "18-month updated analysis" for simplicity.

with EGFR mutation-positive status; however, the CIs in this sub-group were wide owing to its small size, and the study was not powered to identify significant differences in this sub-group. Further, nivolumab would not be used in this population in clinical practice.

- The results of the CheckMate 057 study demonstrate that nivolumab offers significantly superior and meaningful clinical efficacy and a favourable safety profile over docetaxel, providing an effective option for previously treated adults with locally advanced or metastatic non-squamous NSCLC in an area of high unmet medical need for treatments.
- Further evidence is provided from two uncontrolled studies, CheckMate 153 and CheckMate 003:
    - CheckMate 153 – a Phase IIIb/IV, open-label study in previously treated patients with locally advanced or metastatic non-squamous and squamous NSCLC and PS0-2.
        - At the time of submission of this dossier to NICE, 147 patients had been treated for 1 year and randomised into cohorts A or B.
        - BMS plan to analyse the results of CheckMate 153 in Q2-Q3 of 2016, and it is estimated that approximately 100 patients who have been randomised into cohorts A or B will have a minimum of 6 months of post-randomisation follow-up available for this analysis.
    - CheckMate 003 – a dose-escalation expansion cohort Phase Ib study in a heavily pre-treated patient population with advanced NSCLC with long-term (4-year) data
    - Results from these two uncontrolled studies demonstrated that the efficacy and safety of nivolumab was consistent to that observed in the pivotal study. CheckMate 153 also included data for patients with PS 2.
- The current standard of care in the UK for second-line non-squamous NSCLC is docetaxel, and this was used as the comparator in the pivotal study. Docetaxel is associated with limited efficacy and poor tolerability; hence, there is a significant unmet medical need for treatments for this group of patients. Nintedanib in combination with docetaxel is recommended by NICE in patients with adenocarcinoma, but market research suggests that use is currently low in the UK; it showed a reduction in the risk of progression or death of 21% versus docetaxel in its pivotal study (HR: 0.79; 95% CI" 0.68, 0.92; p = 0.0019) (European Medicines Agency, 2015). However, although the safety profile of nintedanib is acceptable, the combination treatment still harbours the toxicity of docetaxel. Further, many patients are not eligible for its use because of its numerous contraindications (European Medicines Agency, 2015).
- Indirect treatment comparisons (ITCs) were undertaken to allow comparisons of nivolumab with (1) nintedanib in combination with docetaxel and (2) BSC. Because of the paucity of available evidence and heterogeneity among the studies, the following results should be interpreted with caution.
    - When all non-squamous patients were considered, the results suggested an OS benefit for nivolumab over nintedanib, although this did not reach statistical significance (HR: 0.85; 95% CI: 0.65, 1.11; p = 0.23). No significant differences were observed in PFS between nivolumab and nintedanib in combination with docetaxel in the all-comers population (HR: 1.17; 95% CI: 0.89, 1.55; p = 0.27). Similar results were seen in the sub-group of patients who were EGFR mutation-negative/unknown.

- Statistically significant benefit in OS with nivolumab was observed against BSC in the entire population group, suggesting a 37% reduction in the risk of death (HR: 0.63; 95% CI: 0.44, 0.91; p = 0.01). Similar results were seen in the sub-group of patients who were EGFR mutation-negative/unknown.

4.1 Identification and selection of relevant studies

4.1.1 Search strategy

A full systematic review has previously been conducted by Liverpool Reviews and Implementation Group (LRiG) as part of the multiple technology appraisal (MTA) by NICE for erlotinib and gefitinib (review of TA162 and TA175; currently ID620) (NICE, 2015g). This review assessed the efficacy, safety and tolerability of erlotinib and gefitinib in an NSCLC patient population whose disease had progressed following prior chemotherapy. As the decision problem for this previous MTA was similar to the decision problem for this single technology appraisal (STA) of nivolumab in terms of population, interventions, comparators and outcomes, a decision was made to update and expand this previous systematic 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. Studies were selected relevant to the NICE decision problem (i.e. non-squamous only) as discussed below. Searches of the electronic databases (Table 5) and relevant conference proceedings (Table 6) were made up to 27 October 2015; conferences were searched for the last 4 years (2012, 2013, 2014 and 2015). The full search strategy is given in Appendix 5.

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 (CADTH, 2014; IQWIG, 2008; NICE, 2015a; NICE, 2015c)	MEDLINE® MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL)	Original review: For erlotinib and gefitinib: 1 January 2013 to 27 October 2015 For all other interventions not included in the MTA of erlotinib and gefitinib: database inception to 27 October 2015

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

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
	2015	http://www.europeancancercongress.org/Scientific-Programme/Abstract-search
World Conference on Lung Cancer (WCLC)*	2011	http://journals.lww.com/jto/toc/2011/06001
	2013	http://www.2013worldlungcancer.org/
	2015	http://wclc2015.iaslc.org/wp-content/uploads/2015/09/WCLC-2015-Abstract-Book1.pdf

* WCLC is held every 2 years.

Abstracts of citations identified through the searches were reviewed for inclusion based on title and abstract alone (see Section 4.1.2). Full-text copies of studies that potentially met the inclusion criteria were obtained. Full-text articles 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, the results of which can be found in Appendix 6.

4.1.2 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 Section 1.4, is a patient population defined as adult patients with locally advanced or metastatic non-squamous NSCLC after prior treatment with chemotherapy. To align with the NICE decision problem for this STA, all included studies were screened to only include studies that recruited patients with non-squamous NSCLC or studies with a mixed population with a sub-group analysis of patients with non-squamous NSCLC. Thus, comparators such as pemetrexed are presented in the inclusion criteria relating to the broad NSCLC population (Table 7), but are not included in the NICE decision problem limited to non-squamous NSCLC in Section 1.4, for which they are not relevant.

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

Table 7: Eligibility criteria used in clinical search strategy

	Criteria	Rationale
Inclusion criteria	Population • Age: adults (≥ 18 years) • Sex: 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 NICE decision problem for nivolumab in the treatment of NSCLC.
	Intervention • Nivolumab	Intervention was 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-based chemotherapy (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 non-squamous population, the comparators we deemed relevant were: • Docetaxel • Nintedanib in combination with docetaxel • 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.

	Criteria	Rationale
	Publication timeframe for literature searches • Erlotinib and gefitinib: 1 January 2013 to 27 October 2015 • Other included interventions: database inception to 27 October 2015 Publication timeframe for conference searching • ASCO: 2012, 2013, 2014 and 2015 • ESMO: 2012, 2013, 2014 and 2015 • WCLC: 2011, 2013 and 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 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 sub-group data for adult patients are not reported • Treatment-naïve 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.

	Criteria	Rationale
	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 the included comparators (e.g. erlotinib) with the combination of the included comparator + a non-included comparator (e.g. erlotinib + bevacizumab)	These comparators are not relevant to the decision problem. Studies assessing the included intervention with the combination of included + a non-included intervention will not contribute to the analysis due to lack of a common comparator.
	Excluded study designs • 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 non-squamous NSCLC	Study population was further restricted to include patients with non-squamous NSCLC only.	Patient population was restricted to non-squamous histology only in line with the NICE decision problem and the anticipated new marketing authorisation for nivolumab.

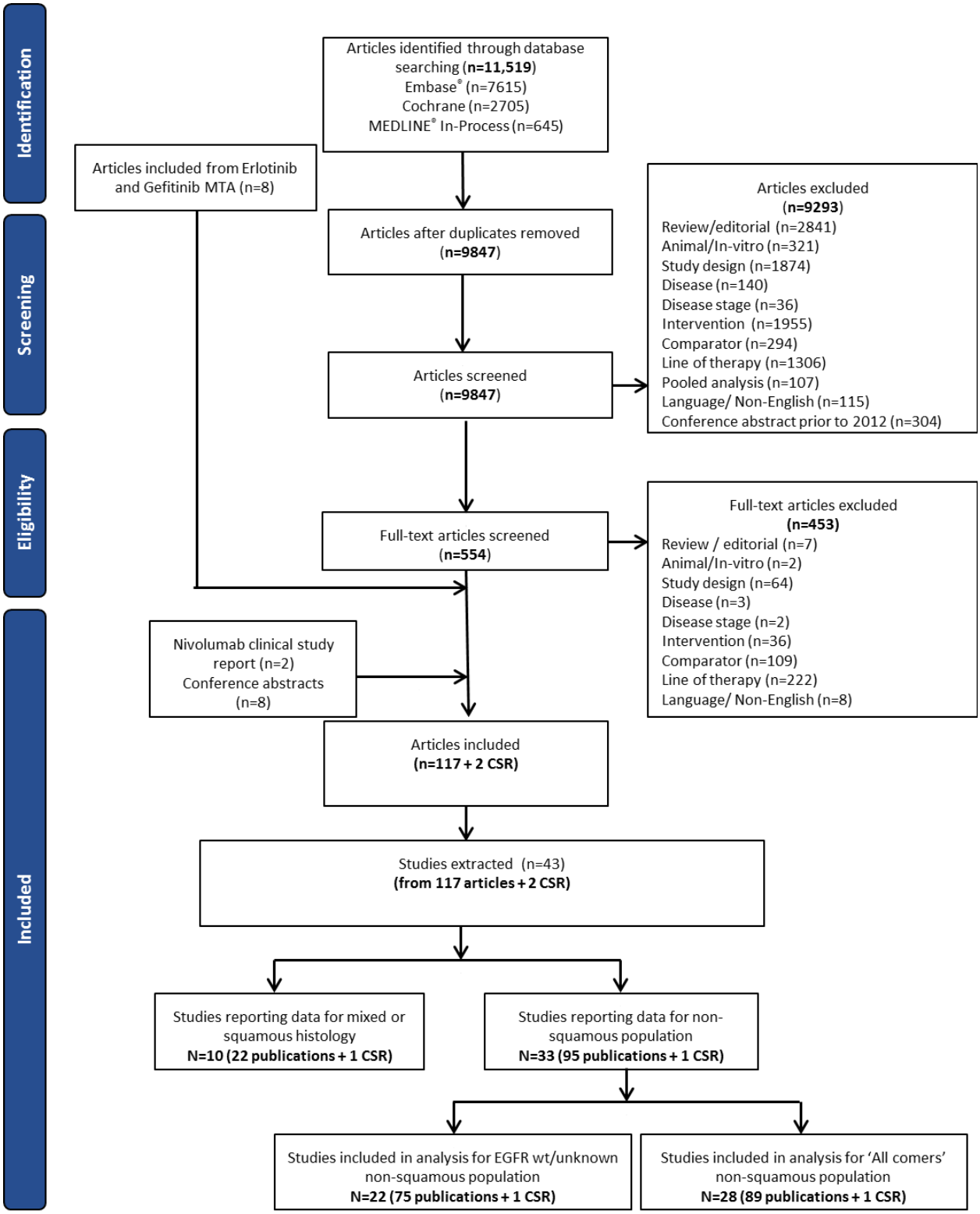
Abbreviations: AE = Adverse Event; ASCO = American Society of Clinical Oncology; BSC = Best Supportive Care; ESMO = European Society for Medical Oncology; MTA = Multiple Technology Appraisal; NICE = National Institute for Health and Care Excellence; NSCLC = Non-Small Cell Lung Cancer; RCT = Randomised Controlled Trial; WCLC = World Conference on Lung Cancer

* Due to the broad inclusion criteria of NSCLC (regardless of histology), comparators relevant to both squamous and non-squamous patients were included.

† BSC includes no treatment, observation alone or any other criteria defined by the authors. 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.

A Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the systematic review is presented in Figure 9.

Figure 9: PRISMA flow diagram of the systematic review process



As shown in the PRISMA flow diagram, 43 studies (reported in 117 publications and 2 clinical study reports [CSRs]) met the broader inclusion/exclusion criteria of the systematic review, which included patients with both squamous and non-squamous histology.

Of these, 33 studies provided data explicitly for previously treated patients with non-squamous NSCLC. Only one of these studies provided data for nivolumab in patients with non-squamous NSCLC (CheckMate 057), and two studies provided data for the comparators (docetaxel and nintedanib in combination with docetaxel) in previously treated patients with non-squamous NSCLC. A further 10 studies included either squamous patients or patients with mixed histology but with no sub-group data for the non-squamous population; these studies were therefore not considered relevant to the decision problem.

A full list of studies relevant to the decision problem is given in Table 9. A full list of studies included in the systematic review but not relevant to the decision problem is given in Appendix 7.12. 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 7.13. A full list of excluded studies is given in Appendix 2.1. A summary of the methodology of RCTs reporting data for the previously treated non-squamous NSCLC population is listed in Table 8.

In UK clinical practice, the most relevant comparator to this patient population is the standard of care, docetaxel; therefore, this is the therapy that is mostly likely to be displaced. Nintedanib in combination with docetaxel is recommended by NICE in patients with adenocarcinoma (which constituted 90% of patients in the CheckMate 057 study), but market research currently suggests that use is currently low in the UK; it showed a reduction in the risk of progression or death of 21% versus docetaxel in its pivotal study (HR: 0.79; 95% CI: 0.68, 0.92; p = 0.0019) (European Medicines Agency, 2015). As such, the combination therapy is included in this submission and is compared with nivolumab via an ITC. However, although the safety profile of nintedanib is acceptable, the combination treatment still harbours the toxicity of docetaxel. Further, many patients are not eligible for its use due to its numerous contraindications (European Medicines Agency, 2015).

Although BSC has been included as a relevant comparator by NICE, there is a paucity of data available for use of BSC alone in previously treated patients with locally advanced or metastatic non-squamous NSCLC, which precludes any comparisons (Thatcher et al., 2005).

Although many of the above comparisons with treatments stated in the NICE final scope are appropriate or justified by the anticipated nivolumab label, these are not possible due to the small number of patients in CheckMate 057, particularly in EGFR- and ALK-positive groups, as well as limited or incomparable data for these mutation-positive groups in the literature.

Evidence for a comparison of nivolumab with docetaxel can be derived from CheckMate 057; comparison of nivolumab with nintedanib in combination with docetaxel and BSC requires an ITC. The systematic review described within this section includes both nintedanib in combination with docetaxel and BSC. The paucity of data for these treatments is addressed in further detail later in this section.

Table 8: Summary of methodology of randomised controlled trials reporting data for previously treated non-squamous NSCLC population

Study ID (Acronym)	Primary reference	Intervention/ comparators (n)	Patient population
Studies connected in networks of both EGFR mutation-negative/unknown and 'all-comers' NSCLC			
Juan 2015	Juan et al. (2015)	Docetaxel + Erlotinib (34) Erlotinib (36)	Age ≥18 years Cytologically or histologically confirmed advanced NSCLC, stage IIIB or stage IV ECOG PS 0-2 Disease progression during previous chemotherapy treatment
DELTA	Kawaguchi et al. (2014)	Docetaxel (151) Erlotinib (150)	Age ≥20 years Pathologically or histologically proven stage IIIB or IV NSCLC Failed at least one platinum agent • ECOG PS 0-2
Li 2014	Li et al. (2014)	Erlotinib (61) Pemetrexed (62)	Age 18 to 75 years ECOG PS of 0 to 2 Pathologically or cytologically confirmed stage IIIB to IV lung adenocarcinoma 1 prior platinum-based chemotherapy Life expectancy of ≥ 3 months.
LUME-Lung 1		Docetaxel (659) Docetaxel + Nintedanib (655)	ECOG PS of 0 to 1 At least one measurable target lesion One previous first-line chemotherapy regimen
Dong 2014	Dong et al. (2014)	Docetaxel (55) Pemetrexed (54)	Age ≥ 18 years ECOG score < 3 Adenocarcinoma: Grade III or IV carcinoma EGFR-TKI failure No evidence of severe hepatic and renal dysfunction

Study ID (Acronym)	Primary reference	Intervention/ comparators (n)	Patient population
Dittrich 2014	Dittrich et al. (2014)	Erlotinib + Pemetrexed (79) Pemetrexed (83)	Age ≥ 18 years NSCLC (Stage IIIA, IIIB, or IV) Failed 1 prior platinum-based chemotherapy regimen ECOG PS 0-2 Measurable lesion ≥ 1 Prior radiation therapy to < 25% of the bone marrow
PROSE	Gregorc et al. (2014)	Docetaxel/Pemetrexed (142) Erlotinib (143)	Age 18 years Histologically or cytologically documented advanced non-small-cell lung cancer (stage IIIB or IV) ECOG PS 0-2 One previous platinum-based chemotherapy regimen At least one measurable lesion
NVALT-10	Aerts et al. (2013)	Erlotinib (115) Erlotinib + Docetaxel/Pemetrexed (116)	Age ≥18 years ECOG PS 0-2 Pathologically confirmed locally advanced or metastatic NSCLC progressed First-line platinum-based chemotherapy
Lee 2013	Lee et al. (2013)	Erlotinib (82) Erlotinib + Pemetrexed (78) Pemetrexed (80)	Non-smoking adults Histological or cytological diagnosis of locally advanced or metastatic non-squamous NSCLC Failed only one prior chemotherapy regimen ECOG PS 0-2 Adequate organ function and life expectancy ≥ 8 weeks
TAILOR	Garassino et al. (2013)	Docetaxel (110) Erlotinib (112)	Histological or cytological confirmed NSCLC Exposed to platinum-based chemotherapy ECOG PS ≤ 2 No previous treatment with taxanes or anti-EGFR drugs
PROFILE 1007	Shaw et al. (2013)	Crizotinib (173) Docetaxel/Pemetrexed (174)	Age ≥ 18 years One prior platinum-based chemotherapy Locally advanced or metastatic non-small cell lung cancer ECOG PS 0, 1, or 2
Li 2013	Li et al. (2013)	Erlotinib + Pemetrexed (52) Pemetrexed (27)	Advanced NSCLC eligible for second-line chemotherapy

Study ID (Acronym)	Primary reference	Intervention/ comparators (n)	Patient population
GOIRC 02-2006	Ardizzoni et al. (2012)	Pemetrexed + Carboplatin (119) Pemetrexed (120)	Age ≥ 18 years ECOG PS ≤ 2 Histologically or cytologically confirmed NSCLC with stage IIIB or IV Disease progression after only one first-line treatment with platinum-based chemotherapy Presence of at least one measurable target lesion
KCSG-LU08-01	Sun et al. (2012)	Gefitinib (71) Pemetrexed (70)	Age ≥ 18 years Histologically or cytologically confirmed pulmonary adenocarcinoma Only 1 previous platinum- based chemotherapy regimen Never-smoker (a total of 100 cigarettes in their lifetime) ECOG PS 0-2 No prior EGFR-TKI or pemetrexed treatment, and symptomatic or uncontrolled brain metastases
LUX-Lung 1	Miller et al. (2012)	Afatinib (390) BSC (195)	Age ≥ 18 years Pathologically confirmed stage IIIB (with pleural effusion) or stage IV adenocarcinoma Failed one or two prior lines of chemotherapy (including adjuvant chemotherapy) ECOG PS 0-2 and a life expectancy of 3 months or longer
TITAN	Ciuleanu et al. (2012)	Docetaxel/Pemetrexed (221) Erlotinib (203)	Age at least 18 years ECOG PS 0-2 Disease progression during the four cycles of first-line standard platinum-based chemotherapy Previous chemotherapy or systemic antineoplastic therapy other than the permitted platinum-based regimens
ATOM 019	Belvedere et al. (2011)	Docetaxel (25) Docetaxel + Oxaliplatin (25)	Age ≥ 18 and < 70 years ECOG PS 0 or 1 Disease progression after one prior chemotherapy Histologically or cytologically proven, stage IIIB (wet) or IV NSCLC

Study ID (Acronym)	Primary reference	Intervention/ comparators (n)	Patient population
ISTANA	Lee et al. (2010)	Docetaxel (79) Gefitinib (82)	Age ≥ 18 years WHO PS 0-2 Histologically or cytologically confirmed NSCLC with stage IIIB or IV disease One previous platinum-based chemotherapy regimen Progressive or recurrent disease following previous chemotherapy
Kim 2015	Kim et al. (2015)	Gefitinib (48) Pemetrexed (47)	Age ≥ 18 years ECOG PS ≤ 2 Histologically- or cytologically proven advanced (stage IIIB or IV) or recurrent NSCLC Disease progression after first-line or second-line chemotherapy
CTONG0806	Zhou et al. (2014)	Gefitinib (81) Pemetrexed (80)	Histologically or cytologically confirmed stage IIIB or IV NSCLC without EGFR mutations in exons 18–21 in tumour samples Failed at least one platinum-based chemotherapy regimen
ISEL	Thatcher et al. (2005)	BSC (563) Gefitinib + BSC (1129)	Age ≥ 18 years WHO PS 0-3 Histologically or cytologically proven, locally advanced or metastatic NSCLC At least one previous platinum-based chemotherapy regimen
CheckMate 057	Borghaei et al. (2015)	Nivolumab (292) Docetaxel (290)	Age ≥ 18 years Stage IIIB/Stage IV or recurrent or progressive non-squamous NSCLC ECOG PS 0-1 Failed at least one prior platinum-based doublet chemotherapy regimen
Studies connected in networks of 'all-comers' NSQ NSCLC			
GFPC 10.02	Auliac et al. (2014)	Docetaxel (76) Docetaxel + Erlotinib (75)	Age 18 years or more PS 0, 1 or 2 Cytologically or histologically proven stage IV or IIIB NSCLC First-line cisplatin-based chemotherapy

Study ID (Acronym)	Primary reference	Intervention/ comparators (n)	Patient population
WJOG 5108L	Katakami et al. (2014)	Erlotinib (280) Gefitinib (279)	Age ≥ 20 years Stage IIIB/IV lung adenocarcinoma Previously treated with at least one chemotherapy regimen ECOG PS 0-2
Li 2012	Li et al. (2012)	Docetaxel (102) Pemetrexed (106)	Age 18 to 75 years Histological or cytological confirmation of NSCLC with stage IIIB or IV Karnofsky PS score ≥70 Expected survival time ≥ 3 months Only one prior chemotherapy regimen for advanced disease At least one objective measurable lesion disease with the maximum diameter ≥ 10 mm
V-15-32	Maruyama et al. (2008)	Docetaxel (245) Gefitinib (245)	Age ≥20 years Histologically or cytologically confirmed NSCLC (stages IIIB to IV) Failure of prior treatment with one or two chemotherapy regimens (≥ 1 platinum-based regimen) Life expectancy of 3 months or greater WHO PS 0-2
Br.21	Shepherd et al. (2005)	Erlotinib (488) Placebo (243)	Age ≥ 18 years Stage IIIB or IV non-small cell lung cancer PS 0-3 One or two prior chemotherapy regimens and not be eligible for further chemotherapy
Kim 2012	Kim et al. (2012)	Erlotinib (48) Gefitinib (48)	Age ≥ 18 years Stage IIIB or IV NSCLC Failure of first-line chemotherapy WHO PS 0-2 Life expectancy: 12 weeks
Studies not connected in networks/not reporting outcomes of interest			
Gong 2013	Gong et al. (2013)	Pemetrexed (21) Pemetrexed (22)	Stage IV NSCLC Second-line therapy

Study ID (Acronym)	Primary reference	Intervention/ comparators (n)	Patient population
HORG	Karampeazis et al. (2013)	Erlotinib (179) Pemetrexed (178)	Patients Age < 65 years Stage IIIB (with pleural effusion) or stage IV NSCLC PS 0 -2 Disease progression after 1 or 2 chemotherapy lines Exposed to prior platinum-based regimen
Shi 2013	Shi et al. (2013)	Cisplatin + Pemetrexed (23) Oxaliplatin + Pemetrexed (22)	Age 18–75 years Locally advanced or metastatic lung adenocarcinoma Failed to respond to Erlotinib as second-line ECOG PS 0-2
JMID	Sun et al. (2013)	Docetaxel (104) Pemetrexed (107)	Age ≥18 years Stage III–IV NSCLC ECOG PS 0-2
NVALT-7	Ardizzoni et al. (2012)	Pemetrexed + Carboplatin (119) Pemetrexed (121)	Age ≥18 years Evidence of disease progression after cytotoxic treatment ECOG PS 0-2

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group; PS = Performance Status

4.2 List of relevant randomised controlled trials

Only one relevant randomised controlled trial (RCT) was identified in the clinical systematic review that evaluated nivolumab in a non-squamous NSCLC patient population; this was the CheckMate 057 study of nivolumab compared with docetaxel in patients with locally advanced or metastatic non-squamous NSCLC after one prior therapy. This is the only study relevant to the decision problem described in Section 1.4. The data presented in Sections 4.3 to 4.8 are from the CheckMate 057 study (Table 9) and are from both published and unpublished sources.

In April 2015, the independent DMC recommended early termination of the CheckMate 057 study on the basis of a pre-specified interim analysis; minimum follow-up was 13.2 months; however, this analysis may be termed the "12-month interim analysis" for simplicity. The interim analysis showed that OS among patients receiving nivolumab was superior to those receiving docetaxel. Planned enrolment was complete before the study was stopped.

Unless otherwise stated, the results presented in Sections 4.3 to 4.8 are from the interim analyses, which are based on a database lock of 18 March 2015 (Borghaei et al., 2015; Bristol-Myers Squibb, 2015b). Updated efficacy results with additional follow-up are also available for OS only, on the basis of data from a 2 July 2015 database lock (Borghaei et al., 2015; Horn et al., 2015). This updated analysis is based on a minimum follow-up of 17.1 months; however, it may be termed the "18-month analysis" for simplicity. Presentation of these follow-up results is clearly indicated throughout the dossier.

Table 9: List of relevant randomised controlled trials to the decision problem

Study no. (acronym)	**CheckMate 057 (CA209-057)**
Phase	Phase III
Population	Adult patients with non-squamous NSCLC whose disease has progressed during or after one prior platinum doublet-based chemotherapy regimen
Intervention	Nivolumab 3 mg/kg every 2 weeks until disease progression
Comparator	Docetaxel 75 mg/m² every 3 weeks until disease progression
References	**Primary reference:** Borghaei et al. (2015) **Secondary references:** Bristol-Myers Squibb (2015b); Horn et al. (2015)

Abbreviations: NSCLC = Non-Small Cell Lung Cancer

CheckMate 057 was the pivotal Phase III, global, randomised, open-label study of nivolumab monotherapy versus docetaxel in patients with advanced or metastatic non-squamous NSCLC whose disease had progressed during or after one prior platinum-based chemotherapy regimen (patients with a known driver mutation could have received a targeted therapy first-line followed by platinum-based therapy second-line). Docetaxel represents the current standard of care therapy upon progression from first-line therapy for patients with locally advanced or metastatic non-squamous NSCLC in the UK and, as such, is listed as a key comparator in the NICE decision problem (Section 1.4). The CheckMate 057 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 1.4), the main comparator for nivolumab in this patient population is docetaxel. CheckMate 057 provides clinical data for a direct comparison of nivolumab with docetaxel. A methodological overview of CheckMate 057 can be found in Table 10.

4.3.1 CheckMate 057

The pivotal CheckMate 057 study was a global Phase III, randomised, open-label study of nivolumab versus docetaxel in adult (≥ 18 years) patients with advanced or metastatic non-squamous NSCLC after failure of prior platinum doublet-based chemotherapy.

An open-label study design was selected because the management of similar AEs differs 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) in response to AEs and different drug-drug interaction profiles would have added complexity to any blinding strategy. Participants were randomised by an interactive voice response system to receive either nivolumab 3 mg/kg every 2 weeks (Q2W) (N = 292) or docetaxel 75 mg/m^2 every 3 weeks (Q3W) (N = 290) until disease progression, discontinuation due to toxicity or withdrawal of consent (Bristol-Myers Squibb, 2013a).

The primary endpoint of CheckMate 057 was overall survival (OS), defined as the time between the date of randomisation and the date of death (Bristol-Myers Squibb, 2015b). Overall survival 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 et al., 2007). Overall survival is also an outcome defined in NICE's decision problem (Section 1.4).

Progression-free survival was one of the secondary outcomes in this study and was defined as the time from randomisation to either (1) the date of the first documented tumour progression as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or (2) death due to any cause (Bristol-Myers Squibb, 2015b). PFS is also a well-established measure of efficacy in cancer studies (Lebwohl et al., 2009). Secondary endpoints also included confirmed investigator-assessed objective response rate (ORR) (defined as complete response [CR] or partial response [PR], divided by the number of patients). Other secondary endpoints included PD-L1 expression level as a predictive biomarker, HRQoL, safety and tolerability (Bristol-Myers Squibb, 2015b).

The parameters used to assess the efficacy and safety profile of nivolumab in CheckMate 057 are consistent with other studies exploring the use of other anti-cancer agents in this patient population.

On 18 March 2015, the clinical database was locked for the planned interim OS analysis based on 413 reported deaths (93% of the 443 deaths required for final analysis). The independent DMC reviewed the interim OS data in April 2015 and declared that the study had reached its primary endpoint, demonstrating superior OS in patients receiving nivolumab as compared with docetaxel.

Table 10: Comparative summary of methodology of the relevant randomised controlled trial

	CheckMate 057 (CA209-057)
Location	106 sites in 22 countries worldwide Argentina, Australia, Austria, Brazil, Canada, Chile, Czech Republic, France, Germany, Hong Kong, Hungary, Italy, Mexico, Norway, Peru, Poland, Romania, Russian Federation, Singapore, Spain, Switzerland and the United States
Study design (including method of randomisation)	Global, Phase III, randomised, open-label study Patients were randomised via interactive voice response system in a ratio of 1:1. Randomisation was stratified according to prior treatment with maintenance therapy vs. no maintenance and second-line therapy vs. third-line therapy.
Study drugs	Nivolumab at 3 mg/kg by intravenous infusion every 2 weeks (N = 292) Docetaxel at 75 mg/m^2 by intravenous infusion every 3 weeks (N = 290)
Overview of patient population	Adult (≥ 18 years) patients with metastatic or recurrent non-squamous NSCLC after failure of prior platinum doublet-based chemotherapy.
Detailed eligibility criteria for participants (inclusion criteria)	• Patients with histologically or cytologically documented locally advanced non-squamous NSCLC who presented with stage IIIb/ stage IV or recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease) • ECOG PS ≤ 1 • Patients must have had measurable disease by computed tomography or magnetic resonance imaging per RECIST 1.1 criteria; radiographic tumour assessment was 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. • Patients who received study therapy after acceptable prior therapy as specified below: ○ Patients who received study therapy as second-line of treatment: ▪ Patients must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. ▪ First-line therapy was defined as therapy used to treat advanced disease. Each subsequent line of therapy was preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity did not define the start of a new line of therapy. Patients must have received at least two cycles of platinum doublet-based chemotherapy before discontinuation for toxicity. Experimental therapies, when given as separate regimen, were considered as separate line of therapy. Maintenance

	CheckMate 057 (CA209-057)
	therapy following platinum doublet-based chemotherapy was not considered as a separate regimen of therapy and could include continuation of one or more of the agents used in the first-line therapy regimen or switch to another non–cross-resistant agent. The initiation of maintenance therapy required the lack of progressive disease with front-line therapy. Treatment given for locally advanced disease was not considered as a line of therapy for advanced disease. 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 who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease and who developed recurrent (local or metastatic) disease within 6 months of completing therapy were eligible. Adjuvant or neoadjuvant platinum-based chemotherapy (after surgery and/or radiation therapy) followed by recurrent or metastatic disease within 6 months of completing therapy was considered as first-line therapy for advanced disease. ○ Patients who received study therapy as third-line of treatment must have experienced disease recurrence or progression during or after a separate EGFR or ALK TKI regimen in addition to one prior platinum doublet-based chemotherapy regimen (regardless of order of administration). ▪ Patients who received an EGFR-TKI (erlotinib, gefitinib or experimental) in addition to a platinum doublet-based chemotherapy must have had a tumour with a known activating EGFR mutation. Patients with a tumour with EGFR mutation-negative/unknown status who received an EGFR-TKI after failure of a prior platinum doublet-based chemotherapy were excluded. ▪ Patients who received an ALK inhibitor (crizotinib or experimental) in addition to a platinum doublet-based chemotherapy must have had a tumour with a known ALK translocation. • 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 were to be excluded. Patients were eligible if CNS metastases had been treated and the patient 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. • Any serious or uncontrolled medical disorder or active infection with hepatitis or human immunodeficiency virus that may have been reactivated. • Other active malignancy requiring concurrent intervention. • Patients with previous malignancies (except non-melanoma skin cancers and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma or breast) were excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy was required or anticipated to be required during the study period.

	CheckMate 057 (CA209-057)
	• Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg 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. • 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. • All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. • Prior therapy with anti-tumour vaccines or other immuno-stimulatory anti-tumour agents. • 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 with docetaxel. • Patients with interstitial lung disease that was symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity. • Patients were to have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose 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 > 10 mg daily prednisone were permitted in the absence of active autoimmune disease. A brief (< 3 weeks) 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 > 10 mg 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 able to receive 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.

	CheckMate 057 (CA209-057)
Secondary outcomes (including scoring methods and timings of assessments)	• Investigator-assessed ORR (defined as the number of patients whose best confirmed objective response was either a confirmed complete or partial response, as determined by the investigator, divided by the number of randomised patients)* • Duration of response (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)† • Time to response (defined as the time from randomisation to the date of the first confirmed response. Time to response 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: ○ Disease-related symptom improvement rate by week 12 as measured by the Lung Cancer Symptom Scale (defined as the proportion of randomised patients who had 10 points or more decrease from baseline in Average Symptom Burden Index score at any time between randomisation and week 12)‖ ○ Overall health status using the EQ-5D Index and Visual Analogue Scale (exploratory outcome)** • Safety and tolerability (exploratory outcome), based on frequency of deaths, AEs, serious AEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, Select AEs and specific clinical laboratory assessments.†† • Immunogenicity of nivolumab (exploratory outcome), based on serum ADA and neutralising ADA response to nivolumab‡‡
Duration of follow-up	The enrolment period was from November 2012 until December 2013. The last patient was randomised on 31 December 2013, and the last patient last visit occurred on 5 February 2015, providing a minimum follow-up of 13.2 months (Bristol-Myers Squibb, 2015b).
Pre-planned sub-groups	• Efficacy (OS, ORR) based on pre-study PD-L1 expression level (Bristol-Myers Squibb, 2015b). ○ 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 (Borghaei et al., 2015). • Efficacy (OS, ORR and PFS) based on: ○ Age ○ Sex ○ Race ○ Region ○ Baseline ECOG PS

	CheckMate 057 (CA209-057)
	○ Smoking status ○ Presence of CNS metastases ○ Prior neoadjuvant vs. adjuvant treatment ○ Prior use of maintenance therapy ○ Line of therapy ○ EGFR mutation status ○ ALK translocation status ○ KRAS mutation status ○ Mesenchymal Epithelial Transition receptor status ○ Cell type ○ Time from diagnosis to randomisation ○ Time from completion of most recent regimen to randomisation

Source: Bristol-Myers Squibb (2015b)

Abbreviations: ADA = Adenosine Deaminase; AE = Adverse Event; CNS = Central Nervous System; CTLA-4 = Cytotoxic T-Lymphocyte-Associated Protein 4; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRQoL = Health-Related Quality of Life; NCI CTCAE = 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; RANK-L = Receptor Activator of Nuclear Factor Kappa-B Ligand; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1

* Best objective response (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. Duration of response will be evaluated for responders (i.e. patients with confirmed complete or partial response) 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-study 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.

ǁ The patient portion of the Lung Cancer Symptom Scale (LCSS) 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. The average symptom burden index score at each assessment was defined as the mean of the six symptom-specific questions of the LCSS.

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

†† Select AE analyses included incidence, time to onset and time to resolution. Analyses were conducted using the 30-day and 100-day safety window from day of last dose received. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. AEs and laboratory values were graded for severity using the NCI CTCAE Version 4.0.

‡‡ Baseline ADA-Positive Patient: A patient with baseline ADA-positive sample. ADA-Positive Patient: A patient with at least one ADA-positive sample at any time after initiation of treatment. Persistent Positive: ADA-positive sample at two or more sequential time points at least 16 weeks apart. Other Positive: Not persistent positive with ADA-negative sample in the last sampling time point. Only the Last Sample Positive: Not persistent positive with ADA-positive sample in the last sampling time point. Neutralising Positive: At least one ADA-positive sample with neutralising antibodies detected. ADA-Negative Patient: A patient with no ADA-positive sample after the initiation of treatment.

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

4.4.1 CheckMate 057

Table 11 gives a summary of the statistical analyses in CheckMate 057.

The primary objective of CheckMate 057 was to determine whether nivolumab compared with docetaxel improves survival in patients with non-squamous cell NSCLC after failure of prior platinum-based chemotherapy. As such, both survival outcomes of OS (primary outcome) and PFS (secondary outcome) were analysed using a two-sided, log-rank test, stratified by prior maintenance treatment and line of therapy (Borghaei et al., 2015).

On 18 March 2015, the clinical database was locked for the planned interim OS analysis based on 413 reported deaths. The independent DMC reviewed the interim OS data in April 2015 and declared that the study reached its primary endpoint, demonstrating superior OS in patients receiving nivolumab as compared with docetaxel.

We report the results of the interim analysis here, based on the database lock of 18 March 2015 (Borghaei et al., 2015) and a minimum follow-up of 13.2 months. However, this analysis may be termed the “12-month analysis” for simplicity. On the basis of data from the updated OS analysis (2 July 2015 database lock), efficacy results with additional follow-up are also available for OS only and reported here (Borghaei et al., 2015). These are based on a minimum follow-up of 17.1 months; however, this analysis may be termed the “18-month analysis” for simplicity.

Table 11: Summary of the statistical analyses of CheckMate 057

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals	Missing data
CheckMate 057 (CA209-057)	To determine whether nivolumab compared with docetaxel improves survival in patients with non-squamous cell NSCLC after failure of prior platinum-based chemotherapy	OS and PFS were analysed with the use of a two-sided log-rank test stratified according to prior maintenance treatment and line of therapy. HR and CI were estimated with the use of a stratified Cox proportional-hazards model. Survival curves and rates were estimated with the use of the Kaplan-Meier method. The rates of ORR were compared with the use of a stratified, two-sided Cochran-Mantel-Haenszel test. Non-conventional benefit (i.e. a reduction in the size or number [or both] of target lesions with simultaneous appearance of new lesions or initial progression followed by either tumour reduction or no further progression for at least two tumour assessments) in patients treated beyond initial progression was not included in response-based analyses (ORR or PFS). Median survival time along with 95% CI were constructed based on log-log transformed CI for the survivor function S(t). Rates at fixed time points (e.g. OS at 6 months) were derived from the Kaplan-Meier estimate, and the formula for corresponding CI was derived based on Greenwood variance derivation and on log-	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 442 deaths were observed among 574 randomised patients. One interim analysis of OS was planned after at least 380 deaths (86% of total deaths required for final analysis) had been observed. The 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 the immuno-oncology drug ipilimumab in recent Phase III studies. HRs between the nivolumab and docetaxel groups followed the following pattern: Months 0-4: HR = 1 Month 6: HR, 0.71; Month 12: HR, 0.59; Month 24: HR, 0.34; Month 36: HR, 0.15. Power at interim and updated OS analysis was 59% and 90%, respectively. The stopping	This study was conducted in accordance with Good Clinical Practice 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, for patients without documented progression or subsequent anti-cancer therapy, all available response designations contributed to the BOR determination. For PFS, patients who died without a reported prior progression were considered to have progressed on the date of their death. Patients who did not progress or die were censored on the date of their last evaluable tumour assessment. Patients who did not have any on-study tumour assessments and did not die were censored on the date they were randomised. Patients who started any subsequent anti-cancer therapy without a prior reported progression were censored at the last evaluable tumour assessment prior to or on the date of initiation of the	<u>Missing assessments and unevaluable designation:</u> 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. <u>PD-L1 expression missing:</u> Patients without an available tumour-biopsy specimen for PD-L1 evaluation were to be considered as PD-L1 expression missing. HRQoL: No imputation for missing data was performed.

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management and patient withdrawals	Missing data
		log transformation applied on the survivor function S(t). Unless otherwise specified, a stratified log-rank test was performed to test the comparison between time to event distributions (e.g. PFS and OS). P values from sensitivity analyses were for descriptive purpose only, and there were no multiplicity adjustments for these analyses. 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 Cochran-Mantel-Haenszel 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 Cochran-Mantel-Haenszel test using a two-sided, 5% α level.	boundaries at interim and updated analyses were derived based on the number of deaths using O'Brien and Fleming alpha spending function.	subsequent anti-cancer therapy. A clinical safety programme was used in this study to uniformly collect additional information on the following adverse events of clinical interest: endocrine, gastrointestinal, hepatic, pulmonary, renal and skin.	

Source: Bristol-Myers Squibb (2015b)

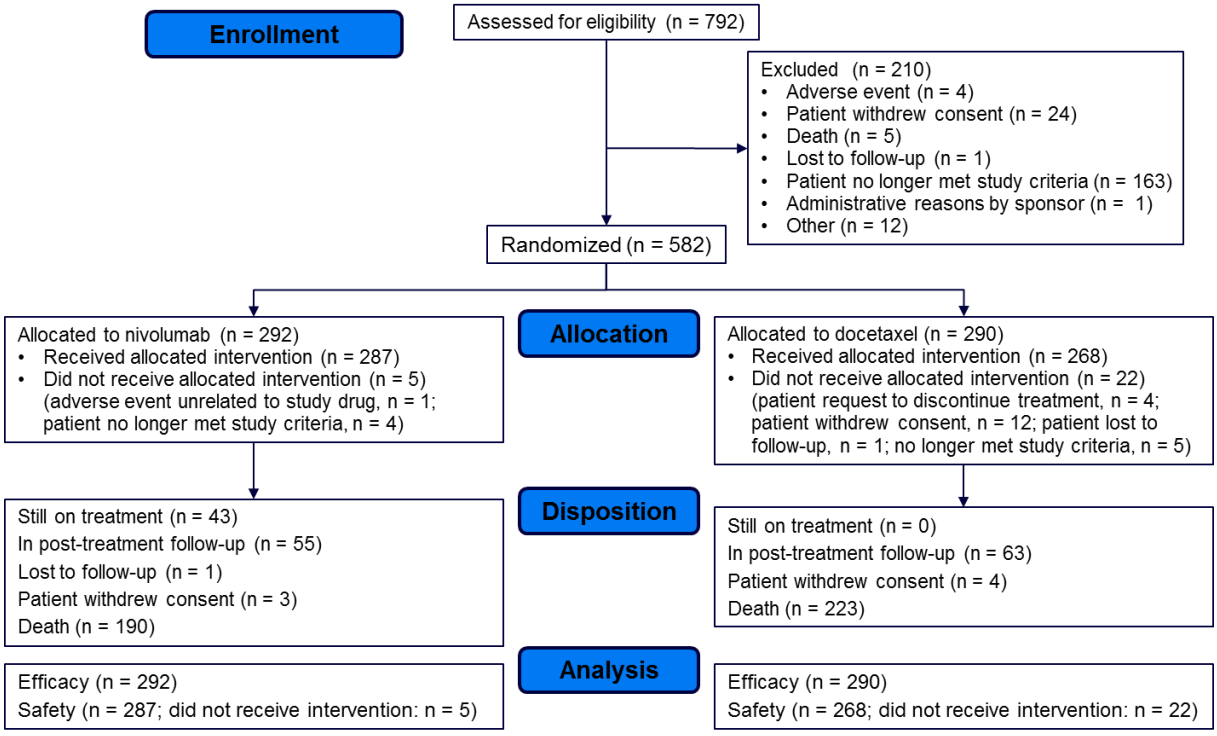
Abbreviations: BOR = Best Objective Response; CI = Confidence Interval; HR = Hazard Ratio; NE = Not Evaluable; NSCLC = Non-Small Cell Lung Cancer; ORR = Objective Response Rate; OS = Overall Survival; PD = progressive disease; PD-L1 = Programmed Death-Ligand 1; PFS = Progression-Free Survival

4.5 Participant flow in the relevant randomised controlled trials

4.5.1 CheckMate 057

The flow of participants through the CheckMate 057 study is presented via a Consolidated Standards of Reporting Trials (CONSORT) flow chart (Figure 10). A total of 582 patients were randomised to either nivolumab (N = 292) or docetaxel (N = 290) (the intention-to-treat population used for the efficacy analysis). Of these patients, 27 did not receive study medication (5 in the nivolumab treatment arm and 22 in the docetaxel treatment arm); therefore, the safety analysis (N = 555) excludes these patients (Borghaei et al., 2015).

Figure 10: CONSORT flow chart of patients in CheckMate 057



Source: Borghaei et al. (2015)

Abbreviations: CONSORT = Consolidated Standards of Reporting Trials

Subsequent therapy was received by some patients and was defined as therapy started on or after first dosing date of study drug (or date of randomisation if a patient was never treated) (Bristol-Myers Squibb, 2015b). In total, 52.1% of patients in the nivolumab arm and 60.3% in the docetaxel arm received subsequent therapy, which included radiotherapy and systemic therapy (Table 12). Patients could receive more than one subsequent therapy.

Table 12: Subsequent cancer therapy received in CheckMate 057

	Nivolumab (N = 292)	**Docetaxel (N = 290)**
Patients with any subsequent therapy,* n (%)	152 (52)‡	175 (60)‡
Subsequent radiotherapy, n (%)	76 (26)	87 (30)
Subsequent systemic therapy, n (%)	123 (42)	144 (50)
Chemotherapy, n (%)	110 (38)‡	100 (35)‡
Taxane	86 (29)	26 (9)
Antimetabolite	49 (17)	78 (27)
Platinum agents	24 (8)	22 (8)
Vinca alkaloids	15 (5)	29 (10)
Alkylating agents	2 (1)	1 (< 1)
Topoisomerase inhibitor	3 (1)	3 (1)
EGFR/ALK inhibitors, n (%)	32 (11)‡	(64 (22)‡
Erlotinib	19 (7)	50 (17)
Afatinib	10 (3)	7 (2)
Crizotinib	3 (1)	4 (1)
Gefitinib	0	5 (2)
Other	3 (1)	3 (1)
VEGF(R) inhibitors, n (%)	12 (4)	7 (3)
Immunotherapy, n (%)	1 (< 1)‡	6 (2)‡
Anti-CA6	1 (< 1)	0
MEDI4736	0	1 (< 1)
MPDL3280A	0	2 (1)
Nivolumab	0	1 (< 1)
Pembrolizumab	0	1 (< 1)
Other	0	1 (< 1)
Experimental therapy,† n (%)	18 (6)	12 (4)

Source: Borghaei et al. (2015); Bristol-Myers Squibb (2015b)

Abbreviations: ALK = Anaplastic Lymphoma Kinase; EGFR = Epidermal Growth Factor Receptor; VEGF(R) = Vascular Endothelial Growth Factor (Receptor)

Note: Subsequent therapy was defined as therapy started on or after first dosing date (randomisation date if patient was never treated).

* Patients may have received more than one type of subsequent therapy.

† Non-immunotherapy experimental agents.

‡ All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb, 2015b).

No deaths due to nivolumab were reported at the time of the database lock. The association of one death (from encephalitis) in a patient in the nivolumab group was changed from not related to treatment to treatment-related after the database lock (Table 13) (Borghaei et al., 2015). Discontinuation due to AEs unrelated to the study drug was observed in 19 patients in the nivolumab arm (6.6%) and 11 patients in the docetaxel arm (4.1%). Five patients (1.7%) in the nivolumab arm and 16 patients (6.0%) in the docetaxel arm requested to discontinue study treatment. Discontinuation due to patient withdrawing consent occurred in 4 patients (1.4%) receiving nivolumab and 6 patients (2.2%) receiving docetaxel (Table 13) (Bristol-Myers Squibb, 2015b).

Table 13: End-of-treatment summary in CheckMate 057

	Nivolumab (N = 287)	**Docetaxel (N = 268)**
Patients continuing in treatment period, n (%)	43 (15)	0
Reason for not continuing in the treatment period, n (%)		
Disease progression	194 (68)	179 (67)
Study drug toxicity	17 (6)	42 (16)
Death	1 (< 1)*	1 (< 1)
Adverse event unrelated to study drug	19 (7)	11 (4)
Patient request to discontinue study treatment	5 (2)	16 (6)
Patient withdrew consent	4 (1)	6 (2)
Maximum clinical benefit	0	10 (4)
Patient no longer meets study criteria	2 (1)	0
Other	2 (1)	3 (1)

Source: Borghaei et al. (2015)

* Unrelated to study drug.

The baseline characteristics were balanced between the treatment groups, with slight between-group imbalances in the percentages of male patients and patients younger than 65 years of age (Table 14) (Borghaei et al., 2015).

For all randomised patients in CheckMate 057, the median age of the patients was 62 years. Although there were limited data for patients ≥ 75 years (which represent the median age at diagnosis of patients with non-squamous NSCLC), patients in CheckMate 057 were selected based on their ability to tolerate second-line treatment in non-squamous NSCLC as defined by the study entry criteria, rather than age, and this reflects clinical decision making in the UK. Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 1, had stage IV cancer and were current or former smokers (Borghaei et al., 2015).

All randomised patients had tumour samples collected at baseline. In total, 231 (79.1%) patients in the nivolumab group and 224 (77.2%) patients in the docetaxel group had quantifiable PD-L1 expression level status at baseline. Baseline PD-L1 expression level status can be seen in Table 14 (Bristol-Myers Squibb, 2015b). PD-L1 expression level is discussed in more detail in the sub-group analysis (Section 4.8).

Table 14: Baseline characteristics of patients in CheckMate 057

Baseline characteristic	CheckMate 057	
	Nivolumab (N = 292)	**Docetaxel (N = 290)**
Median age, years (range)	**61 (37-84)**	**64 (21-85)**
< 65, n (%)	184 (63)	155 (53)
65-74, n (%)	88 (30)	112 (39)
≥ 75, n (%)	20 (7)	23 (8)
Sex, n (%) Male	151 (52)	168 (58)
Race, n (%) White	267 (91)	266 (92)
Patients with quantifiable PD-L1 status at baseline, n (%)	231 (79.1%)†	224 (77.2%)†
PD-L1 expression level* n (%)		
< 1%	108 (46.8)†	101 (45.1)†
≥ 1%	123 (53.2)†	123 (54.9)†
< 5%	136 (58.9)†	138 (61.6)†
≥ 5%	95 (41.1)†	86 (38.4)†
< 10%	145 (62.8)†	145 (64.7)†
≥ 10	86 (37.2)†	79 (35.3)†
Not quantifiable at baseline‡	61 (20.9)†	66 (22.8)†
Smoking status, n (%)		
Current/Former	231 (79)	227 (78)
Never smoked	58 (20)	60 (21)
Unknown	3 (1)	3 (1)
ECOG PS, n (%)		
0	84 (29)	95 (33)
1	208 (71)	193 (67)
Not reported	0	1 (< 1)
Disease stage, n (%)		
IIIb	20 (7)	24 (8)
IV	272 (93)	266 (92)
CNS metastases, n (%) Yes	34 (12)	34 (12)
Median time from initial diagnosis, years (range)	0.8 (0.2-8.4)†	0.8 (0.0-8.5)†
Number of prior systemic cancer therapies received, n (%)		
1	256 (88)	259 (89)
2	35 (12)	31 (11)
Other	1 (< 1)	0
Prior radiotherapy, n (%)		
Yes	139 (48)	138 (48)

Baseline characteristic	CheckMate 057	
	Nivolumab (N = 292)	**Docetaxel (N = 290)**
Type of prior systemic cancer therapy, n (%)		
Prior platinum-based therapy	292 (100)	290 (100)
Prior ALK inhibitor	1 (0.3)	2 (0.7)
Prior EGFR-TKI	29 (9.9)	24 (8.3)
Other – chemotherapy	292 (100)	290 (100)
Other – experimental drugs	23 (7.9)	18 (6.2)
Time from completion of most recent prior systemic therapy regimen to randomisation, n (%)		
< 3 months	181 (62)	183 (63.1)
3-6 months	59 (20.2)	56 (19.3)
> 6 months	52 (17.8)	51 (17.6)
Best response to most recent prior regimen, n (%)		
CR or PR	73 (25)	68 (23.4)
SD	103 (35.3)	96 (33.1)
PD	111 (38.0)	116 (40.0)
Unknown/Not reported	5 (1.7)	10 (3.4)

Source: Borghaei et al. (2015); Bristol-Myers Squibb (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; TKI = tyrosine kinase inhibitor

* Percent membranous staining in ≥ 100 tumour cells.

† All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb, 2015b).

‡ No quantifiable PD-L1 expression level

4.6 Quality assessment of the relevant randomised controlled trials

The quality assessment of RCT results for CheckMate 057 can be found in Table 15.

Table 15: Quality assessment of CheckMate 057

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 057 are thought to reflect patients seen in UK clinical practice • Comparator in the study is docetaxel, which represents standard of care in previously treated patients in the UK. • First-line treatment in the UK is a platinum-based chemotherapy; patients who had received a platinum-based chemotherapy were included in the study. • Doses for both nivolumab and docetaxel used in the study are reflective of UK clinical practice. • Baseline characteristics are similar to patients seen in UK clinical practice (e.g. ex-smokers).

Abbreviations: RCT = Randomised Controlled Trial

4.7 Clinical effectiveness results of the relevant randomised controlled trials

- CheckMate 057 met its primary objective, demonstrating a significant improvement in OS with nivolumab versus docetaxel in patients with advanced non-squamous NSCLC at the interim analysis[10]:
    - 1-year OS: 51% (95% CI: 45, 56) versus 39% (95% CI: 33, 45) for docetaxel[11]
    - 27% reduction in risk of death with nivolumab (HR: 0.73; 95% CI: 0.59, 0.89; p = 0.002)
    - Median OS: 12.2 months (95% CI: 9.7, 15.0) versus 9.4 months for docetaxel (95% CI: 8.1, 10.7)
- With additional follow-up[12], the OS rate at 18 months was 39% (95% CI: 34, 45) with nivolumab versus 23% (95% CI: 19, 28) with docetaxel, and there was a 28% reduction in risk of death (HR: 0.72; 95% CI: 0.60, 0.88; p = 0.0009).
- The study demonstrated statistically significant superiority of nivolumab over docetaxel in the secondary endpoint of objective response rate (ORR):
    - ORR: 19% (95% CI: 14.8, 24.2) for nivolumab and 12% (95% CI: 8.8, 16.8) for docetaxel (p = 0.02)
- 1-year PFS was higher for nivolumab (19%) than for docetaxel (8%). Although median PFS did not favour nivolumab (2.3 months [95% CI: 2.2, 3.3] vs. 4.2 months [95% CI: 3.5, 4.9] for docetaxel), the nivolumab and docetaxel KM curves showed markedly different profiles (Figure 13), and the overall HR for PFS or death favoured nivolumab (HR: 0.92; 95% CI: 0.77, 1.11; p = 0.39).
- In high PD-L1 expressors, superior efficacy with nivolumab was observed for all endpoints (OS, PFS, ORR) regardless of expression level. In low expressors, clinical efficacy for nivolumab was similar to that for docetaxel, and tolerability was favourable, regardless of expression level.
- Further, the OS benefit observed for nivolumab compared with docetaxel in the whole study population was observed when a sub-group analysis examined patients known to have EGFR mutation-negative/unknown status. A statistically significant benefit was not observed in patients with EGFR mutation-positive status; however, the CIs in this sub-group were wide because of its small size, and the study was not powered to identify significant differences in this sub-group. Further, nivolumab would not be used in this population in clinical practice.

  The results of the CheckMate 057 study demonstrate that nivolumab offers significantly superior and meaningful clinical efficacy and a favourable safety profile over docetaxel, providing an effective option for previously treated adults with locally advanced or metastatic non-squamous NSCLC in an area of high unmet medical need for treatments.

[10] Results from the interim analysis are based on a minimum follow-up of 13.2 months; however, this analysis is sometimes termed the “12-month interim analysis” for simplicity.

[11] The 1-year OS for docetaxel is higher in this study than in other studies (e.g. Checkmate 017) (Brahmer et al., 2015).

[12] Updated efficacy results with additional follow-up are based on a minimum follow-up of 17.1 months; however, this analysis is sometimes termed the “18-month updated analysis” for simplicity.

4.7.1 CheckMate 057

As detailed in Section 4.4, on 18 March 2015, the clinical database was locked for the planned interim OS analysis. The independent DMC reviewed the interim OS data and declared that the study had reached its primary endpoint, demonstrating superior OS in patients receiving nivolumab as compared with docetaxel. The results presented here are based on this database lock and a minimum follow-up of 13.2 months; however, this analysis is sometimes termed the "12-month interim analysis" for simplicity.

On the basis of data from the final OS analysis (2 July 2015 database lock), updated efficacy results with additional follow-up are also available for OS only and reported here (Borghaei et al., 2015). These are based on a minimum follow-up of 17.1 months; however, this analysis is sometimes termed the "18-month updated analysis" for simplicity.

Results presented in this section represent all patients relevant to NICE's decision problem; analyses are based on the entire population of the CheckMate 057 study (sometimes termed "all comers," reflecting the marketing authorisation indication of "patients with previously treated, locally advanced or metastatic non-squamous NSCLC." Sub-group analyses, including analysis by PD-L1 expression level, are given in Section 4.8.

Primary outcome

Overall survival

Overall survival was the primary outcome in CheckMate 057.

At the interim analysis (minimum follow-up for OS, 13.2 months), nivolumab demonstrated superior OS compared with docetaxel in patients with advanced non-squamous NSCLC, with a clinically meaningful and statistically significant improvement observed (Table 16) (Borghaei et al., 2015). Treatment with nivolumab reduced the risk of death by 27% when compared with docetaxel (HR: 0.73 [95% CI: 0.59, 0.89]; p = 0.002) (Borghaei et al., 2015). The median OS was 2.8 months longer with nivolumab monotherapy than with docetaxel (Bristol-Myers Squibb, 2015b) (median, 12.2 months [95% CI: 9.7, 15.0] vs. 9.4 months [95% CI: 8.1, 10.7]) (Borghaei et al., 2015). At 12 months, the OS rates were higher in the nivolumab group than the docetaxel group: 50.5% (95% CI: 45, 56) for nivolumab compared with 39.0% (95% CI: 33, 45) for docetaxel (Table 16) (Borghaei et al., 2015).

With additional follow-up, the OS rate at the 18-month updated analysis was 39% (95% CI: 34, 45) with nivolumab versus 23% (95% CI: 19, 28) with docetaxel (Table 16) (Horn et al., 2015).

It should be noted that the survival benefit of docetaxel was higher than expected in the CheckMate 057 study, as compared with previous studies (e.g. CheckMate 017, which included a similar population and where the median OS for patients treated with docetaxel was 6.0 months [95% CI 5.1, 7.3] (Brahmer et al., 2015)). This results in a seemingly lower relative efficacy benefit for nivolumab in CheckMate 057; which therefore may underestimate the true survival benefit of nivolumab.

Table 16: CheckMate 057: overall survival results from all randomised patients in the study

OS	CheckMate 057	
	Nivolumab (N = 292)	**Docetaxel (N = 290)**
Events, n (%)	190 (65.1)	223 (76.9)
Stratified log-rank test p value	0.002	
HR for death (95% CI) at 12 months	0.73 (0.59, 0.89)	
Median OS, months (95% CI)	12.2 (9.7, 15.0)	9.4 (8.1, 10.7)
OS rate at 12 months (95% CI)	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)
OS rate at 18 months (95% CI)	39 (34, 45)	23 (19, 28)

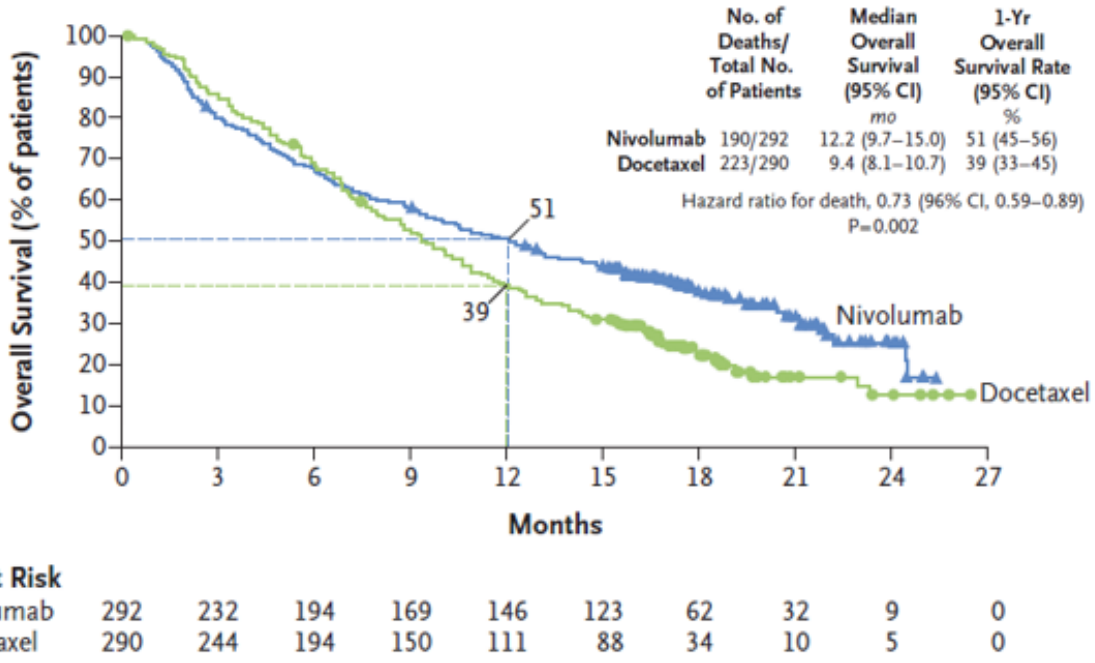
Sources: Borghaei et al. (2015); Bristol-Myers Squibb (2015b)

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, 2015b).

As shown in Figure 11, a separation of the KM curves for OS was observed after approximately 7 months, favouring nivolumab. Pseudo-progression (as described in section 2.1) may be responsible for the 7-month delay in OS benefit for patients treated with nivolumab; however, a number of theories exist for this delay, and the exact underlying mechanism is unclear.

Figure 11: CheckMate 057: Kaplan-Meier overall survival plot – all randomised patients in the study



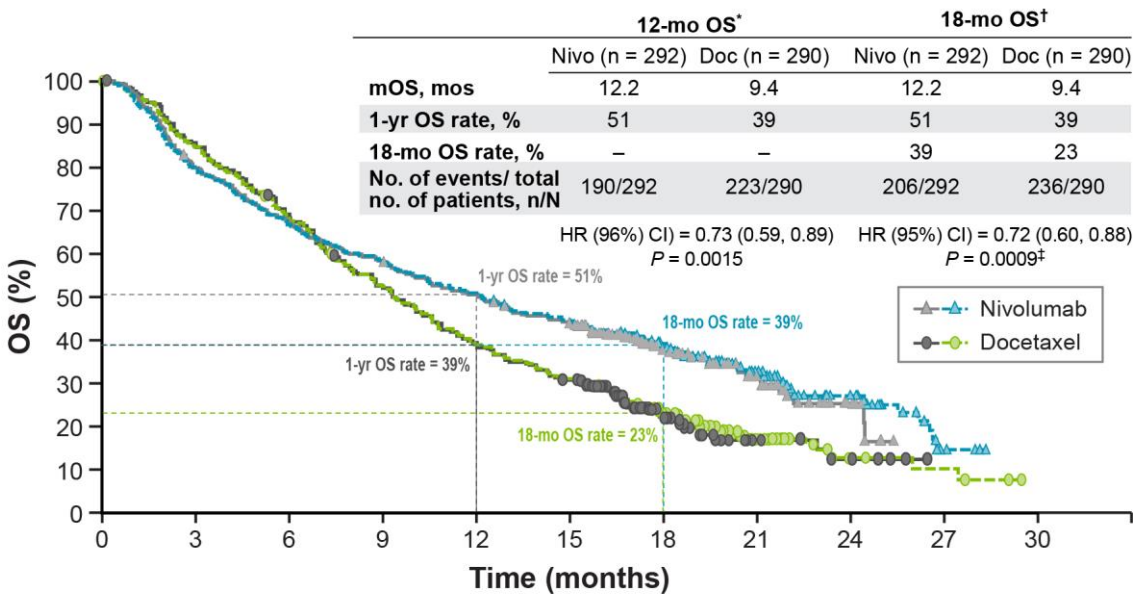
Source: Borghaei et al. (2015)

Abbreviations: CI = Confidence Interval; OS = Overall Survival

Note: The analysis included all the patients who underwent randomisation. Symbols indicate censored observations, and horizontal lines the rates of OS at 1 year.

The KM curves for OS rate at 18 months are also shown in Figure 12 (Horn et al., 2015).

Figure 12: CheckMate 057: Kaplan-Meier overall survival plot – overall survival at 12 months and 18 months of follow-up – all randomised patients in the study



No. of patients at risk (12-mo OS)*

Nivolumab	292	232	194	169	146	123	62	32	9	0	0
Docetaxel	290	244	194	150	111	88	34	10	5	0	0

No. of patients at risk (18-mo OS)†

Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

Source: Horn et al. (2015)

Abbreviations: CI = Confidence Interval; Doc = Docetaxel; HR = Hazard Ratio; mOS = Median Overall Survival; Mo = Months; Nivo = Nivolumab; OS = Overall Survival

* Based on a database lock of 18 March 2015.

† Based on a database lock of 2 July 2015.

Secondary outcomes

Progression-free survival

One-year PFS was higher for nivolumab (19%) than for docetaxel (8%). Although median PFS did not favour nivolumab (2.3 months [95% CI: 2.2, 3.3] for nivolumab vs. 4.2 months [95% CI: 3.5, 4.9] for docetaxel), the nivolumab and docetaxel KM curves showed markedly different profiles (Figure 13), and the overall HR for disease progression or death also favoured nivolumab (HR: 0.92; 95% CI: 0.77, 1.11; p = 0.39) (Table 17) (Borghaei et al., 2015; Bristol-Myers Squibb, 2015b).

Table 17: CheckMate 057: Summary of progression-free survival results from all randomised patients in the study

PFS	CheckMate 057	
	Nivolumab (N = 292)	**Docetaxel (N = 290)**
Events, n (%)	234 (80.1)	245 (84.5)
Stratified log-rank test p value	0.3932	
HR for progression or death (95% CI) at 12 months	0.92 (0.77, 1.11)	
Median, months (95% CI)	2.3 (2.2, 3.3)	4.2 (3.5, 4.9)
PFS rate at 12 months (95% CI)	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)

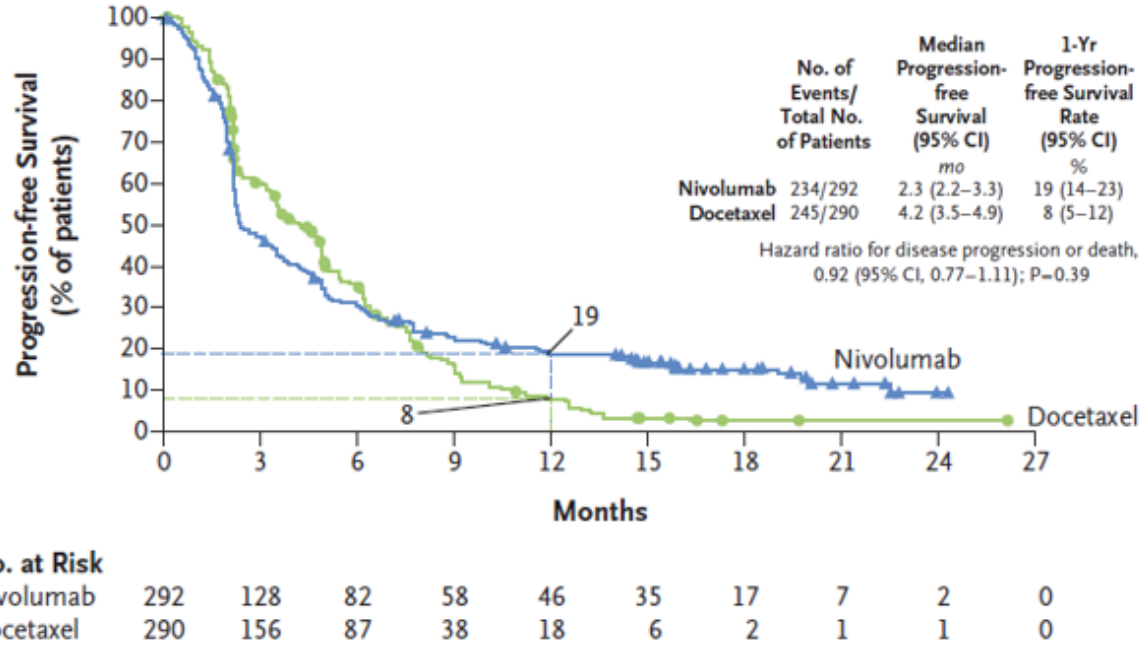
Source: Borghaei et al. (2015); Bristol-Myers Squibb (2015b)

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

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

As shown in Figure 13, delayed separation of the KM curves for PFS for nivolumab and docetaxel starts at approximately 7 months: over time this separation continues to increase. Pseudo-progression (as described in section 2.1) may be responsible for the 7-month delay in OS benefit for patients treated with nivolumab; however, a number of theories exist for this delay, and the exact underlying mechanism is unclear. Tumour response was assessed at week 9 and every 6 weeks thereafter until disease progression (Borghaei et al., 2015).

Figure 13: CheckMate 057: Kaplan-Meier progression-free survival plot – all randomised patients in the study



Source: Borghaei et al. (2015)

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

With additional follow-up, the HR for PFS with nivolumab versus docetaxel was 0.91 (95% CI: 0.76, 1.09) (Bristol-Myers Squibb, 2015e).

Response

Nivolumab demonstrated benefits compared with docetaxel in terms of ORR, duration of response (DOR) and time to response (TTR) (Table 18). A greater number of responders were observed in the nivolumab treatment group compared with the docetaxel treatment group (Figure 14). Four patients in the nivolumab group (1.4%) achieved a CR compared with one patient (0.3%) in the docetaxel group (Borghaei et al., 2015).

In both treatment arms, responders (patients who achieved a PR or CR) achieved response early, often by the time of the first scan (Figure 14) (Bristol-Myers Squibb, 2015b), while the median TTR was shorter in the nivolumab group versus the docetaxel group (Table 18).

However, in patients responding to treatment with nivolumab, the response was sustained, durable and longer than in patients responding to treatment with docetaxel (Table 18). Patients achieving response demonstrated a longer DOR with nivolumab than with docetaxel (Figure 14), where median DOR was 17.2 months in the nivolumab group compared with 5.6 months in the docetaxel group (Borghaei et al., 2015).

Table 18: CheckMate 057: Summary of response analyses from all randomised patients in the Phase III study

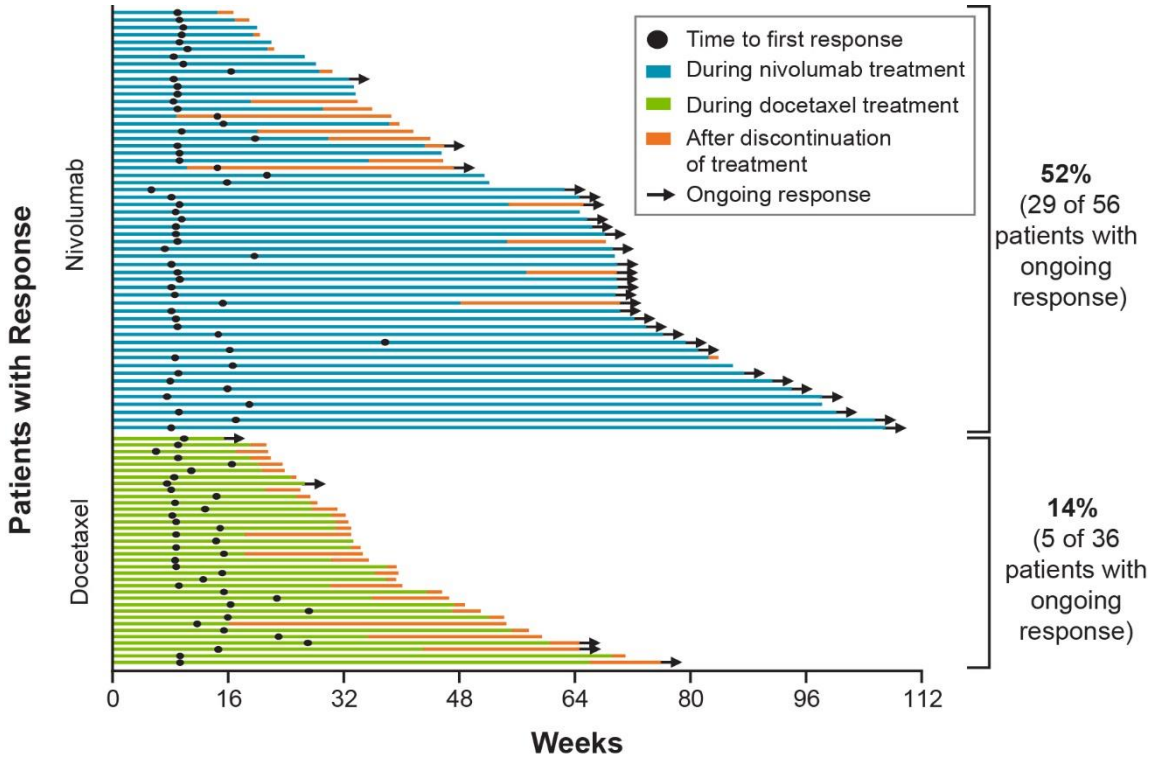
	CheckMate 057	
	Nivolumab (N = 292)	**Docetaxel (N = 290)**
Objective response rate		
n, responders	56	36
% of patients (95% CI)	19 (15, 24)	12 (9, 17)
Odds ratio estimate (95% CI)	1.7 (1.1, 2.6)	
P value	0.02	
Time to response		
Median, months	2.1	2.6
Min-Max (months)	1.2-8.6	1.4-6.3
Duration of response		
N, responders	56	36
Median, months (95% CI)	17.2	5.6
Min-Max (months)	1.8-22.6+	1.2+-15.2+

Source: Borghaei et al. (2015)

Abbreviations: CI = Confidence Interval

The + symbol indicates a censored value. The value of 1.2 was censored because the patient discontinued treatment without disease progression, and the other values were censored because the response was ongoing at the time of the analysis.

Figure 14: CheckMate 057: characteristics of response



Source: Borghaei et al. (2015)

Abbreviation: DOR = duration of response

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 (orange) represents ongoing response at the time of data censoring

Please note: Response as defined by RECIST 1.1 may not be the most appropriate method of evaluating clinical benefit with immunotherapies because patients who ultimately derive clinical benefit may progress by RECIST criteria before responding. The relationship between RECIST response and clinical benefit remains poorly understood. Nevertheless, RECIST remains the imaging criteria accepted by regulatory agencies, and a more appropriate immunotherapy-specific evaluation technique has not yet been developed.

Treatment beyond progression

For the nivolumab treatment group, 71 patients were treated beyond progression, defined by RECIST criteria (version 1.1), 16 of whom demonstrated a non-conventional pattern of benefit (Bristol-Myers Squibb, 2015b). This was defined as patients who had not experienced a best objective response of PR or CR prior to initial RECIST-defined progression and met at least one of the following criteria:

- Criterion 1: Appearance of a new lesion followed by decrease from baseline of ≥ 10% in the sum of the target lesions (12 patients).
- Criterion 2: Initial increase from nadir ≥ 20% in the sum of the target lesions followed by reduction from baseline of ≥ 30% (no patients).
- Criterion 3: Initial increase from nadir ≥ 20% in the sum of the target lesions or appearance of new lesion followed by at least two tumour assessments showing no further progression defined as a 10% additional increase in sum of target lesions and new lesions (7 patients).

In addition, 14 patients had extended nivolumab treatment (defined as > 3 doses received after initial progression) and extended OS (defined as more than the median OS of 12.2 months in the nivolumab group) after initial RECIST-defined progression but did not meet the technical criteria for non-conventional benefit as defined above (Bristol-Myers Squibb, 2015b).

Health-related quality of life (HRQoL)

In CheckMate 057, the effect of nivolumab treatment on patients' HRQoL was measured according to the Lung Cancer Symptom Scale (LCSS) and the EQ-5D.

Lung Cancer Symptom Scale

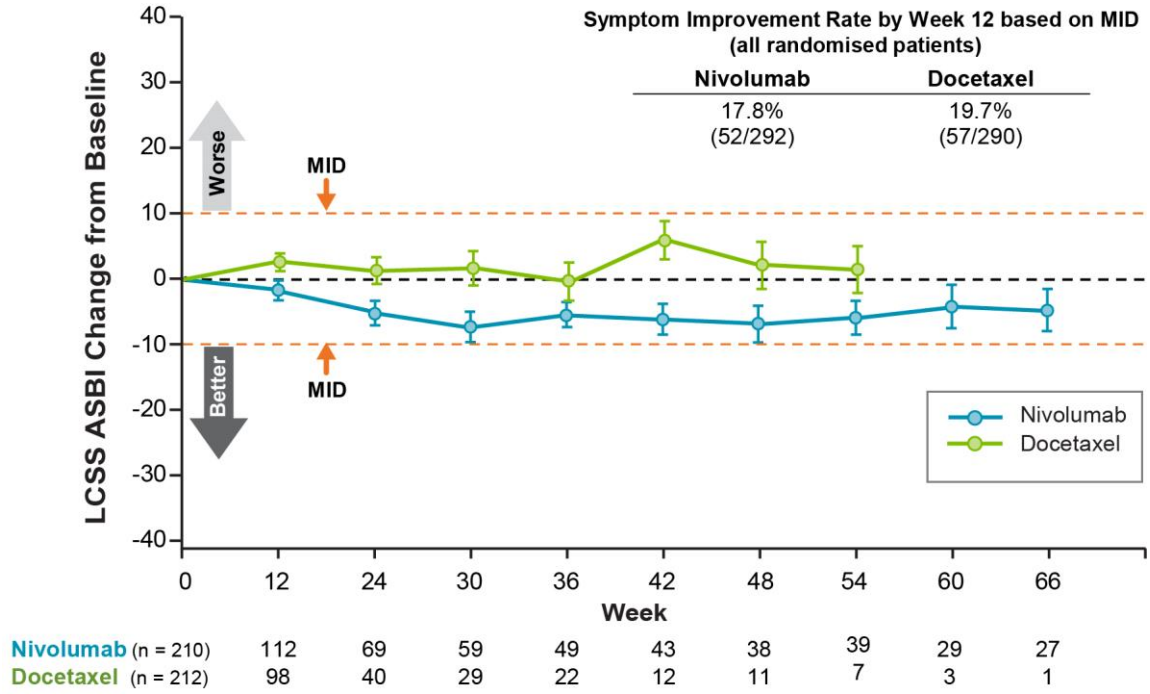
The LCSS includes six symptom-specific questions that address cough, dyspnoea, fatigue, pain, haemoptysis and appetite. The scores range from 0 to 100, with 0 representing the best possible score and 100 being the worst possible score. Disease-related symptom improvement rate is defined as a decrease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

The LCSS questionnaire compliance rate in all randomised patients was ≥ 75.0% at baseline and ≥ 65% at all on-treatment assessments through week 66. After week 66, the compliance rate was somewhat lower but remained ≥ 45% through the last recorded on-treatment assessment at week 108 (Bristol-Myers Squibb, 2015b). Results of the LCSS Average Symptom Burden Index (ASBI) score, which is the mean (SD) computed from the six symptom-specific questions of the LCSS, demonstrated similar scores at baseline for nivolumab (26.2 [16.2]) and docetaxel (24.4 [15.5]) (Figure 15) (Bristol-Myers Squibb, 2015b). Overall, the rate of disease-related symptom improvement by week 12 was comparable between the nivolumab group (17.8%) and the docetaxel group (19.7%) (Horn et al., 2015).

In both treatment groups, patients' average symptom burden scores remained stable while on treatment. Patients in the nivolumab group demonstrated, on average, a numerical decrease (improvement) in the ASBI score from baseline, except for the first assessment following baseline (week 4), when there was a small increase (2.3; standard deviation: 14.5) in the score. For docetaxel, the scores numerically increased (worsened) compared with baseline at every assessment through week 48, except at week 36, when there was a decrease in the score of less than 1 mm (−0.3; standard deviation: 13.7). In the two follow-up visits after treatment discontinuation, both the average symptom burden for nivolumab and docetaxel patients indicated a worsening of symptoms relative to baseline (range: 3.6-6.3) (Bristol-Myers Squibb, 2015b).

These results show numerical reductions (improvements) from baseline in lung cancer symptoms for patients with non-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 after treatment discontinuation (Bristol-Myers Squibb, 2015b).

Figure 15: CheckMate 057: change in LCSS ASBI (on treatment)



Source Horn et al. (2015)

Abbreviations: ASBI = Average Symptom Burden Index; LCSS = Lung Cancer Symptom Scale; MID = Minimally Important Difference

Higher scores indicate greater symptom burden. Mean (standard deviation) scores at baseline were 24.8 (15.9) for nivolumab and 24.4 (15.8) for docetaxel. Only time points that had patient-reported outcome data available for ≥ 5 patients in either treatment arm are plotted on the graph. MID consists of a change of ≥ 10 points.

EQ-5D Visual Analogue Scale and utility index

The patients' overall health was assessed using the EQ-5D 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 minimally important difference (MID) for the EQ-VAS has been estimated to be 7 points (Reck et al., 2015). The EQ-5D utility index is computed using the EQ-5D descriptive system including 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 (Bristol-Myers Squibb, 2015b; Bristol-Myers Squibb, 2015f; Pickard et al., 2007).

Completion rates of the EQ-5D were high in the CheckMate 057 study, and the rates across the nivolumab and docetaxel arms were similar (Table 19).

Table 19. Summary of EQ-5D completion rates in CheckMate 057

Time point	Nivolumab (N = 292) n (%)	Docetaxel (N = 290) n (%)
Any baseline	240 (82.2%)	222 (76.6%)
Baseline	206 (70.5%)	202 (69.7%)
Week 3		153 (63.2%)
Week 4	186 (76.9%)	
Week 6		157 (75.1%)
Week 8	143 (76.9%)	
Week 9		108 (70.6%)
Week 12	112 (77.2%)	100 (75.8%)
Week 15		72 (67.9%)
Week 16	86 (74.1%)	
Week 18		66 (72.5%)
Week 20	78 (75.0%)	
Week 21		41 (67.2%)
Week 24	69 (75.0%)	40 (80.0%)
Week 30	59 (74.7%)	29 (80.6%)
Week 36	49 (70.0%)	22 (91.7%)
Week 42	43 (71.7%)	12 (80.0%)
Week 48	38 (66.7%)	11 (91.7%)
Week 54	39 (69.6%)	7 (87.5%)
Week 60	29 (58.0%)	3 (100.0%)
Week 66	27 (60.0%)	1 (100.0%)

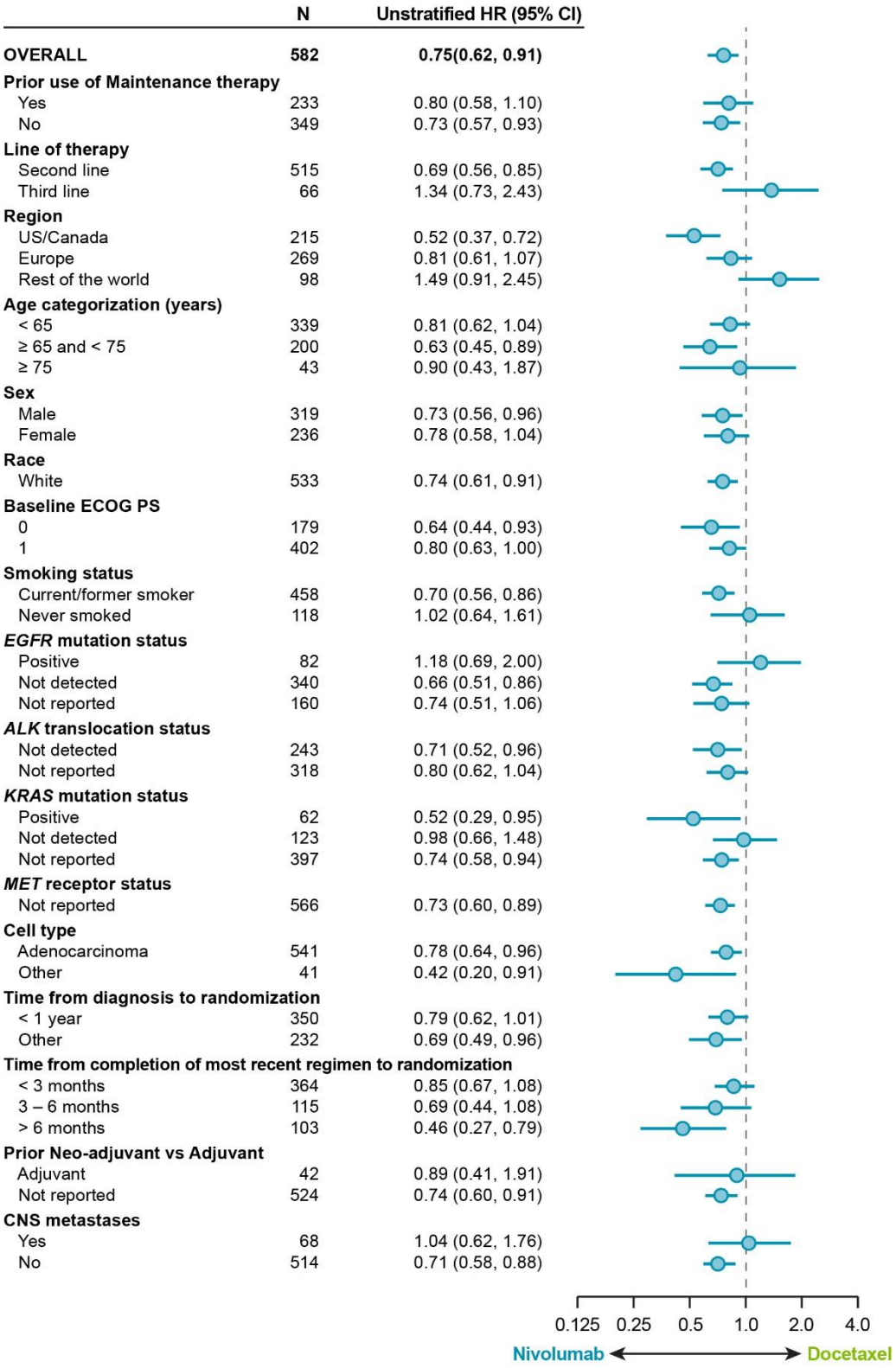
Compliance at subsequent assessments (defined as a response to assessment in addition to a baseline assessment) remained greater than 50% for most of the on-treatment assessments through week 78, after which the sample of responders included fewer than 10 patients, all of them in the nivolumab arm. The compliance in the follow-up visits ranged from 40-47% (Bristol-Myers Squibb, 2015f). Generally, the average EQ-VAS increased over time for both treatment groups (although the increase began later for docetaxel patients), indicating better overall health status for patients remaining on treatment. The average EQ-VAS score exceeded the average baseline score by more than the 7-point MID from week 16 through week 72 in the nivolumab group and from week 36 through week 48 for the docetaxel group. For both treatment groups, the EQ-VAS assessments in the follow-up visits following discontinuation returned to values in the region of the baseline scores (range: 60.6-66.4) (Bristol-Myers Squibb, 2015b). These results are in line with those from the CheckMate 017 study, which evaluated nivolumab in a similar squamous NSCLC population (Brahmer et al., 2015).

4.8 Sub-group analysis

4.8.1 Efficacy results by demographic sub-groups in CheckMate 057

The OS benefit observed for nivolumab compared with docetaxel in the whole study population (Section 4.7) was also observed across most pre-defined demographic sub-groups, except for the following groups: third-line therapy, rest of world region, brain metastases, never-smokers and EGFR mutation-positive status (Figure 16). However, the CIs in these sub-groups were wide due to small sub-group sizes, and the study was not powered to identify significant differences in these sub-groups. The “Rest of the World” sub-group may also have been confounded by smoking status.

Figure 16: CheckMate 057: Forest plot of treatment effect on overall survival in pre-defined subsets



Source: Borghaei et al. (2015)

Abbreviations: ALK = Anaplastic Lymphoma Kinase; CI = Confidence Interval; CNS = Central Nervous System; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = Epidermal Growth Factor Receptor; KRAS = Kirsten rat Sarcoma 2 Viral Oncogene Homolog; MET = Mesenchymal Epithelial Transition; OS = Overall Survival; US = United States

Similarly, the PFS HR numerically favoured nivolumab versus docetaxel for all pre-defined sub-groups, except for third-line therapy, rest of world region, never-smokers, KRAS mutation not detected and EGFR mutation-positive status.

4.8.2 Efficacy results by EGFR mutation status in CheckMate 057

Determination of mutation status was not mandatory per the protocol but was reported by the investigator and collected from case-report forms if the test was performed as part of the patient's routine care prior to study entry; therefore, no definitive data were available for many patients, and results should be interpreted with caution.

The OS benefit observed for nivolumab compared with docetaxel in the whole study population (Section 4.7) was observed when a sub-group analysis examined patients known to have EGFR mutation-negative/unknown status (Table 20 and Figure 17). At the 12-month interim analysis, the HR for OS with nivolumab versus docetaxel was 0.69 (95% CI: 0.56, 0.85) in patients with EGFR mutation-negative/unknown (combined). In patients with EGFR mutation-positive status, the HR for OS was 1.18 (95% CI: 0.69, 2.00) versus docetaxel. The CIs were wide owing to the small sample size, suggesting these results should be interpreted with caution. At the 18-month updated follow-up, the HR for nivolumab versus docetaxel in the EGFR mutation-negative/unknown sub-group was 0.68 (95% CI: 0.55, 0.83) (Bristol-Myers Squibb, 2015b; Bristol-Myers Squibb, 2015g).

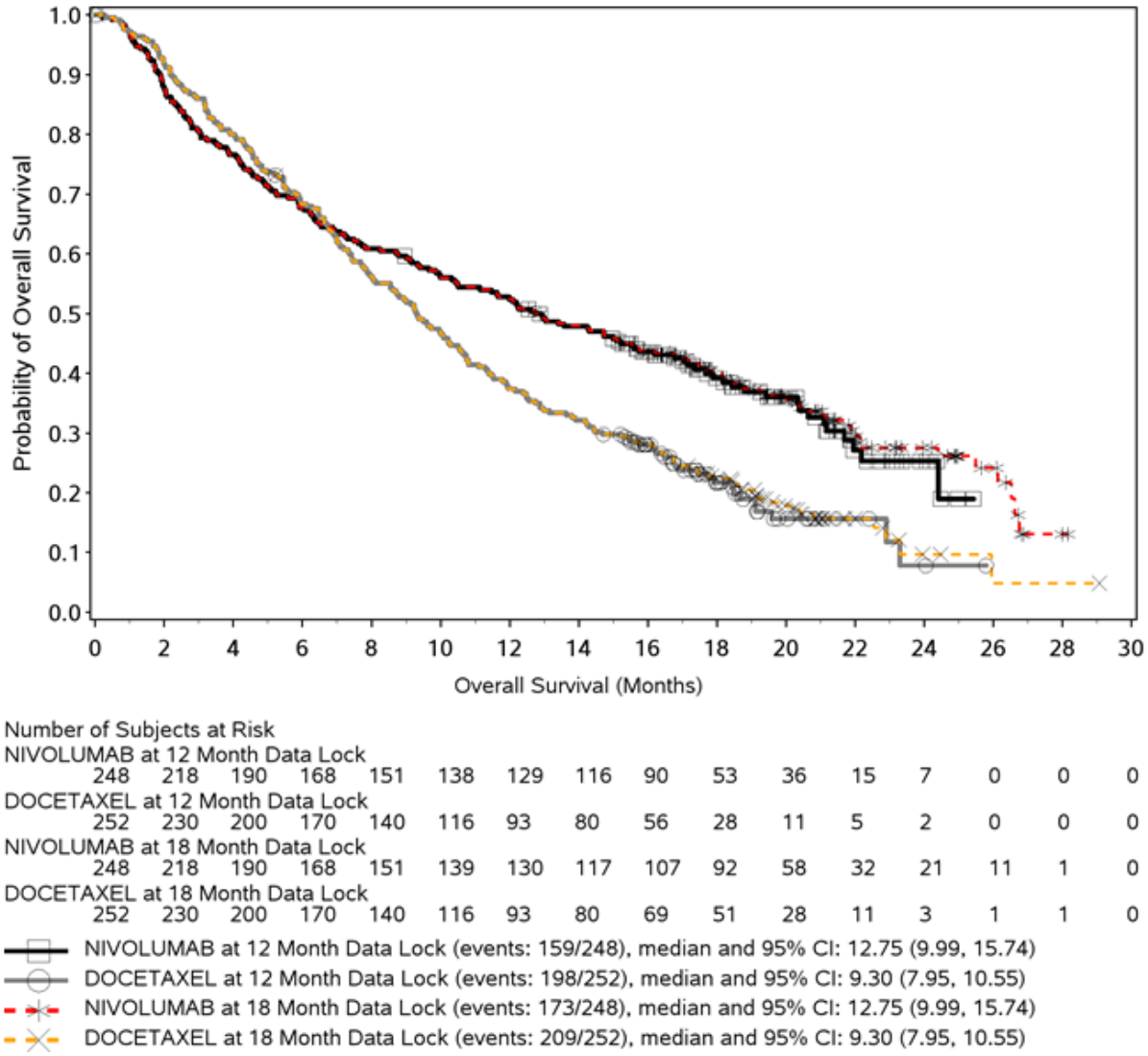
Table 20: CheckMate 057: treatment effect on overall survival by EGFR mutation status

	CheckMate 057				
		Nivolumab (N = 292)		**Docetaxel (N = 290)**	
EGFR mutation status	**N**	**Event no. (pt no.)**	**mOS (95% CI)**	**Event no. (pt no.)**	**mOS (95% CI)**
12-month interim analysis					
Positive	82	31 (44)	9.2 (5.2, 13.1)	25 (38)	11.5 (5.8, 17.8)
Not detected	340	104 (168)	13.6 (10.4, 18.4)	133 (172)	9.3 (7.7, 10.7)
Not reported	160	55 (80)	11.3 (7.7, 15.7)	65 (80)	9.3 (7.2, 12.0)
Not detected/not reported (combined)	500	159	12.8 (10.0, 15.7)	198	9.30 (8.0, 10.6)
18-month updated analysis					
Not detected/not reported (combined)	500	173	12.8 (10.0, 15.7)	209	9.3 (8.0, 10.6)

Source: Bristol-Myers Squibb (2015b); Bristol-Myers Squibb (2015g)

Abbreviations: CI = Confidence Interval; mOS = Median Overall Survival; no = Number; pt = Patient

Figure 17. CheckMate 057: Kaplan-Meier Plot of overall survival at interim and updated follow-up in randomised patients with undetected or unknown EGFR mutation status (combined)



Source: Bristol-Myers Squibb (2015g)

Abbreviation: CI = Confidence Interval

No meaningful differences in median PFS were observed across the pre-defined EGFR mutation status sub-groups (Table 21) (Figure 18). At the interim analysis, the HR for PFS with nivolumab versus docetaxel was 0.83 (95% CI 0.68, 1.02) in patients with EGFR mutation-negative/unknown (combined). In patients with EGFR mutation-positive status, the HR for PFS was 1.46 (95% CI: 0.90, 2.37) versus docetaxel. At the updated follow-up, the HR for nivolumab versus docetaxel was 0.82 (95% CI 0.67, 1.00) in the sub-group of patients with EGFR mutation-negative/unknown disease (Bristol-Myers Squibb, 2015j).

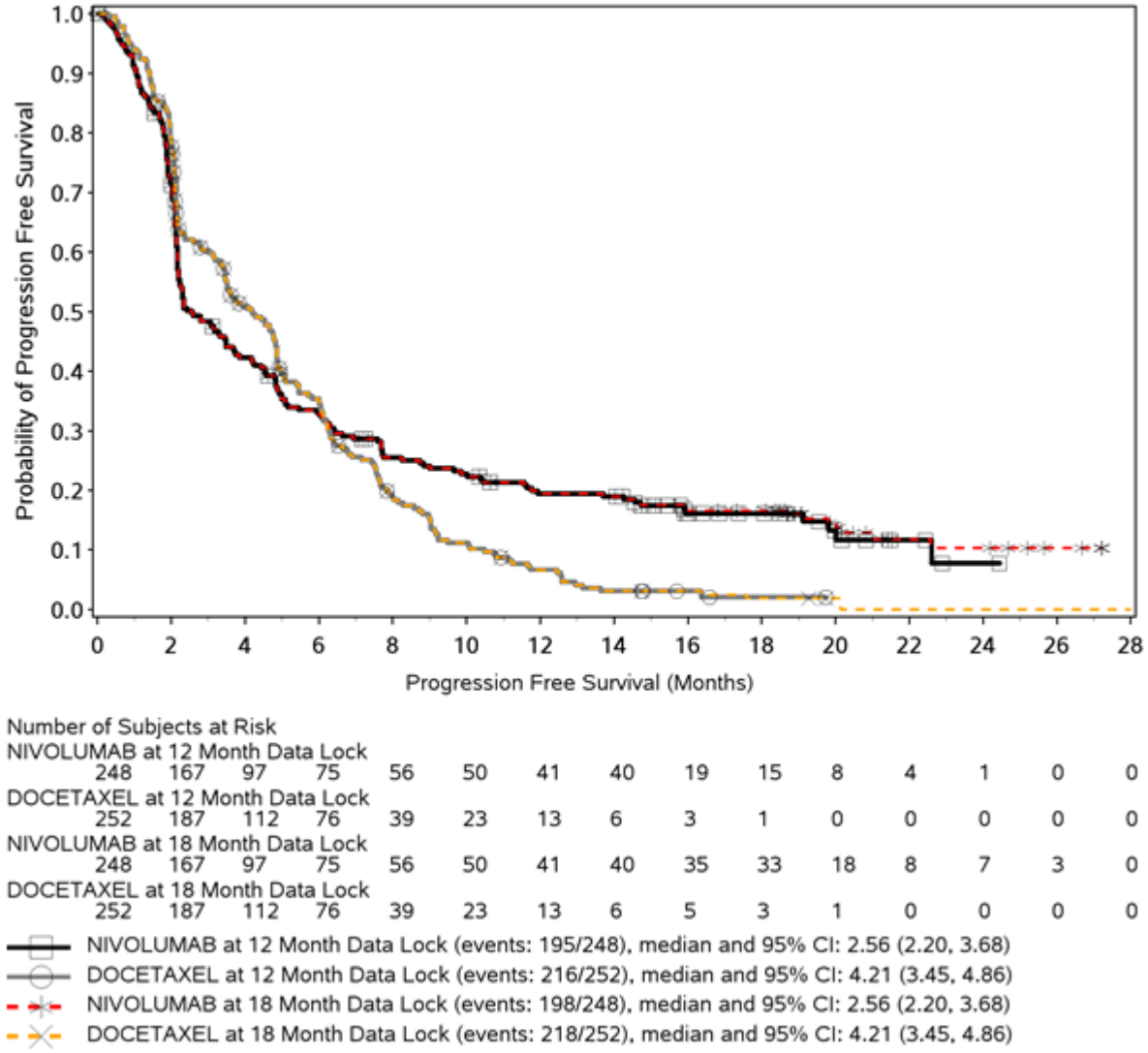
Table 21: CheckMate 057: treatment effect on progression-free survival by EGFR mutation status

	CheckMate 057				
		Nivolumab (N = 292)		Docetaxel (N = 290)	
EGFR mutation status	**N**	**Event no. (pt no.)**	**mOS (95% CI)**	**Event no. (pt no.)**	**mOS (95% CI)**
12-month interim analysis					
Positive	82	39 (44)	2.1 (1.6, 3.3)	29 (38)	4.8 (2.1,6.9)
Not detected	340	131 (168)	3.1 (2.2, 4.2)	144 (172)	3.9 (3.5, 4.9)
Not reported	160	64 (80)	2.3 (2.1, 5.0)	72 (80)	4.7 (2.2, 5.5)
Not detected/not reported (combined)	500	195	2.6 (2.2, 3.7)	216	4.2 (3.5, 4.9)
18-month updated analysis					
Not detected/not reported (combined)	500	198	2.6 (2.2, 3.7)	218	4.2 (3.5, 4.9)

Abbreviations: CI = Confidence Interval; mOS = Median Overall Survival; no = Number; pt = Patient

Sources: Bristol-Myers Squibb (2015b); Bristol-Myers Squibb (2015j)

Figure 18. CheckMate 057: Kaplan-Meier Plot of progression-free survival at interim and updated follow-up in randomised patients with undetected or unknown EGFR mutation status (combined)



Source: Bristol-Myers Squibb (2015j)

Abbreviation: CI = Confidence Interval

4.8.3 Efficacy results by PD-L1 expression level in CheckMate 057

Availability of archival or fresh tissue for evaluation of PD-L1 status was required for study entry, and 78% (455/582) of randomised patients had an evaluable PD-L1 status (Borghaei et al., 2015) (231/292 in the nivolumab arm and 224/290 in the docetaxel arm); for technical reasons, the PD-L1 status of the remaining 22% could not be accurately measured; thus, these patients were not evaluable (Bristol-Myers Squibb, 2015b). PD-L1 expression levels were balanced between the two treatment groups at each of the pre-defined PD-L1 expression levels (1%, 5% and 10%) (Borghaei et al., 2015).

Nivolumab was associated with longer OS and PFS and higher ORR than docetaxel at the pre-specified PD-L1 expression levels of ≥ 1%, ≥ 5% and ≥ 10% (Borghaei et al., 2015). Although the benefit of nivolumab was observed in the overall population, the magnitude of benefit across all the efficacy endpoints appeared to be greater at ≥ 1%, ≥ 5% and ≥ 10% PD-L1 expression levels (Borghaei et al., 2015). However, the study was not powered to measure this. As such, caution should be taken in interpreting the results.

Median OS was 17.2, 18.2 and 19.4 months for nivolumab patients compared with 9.0, 8.1 and 8.0 months for docetaxel patients in PD-L1 sub-groups defined by the ≥ 1%, ≥ 5% and ≥ 10% expression levels, respectively (Paz-Ares et al., 2015). The HRs (nivolumab vs. docetaxel) were 0.59, 0.43, and 0.40 according to the ≥ 1%, ≥ 5% and ≥ 10% expression levels, respectively (Figure 19) (Borghaei et al., 2015).

Figure 19: CheckMate 057: Forest plot of overall survival and progression-free survival according to PD-L1 expression level at baseline

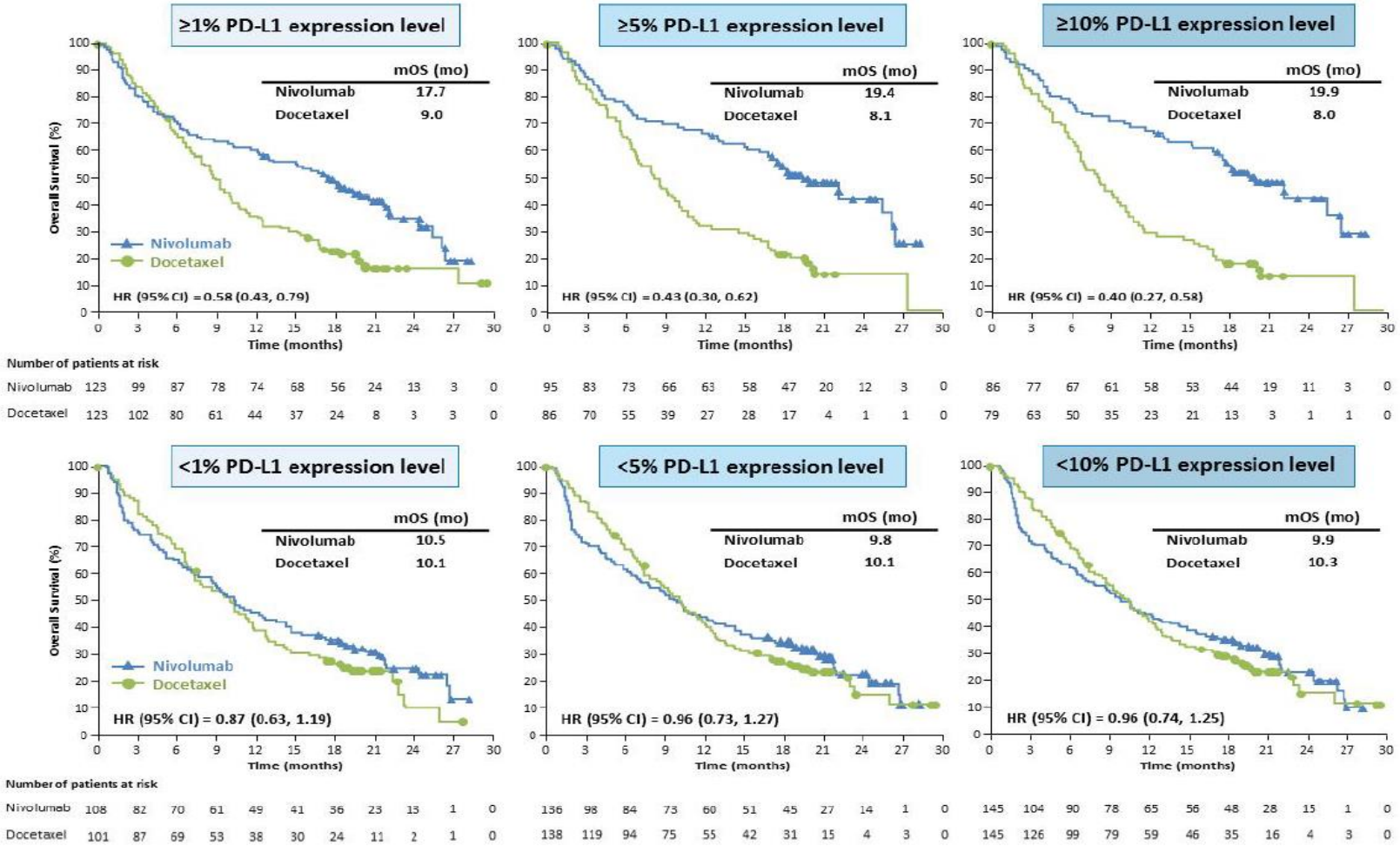
PD-L1 expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥ 1%	123	123	0.59 (0.43, 0.82)	0.06
< 1%	108	101	0.90 (0.66, 1.24)	
≥ 5%	95	86	0.43 (0.30, 0.63)	< 0.001
< 5%	136	138	1.01 (0.77, 1.34)	
≥ 10%	86	79	0.40 (0.26, 0.59)	< 0.001
< 10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥ 1%	123	123	0.70 (0.53, 0.94)	0.002
< 1%	108	101	1.19 (0.88, 1.61)	
≥ 5%	95	86	0.54 (0.39, 0.76)	< 0.001
< 5%	136	138	1.31 (1.01, 1.71)	
≥ 10%	86	79	0.52 (0.37, 0.75)	< 0.001
< 10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	

Source: Borghaei et al. (2015)

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

The difference in OS between the two study groups among patients whose tumours expressed PD-L1 was still evident with additional follow-up at the 18-month updated analysis (2 July 2015 database lock) (Figure 20) (Borghaei et al., 2015).

Figure 20: CheckMate 057: Kaplan-Meier curve of overall survival with updated follow-up according to PD-L1 expression level

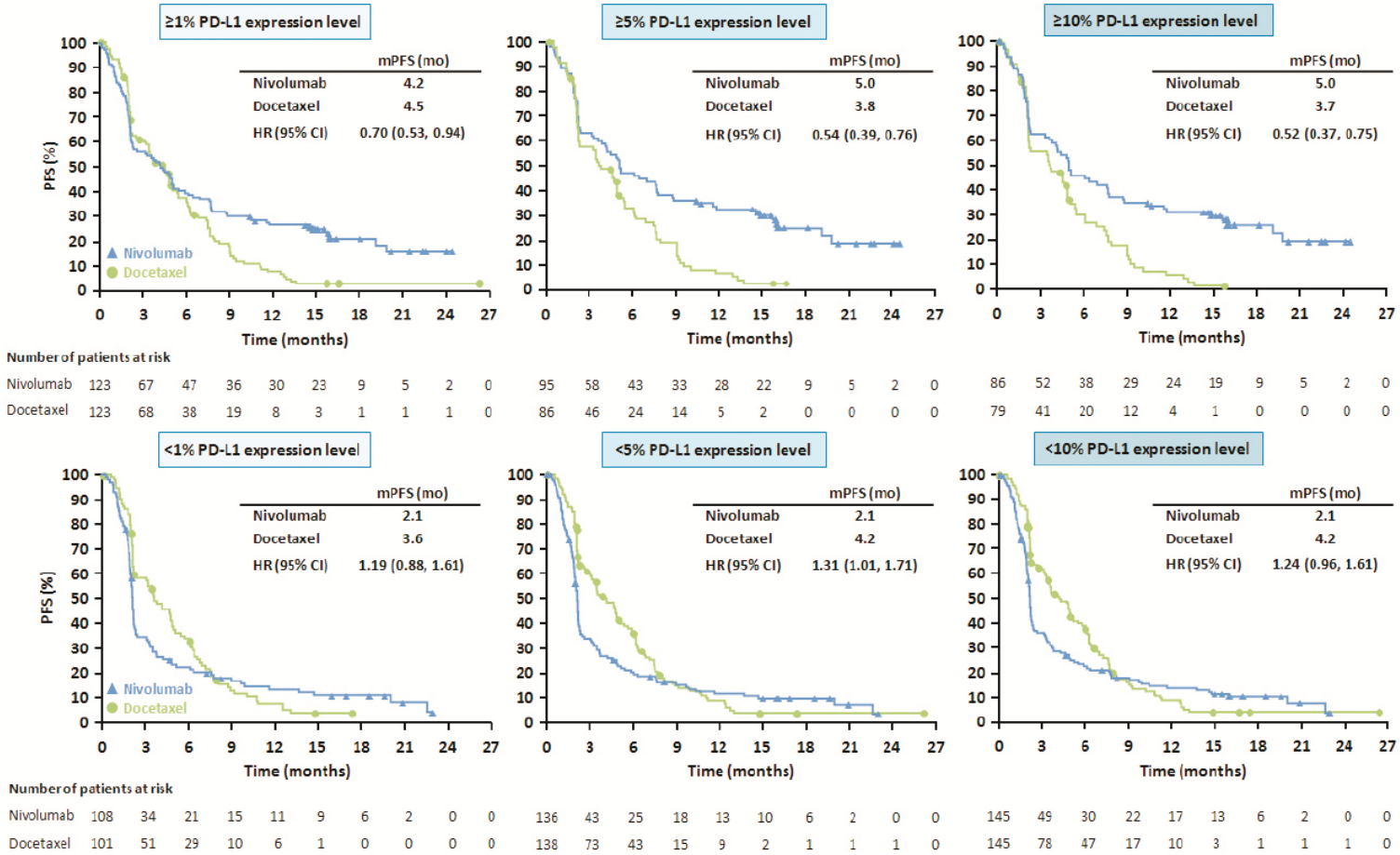


Source: Borghaei et al. (2015)

Abbreviations: CI = Confidence Interval; HR = Hazard Ratio; mo = Months; mOS = Median Overall Survival; OS = Overall Survival; PD-L1 = Programmed Death-Ligand 1

The HRs for PFS (nivolumab vs. docetaxel) were 0.70, 0.54 and 0.52 according to the ≥ 1%, ≥ 5% and ≥ 10% expression levels, respectively (Figure 19 and Figure 21) (Borghaei et al., 2015).

Figure 21: CheckMate 057: Kaplan-Meier curve of progression-free survival according to PD-L1 expression level



Source: Borghaei et al. (2015)

Abbreviations: CI = Confidence Interval; HR = Hazard Ratio; mo = Months; mPFS = Median Progression-Free Survival; PFS = Progression-Free Survival; PD-L1 = Programmed Death-Ligand 1

Higher ORRs were observed in nivolumab versus docetaxel patients (31% vs. 12% by the ≥ 1% expression level, 36% vs. 13% by the ≥ 5% expression level and 37% vs. 13% by the ≥ 10% expression level) (Table 22). In low expressors (< 1%, < 5% and < 10%), a benefit was observed in terms of DOR, which exceeded that of high expressors regardless of expression level. The odds ratios (nivolumab over docetaxel) were 3.2, 3.8 and 4.1 by the ≥ 1%, ≥ 5% and ≥ 10% expression levels, respectively (Borghaei et al., 2015).

Table 22: CheckMate 057: Clinical activity of nivolumab versus docetaxel by baseline PD-L1 expression level

	Baseline PD-L1 expression level						**Not quantifiable†**
	1%*		**5%***		**10%***		
	< 1%	**≥ 1%**	**< 5%**	**≥ 5%**	**< 10%**	**≥ 10%**	
Nivolumab							
n (%)	108 (47)	123 (53)	136 (59)	95 (41)	145 (63)	86 (37)	61 (21)
Objective response rate,‡ n (%) [95% CI]	10 (9) [5, 16]	38 (31) [23, 40]	14 (10) [6, 17]	34 (36) [26, 46]	16 (11) [6, 17]	32 (37) [27, 48]	8 (13) [6, 24]
Median DOR, mos (95% CI) n	18.3 (4.2, NE) 10	16.0 (8.4, NE) 38	18.3 (5.5, NE) 14	16.0 (8.4, NE) 34	18.3 (7.5, NE) 16	16.0 (6.9, NE) 32	7.3 (2.2, NE) 8
Docetaxel							
n* (%)	101 (45)	123 (55)	138 (62)	86 (38)	145 (65)	79 (35)	66 (23)
Objective response rate,‡ n (%) [95% CI]	15 (15) [9, 23]	15 (12) [7, 19]	19 (14) [9, 21]	11 (13) [7, 22]	20 (14) [9, 21]	10 (13) [6, 22]	6 (9) [3, 19]
Median DOR, mos (95% CI) n	5.6 (4.2, 9.9) 15	5.6 (3.0, 5.7) 15	5.6 (4.2, 7.1) 19	5.6 (3.0, 7.0) 11	5.6 (4.2, 7.1) 20	5.6 (1.6, 6.2) 10	6.6 (2.8, 14.2) 6
Odds ratio‖ (95% CI)	0.6 (0.2, 1.5)	3.2 (1.6, 6.7)	0.7 (0.3, 1.6)	3.8 (1.7, 9.0)	0.8 (0.4, 1.7)	4.1 (1.8, 10.1)	1.5 (0.4, 5.6)

Source: Borghaei et al. (2015)

Abbreviations: CI = Confidence Interval; DOR = Duration of Response; mos = Months; NE = Not Evaluable; PD-L1 = Programmed Death-Ligand 1

* Number and percent of evaluable patients with membranous staining at the respective expression level in ≥ 100 tumour cells.

† Number and percent of randomised patients with PD-L1 expression not quantifiable.

‡ Confirmed complete and partial responses per RECIST v1.1 criteria, as assessed by the investigator. CI based on the Clopper-Pearson method.

‖ Ratio of nivolumab over docetaxel

4.9 Meta-analysis

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

4.10 Indirect and mixed treatment comparisons

- The clinical systematic review identified 33 studies that met the inclusion criteria for the review. In line with the final NICE scope, the non-squamous population is further split into EGFR mutation-positive and EGFR mutation-negative/unknown populations. Ten studies were included in the networks of EGFR mutation-positive non-squamous population, while 30 were included in those of EGFR mutation-negative/unknown population.
- Because of the paucity of available evidence and heterogeneity among the studies, the following results should be interpreted with caution.
- Among the patient population with 'all-comers' non-squamous NSCLC (all non-squamous patients included in the studies), the results suggested a [redacted]% reduction in the risk of death for patients treated with nivolumab compared with nintedanib plus docetaxel (HR: [redacted]; 95% CI: [redacted]; p = [redacted]).
    - No significant differences were observed in PFS between nivolumab and nintedanib in combination with docetaxel in the all-comers population (HR: [redacted] 95% CI: [redacted] p = [redacted])
    - Results of restricted mean survival time (RMST) difference indicated that nivolumab increases the life expectancy by [redacted] months, compared with nintedanib in combination with docetaxel, although this did not reach statistical significance (RMST difference: [redacted] months; 95% CI: [redacted]; p = [redacted]). Using RMST, PFS was slightly longer with nintedanib in combination with docetaxel than with nivolumab (RMST difference: [redacted] months; 95% CI: [redacted]; p = [redacted]), but this did not reach statistical significance.
    - Objective response rate was numerically better among patients treated with nivolumab compared with nintedanib in combination with docetaxel in the all-comers population (RR: [redacted] 95%CI: [redacted]; p =[redacted]), but the difference was not statistically significant.
    - In terms of safety, the risk of any grade 3 or 4 adverse event was statistically significantly lower among patients treated with nivolumab compared with nintedanib in combination with docetaxel (RR[redacted]; 95% CI: [redacted] p [redacted]).
- Statistically significant benefit in OS with nivolumab was observed against BSC in the all-comers group, suggesting a [redacted] reduction in the risk of death (HR[redacted]; 95% CI: [redacted]; p [redacted]).
    - Restricted mean survival time results suggested that there was a statistically significant increase in life expectancy by [redacted] months with nivolumab compared with BSC (RMST difference: [redacted] months; 95% CI: [redacted]; p = [redacted]).
- Among the patient population with EGFR mutation-negative/unknown non-squamous NSCLC, the results suggested a [redacted] reduction in the risk of death with nivolumab compared with nintedanib in combination with docetaxel, although this did not reach statistical significance (HR: [redacted]; 95% CI: [redacted]; p = [redacted]).[13]
    - No significant differences were observed in PFS between nivolumab and

[13] Data for nintedanib in combination with docetaxel were only available for the adenocarcinoma sub-population, while data for nivolumab include all patients with non-squamous NSCLC, of which 93% had adenocarcinoma histology (Bristol-Myers Squibb, 2015b).

nintedanib in combination with docetaxel (HR: [redacted]; 95% CI: [redacted] p = [redacted]).

- Results of the RMST analysis suggested favourable survival with nivolumab compared with nintedanib in combination with docetaxel, although this did not reach statistical significance. Nivolumab increased the life expectancy during 13 months by [redacted] months compared with nintedanib in combination with docetaxel (RMST difference: [redacted] months; 95% CI: [redacted] p = [redacted]). No difference in PFS was observed between nivolumab and nintedanib in combination with docetaxel using the RMST approach (RMST difference: [redacted]months; 95% CI: [redacted]; p = [redacted]).
- Objective response rate was numerically better among patients treated with nivolumab compared with nintedanib in combination with docetaxel (RR: [redacted]; 95% CI: [redacted]; p = [redacted]).

- In the sub-group of patients who are EGFR mutation-negative/unknown, there was a [redacted]% reduction in the risk of death for patients treated with nivolumab compared with BSC; however, this did not reach statistical significance (HR: [redacted]; 95% CI: [redacted]; p = [redacted]). Analyses were not possible for other outcomes.

4.10.1 Search strategy

The systematic review detailed in Section 4.1 was used to identify studies included in the indirect treatment comparison (ITC) for both the treatment under consideration (nivolumab) and relevant comparator treatments.

4.10.2 Study selection

The systematic review detailed in Section 4.1 was used to identify studies relevant to the decision problem (i.e. for nivolumab and comparators included in the NICE decision problem; docetaxel and nintedanib in combination with docetaxel). It should be noted that the clinical evidence for nivolumab is in those patients with locally advanced or metastatic non-squamous NSCLC who have been previously treated with at least one prior therapy, including a platinum-based chemotherapy; therefore, studies of nintedanib in a similar population were of interest.

4.10.3 Methods and outcomes of included studies

The clinical systematic review identified 33 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 NICE's decision problem. Of the 33 studies included in the review for non-squamous NSCLC, 29 contributed to the network diagrams for outcomes of interest. It should be noted that the following breakdown of the number of studies does not sum to 29, as some studies included more than one comparator.

Of the 29 studies, 22 studies (reported in 71 publications and 1 CSR) could be used for analysis in the EGFR mutation-negative/unknown non-squamous NSCLC population, and 28 studies (reported in 85 publications and 1 CSR) could be used for analysis in the 'all-comers' non-squamous NSCLC populations, as not all studies included both groups of patients, or reported data for them.

Sixteen studies included treatments relevant to the decision problem: one study (CheckMate 057) included nivolumab; 11 studies included docetaxel monotherapy; one study included

nintedanib in combination with docetaxel (LUME-Lung 1); and three studies evaluated the use of BSC in non-squamous NSCLC (LUX-Lung 1, ISEL, Br.21).

Five studies among all comers (all non-squamous patients included) contributed to the ITC (LUME-Lung 1, ISTANA, ISEL, CheckMate 057, V-15-32), while four studies among patients with EGFR mutation-negative/unknown status contributed to the analysis (LUME-Lung 1, ISTANA, ISEL, CheckMate 057).

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.

A full description of the ITC analysis is given in Appendix 7, including network diagrams (Appendix 7.15). A brief overview of the five studies included in the ITC analysis is given in Table 23; baseline characteristics of the patients included in these studies are provided in Table 24 and Table 25.

Table 23: Summary of randomised controlled trial reporting data for previously treated non-squamous NSCLC population and included in analysis

Study ID	Design	Location	Intervention/ comparators (n)	Duration	Patient population
Studies connected in networks of both EGFR mutation-negative/unknown and 'all-comers' NSCLC					
LUME-Lung 1 (Reck et al., 2014)	Randomised, Multicentre international, Double-blind, Placebo controlled, Phase III	27 countries (211 centres)	Docetaxel (659) Docetaxel + Nintedanib (655)	31·7 months	ECOG PS 0-1 At least one measurable target lesion One previous first-line chemotherapy regimen
ISTANA (Lee et al., 2010)	Randomised, Multicentre, Open-label, Active-controlled, Phase III	Korea(6 centres)	Docetaxel (79) Gefitinib (82)	NR	Age ≥18 years WHO PS 0-2 Histologically or cytologically confirmed NSCLC with stage IIIB or IV disease One previous platinum-based chemotherapy regimen Progressive or recurrent disease following previous chemotherapy
ISEL (Thatcher et al., 2005)	Randomised, Multicentre international, Double-blind, Placebo controlled, Phase III	28 countries (210 centres)	BSC (563) Gefitinib + BSC (1129)	7.2 month	Age ≥18 years WHO PS 0-3 Histologically or cytologically proven, locally advanced or metastatic NSCLC At least one previous platinum-based chemotherapy regimen
CheckMate 057 (Borghaei et al., 2015; Bristol-Myers Squibb, 2015b)	Randomised, Multicentre international, open-label, active-controlled Phase III study	22 countries (106 sites)	Nivolumab (292) Docetaxel (290)	30 months	Age ≥18 years Stage IIIB/Stage IV or recurrent or progressive non-squamous NSCLC ECOG PS 0-1 Failed at least one prior platinum-based doublet chemotherapy regimen
Studies connected in networks of 'all-comers' NSQ NSCLC					
V-15-32 (Maruyama et al., 2008)	Randomised, Multicentre, open-label, active-controlled Phase III study	Japan	Docetaxel (244) Gefitinib (245)	21 months	Age ≥20 years Histologically or cytologically confirmed NSCLC (stages IIIB to IV) Failure of prior treatment with one or two chemotherapy regimens (≥ 1 platinum-based regimen) Life expectancy of 3 months or greater WHO PS 0-2

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = Epidermal Growth Factor Receptor; NSCLC = Non-Small Cell Lung Cancer; NR = Not Reported; NSQ = Non-squamous; PS = Performance Status; WHO = World Health Organization

Table 24: Summary of baseline characteristics of studies reporting data for previously treated non-squamous NSCLC population and included in analysis

Study ID	Treatment arm	N	Smokers, n (%)				PS (ECOG*/WHO†), n (%)					
			Current	Former	Never	Current or former	PS 0	PS 0-1	PS 1	PS 2	PS 3	PS 2-3
Studies connected in networks of both EGFR mutation-negative/unknown and 'all-comers' NSCLC												
LUME-Lung 1 (Reck et al., 2014)	Docetaxel	659			161 (24·4)	498 (75·6)	189* (28·7)		470* (71·3)			
	Docetaxel + Nintedanib	655			165 (25·2)	490 (74·8)	187* (28·5)		467* (71·3)			
ISTANA (Lee et al., 2010)	Docetaxel	79	0 (0.0)	43 (54.4)	36 (45.6)	43 (54.4)	3† (3.8)		71† (89.9)	5† (6.3)		
	Gefitinib	82	1 (1.2)	51 (62.2)	30 (36.6)	52 (63.4)	2† (2.4)		74† (90.2)	6† (7.3)		
ISEL (Thatcher et al., 2005)	BSC	563	97 (17)	340 (60)	125 (22)	77	70† (12)		318† (56)	145† (26)	29† (5)	
	Gefitinib + BSC	1129	201 (18)	678 (60)	250 (22)	78	140† (12)		598† (53)	332† (29)	55† (5)	
CheckMate 057 (Borghaei et al., 2015; Bristol-Myers Squibb, 2015b)	Nivolumab	292			58 (19.9)	231 (79.1)	84 (28.8)		208 (71.2)		0 (0)	
	Docetaxel	290			60 (20.7)	227 (78.3)	95 (32.8)		193 (66.6)		1 (0.3)	
Studies connected in networks of 'all-comers' NSQ NSCLC												
V-15-32 (Maruyama et al., 2008)	Docetaxel	244			87 (35.7)	157 (64.3)		93* (38.1)	141* (57.8)	10* (4.1)		
	Gefitinib	245			71 (29)	174 (71)		85* (34.7)	149* (60.8)	11* (4.5)		

Abbreviations: BSC = Best Supportive Care; ECOG = Eastern Cooperative Oncology Group; EGFR = Epidermal Growth Factor Receptor; NSCLC = Non-Small Cell Lung Cancer; NR = Not Reported; NSQ = Non-squamous; PS = Performance Status; WHO = World Health Organization

* PS rated on the ECOG scale.

† PS rated on the WHO scale.

Table 25: Summary of baseline characteristics of studies reporting data for previously treated non-squamous NSCLC population and included in analysis

Study ID	Treatment arm	N	Disease stage (%)			EGFR mutation status	Histology	Median age (years)	Male (%)
			Stage III	Stage IV	stage III/ IV				
Studies connected in networks of both EGFR mutation-negative/unknown and 'all-comers' NSCLC									
LUME-Lung 1 (Reck et al., 2014)	Docetaxel	659	22·2	61·9		EGFR mutation-negative/unknown: 100%	NSQ: 57.7% SQ: 42.3%	60 (54–66)	72.7
	Docetaxel + Nintedanib	655	22·6	60·9			NSQ: 57.9% SQ: 42.1%	60 (53–67)	72.7
ISTANA (Lee et al., 2010)	Docetaxel	79			100	Unclear	NSQ: 86.3% SQ: 13.7%	58 (20-73)	57
	Gefitinib	82			100		NSQ: 79.3% SQ: 20.7%	57 (21-74)	67.1
ISEL (Thatcher et al., 2005)	BSC	563	39	50		EGFR mutation-negative/unknown: 87.9% EGFR mutation-positive: 12.1%	NSQ: 67% SQ: 33%	61 (31–87)	67
	Gefitinib + BSC	1129	44	47			NSQ: 65% SQ: 35%	62 (28–90)	67
CheckMate 057 (Borghaei et al., 2015; Bristol-Myers Squibb, 2015b)	Nivolumab	292	6.8	93.2		EGFR mutation testing: N=212 EGFR mutation-positive: 20.7% EGFR mutation-negative/unknown: 79.3%	NSQ: 100%	61 (37-84)	51.7
	Docetaxel	290	8.3	91.7		EGFR mutation testing: N=210 EGFR mutation-positive: 18.1% EGFR mutation-negative/unknown: 79.9%	NSQ: 100%	64 (21-85)	57.9
Studies connected in networks of 'all-comers' NSQ NSCLC									
V-15-32 (Maruyama et al., 2008)	Docetaxel	244	20.5	61.5		EGFR mutation testing: N=54 EGFR mutation-positive: 54.4%	NSQ: 83.2% SQ: 16.8%	NR	61.9
	Gefitinib	245	19.2	64.9			NSQ: 84.9% SQ: 15.1%	NR	61.6

Abbreviations: BSC = Best Supportive Care; EGFR = Epidermal Growth Factor Receptor; NR = Not Reported; NSQ = Non-squamous; SQ = Squamous;

4.10.4 Risk of bias

Five studies contributed to the analysis for the “all-comers” non-squamous NSCLC population, while four studies contributed to the analysis in patients with EGFR mutation-negative/unknown status. A detailed critical appraisal of the studies was conducted, using the minimum criteria recommended by NICE for the quality assessment (based on Centre for Reviews and Dissemination’s guidance), Jadad score (Jadad et al., 1996), and allocation concealment grade (Grade A: adequate; Grade B: uncertain; Grade C: inadequate; Grade D: no allocation concealment attempted). Details of the critical appraisal of studies that contributed to the analysis is given in Table 26 and a quality assessment of all the studies included in the systematic review (n = 33) is given in Appendix 3.

All comers

Only five studies (LUME-Lung 1, ISTANA, ISEL, CheckMate 057, V-15-32) contributed to the ITC. Three of these studies were open-label (CheckMate 057, ISTANA, V-15-32), while two were double-blind (LUME-Lung 1; ISEL).

The patient populations included in these studies also differed; CheckMate 057 recruited previously treated patients with only non-squamous advanced and/or metastatic NSCLC, whereas the other four studies included patients with both squamous and non-squamous NSCLC with sub-group data provided for the non-squamous population. Furthermore, CheckMate 057, ISTANA, ISEL and V-15-32 recruited patients who had failed a platinum-based chemotherapy and had PS 0-1, PS 0-2, PS 0-3 and PS 0-2, respectively; however, LUME-Lung 1 included patients who had failed one line of chemotherapy and had a PS 0-1.

Due to the paucity of the available evidence, it was not possible to control for this heterogeneity in the analysis.

EGFR mutation-negative/unknown status

Only four studies (LUME-Lung 1, ISTANA, ISEL, CheckMate 057) contributed to the ITC. Two of these studies were open-label (CheckMate 057, ISTANA), while two were double-blind studies (LUME-Lung 1; ISEL).

The patient populations included in these studies also differed; CheckMate 057 recruited previously treated patients with only non-squamous advanced and/or metastatic NSCLC, whereas the other three studies included patients with both squamous and non-squamous NSCLC with sub-group data provided for the non-squamous population. Furthermore, the CheckMate 057, ISTANA and ISEL studies recruited patients who had failed a platinum-based chemotherapy and had PS 0-1, PS 0-2 and PS 0-3, respectively; however, LUME-Lung 1 included patients who had failed one line of chemotherapy and had a PS 0-1.

Due to the paucity of the available evidence, it was not possible to control for this heterogeneity in the analysis.

Table 26: Summary of quality assessment of randomised controlled trials included in the analysis

Study ID	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?
Studies connected in networks of both EGFR mutation =negative/unknown and 'all-comers' NSCLC									
LUME-Lung 1 (Reck et al., 2014)		4	A	Low risk; The randomisation was carried out appropriately as treatment was assigned by an interactive third party telephone via an interactive voice response system, or web-based randomisation via interactive web-based response system Allocation concealment was adequate.	Low risk; Demographics and baseline characteristics were well balanced between the two treatment	Low risk; This was a double-blind study. Patients and investigators were masked to assignment, and none of the individuals directly involved in the conduct and analysis of the study had access to treatment allocation before the final database lock	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were adequately reported at data cut-off	Low risk; Author has measured all the outcomes that have been reported in published protocol land in clinical study registry NCT00805194	Low risk; The efficacy and safety analysis was done using ITT/mITT population
ISTANA (Lee et al., 2010)		1	B	Not clear; This was a randomised study but the method of randomisation was not reported. Allocation concealment was also not reported	Low risk; The treatment groups were well balanced for baseline characteristics, with the exception of slightly fewer females (33% versus 43%) and never-smokers (37% versus 46%) in the gefitinib treatment group than in the docetaxel group.	High risk: This was an open-label study	High Risk: Withdrawals were not reported.	Low risk; The author analysed all the primary outcomes in this final analysis as described in the protocol and the clinical study registry NCT00478049.	Low risk; ITT and mITT population was analysed for efficacy and safety outcomes

Study ID	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?
ISEL (Thatcher et al., 2005)		4	A	Not clear; This was a randomised study and the randomisation was carried out by minimisation method.	Low risk; The baseline characteristics of the two treatment arms were well balanced.	Low risk; This was a double-blind study and the details of blinding were reported. Physically identical tablets and packaging, assigned by the central registration and randomisation centre (Clinphone Ltd, UK), were used to ensure masking of both patients and investigators. In medical emergencies, unmasking was allowed (through the central registration and randomisation centre), after discussion with the study sponsors and after a decision to discontinue treatment had been made.	Low risk; Withdrawals and reasons for withdrawals were reported	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Low risk; The safety and efficacy analysis was done using ITT/mITT population

Study ID	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?
CheckMate 057 (Borghaei et al., 2015; Bristol-Myers Squibb, 2015b)		3	A	Low risk; the patients were randomised to the two active treatments using interactive voice response system; Allocation concealment was adequate.	Low risk; the baseline characters in the two treatment arms were well balanced.	High risk; the study was conducted as an open-label study.	Low risk; study withdrawals were adequately reported.	Low risk; the authors measured all outcomes as reported in the protocol (NCT01673867).	Low risk; the efficacy and safety analysis were performed using ITT and mITT analysis respectively.
Studies connected in networks of 'all-comers' NSQ NSCLC									
V-15-32 (Maruyama et al., 2008)		2	B	Not clear; This was a randomised study but the method of randomisation was not reported	Low risk; Treatment groups were generally well balanced for baseline demographics except for some small imbalances in smoking history (7% fewer never-smokers and 10% more ex-smokers in the gefitinib arm)	High risk; This was an open-label study	Low risk; The withdrawals and the specific reasons for withdrawal were reported	Low risk; There was a published protocol NCT00252707 that describes that the author has measured all the outcomes that have been reported	Low risk; ITT population was considered for both safety and efficacy analysis

Abbreviations: ITT = Intent-to-Treat; mITT=modified Intent-to-Treat

Note: The Jadad Score is used to assess quality of RCTs, allocating them a score between 0 (very poor) and 5 (rigorous) (Jadad et al., 1996).

4.10.5 Methods of analysis and presentation of results

Detailed methods of the ITC are presented in Appendix 7. A summary of the outcomes data from the five studies that contributed to the ITC is presented in Table 27.

Table 27: Summary of data from studies reporting data for pre-treated non-squamous NSCLC population and included in analysis

Study ID (acronym)	Primary reference	Treatment (N)	ORR, n (%)	OS (Reported as HR) (95% CI)	OS (RMST; Mean (SE; 95% CI) (months)	PFS (Reported as HR) (95% CI)	PFS (RMST; months)	Any adverse event	Any grade 3 or 4 adverse event
Studies connected in networks of both EGFR mutation-negative/unknown and 'all-comers' NSCLC									
LUME-Lung 1 (Reck et al., 2014)		Docetaxel (659) Results presented for adenocarcinoma sub-group (n = 336)	12 (3.6%)	0.83 (0.70, 0.99)	For all comers at tau = 13 months: 9.313 (0.228; 8.866, 9.76). For EGFR mutation-negative/unknown at tau = 28 months: 13.213 (0.512; 12.211, 14.216).	0.77 (0.62, 0.96)	For all comers at tau = 12 months: 4.173 (0.241; 3.70, 4.645)	314/333 (94%)	228/333 (68%)
		Docetaxel + nintedanib (655) Results presented for adenocarcinoma sub-group (n = 322)	15 (4.7%)		For all comers at tau = 13 months: 9.726 (0.241; 9.253, 10.2). For EGFR mutation-negative/unknown at tau = 28 months: 14.767 (0. 565; 13.659, 15.874).		For all comers at tau = 12 months: 4.826 (0.258; 4.32, 5.332)	308/320 (96%)	243/320 (76%)
ISTANA (Lee et al., 2010)		Docetaxel (79)	6 (7.6%)	0.87 (0.61, 1.24)	For all comers at tau = 13 months: 9.743 (0.495; 8.772, 10.713)	0.634 (0.459, 0.875)	NR	NR	NR
		Gefitinib (82)	23 (28%)		For all comers at tau = 13 months: 9.949 (0.482; 9.004, 10.90)		NR	NR	NR

Study ID (acronym)	Primary reference	Treatment (N)	ORR, n (%)	OS (Reported as HR) (95% CI)	OS (RMST; Mean (SE; 95% CI) (months)	PFS (Reported as HR) (95% CI)	PFS (RMST; months)	Any adverse event	Any grade 3 or 4 adverse event
ISEL (Thatcher et al., 2005)		BSC (563)	NR	0.84 (0.68, 1.03)	For all comers at tau = 13 months: 6.752 (0.314; 6.138, 7.367)	NR	NR	NR	NR
		Gefitinib +BSC (1,129)	NR		For all comers at tau = 13 months: 7.508 (0.233; 7.052, 7.963)		NR	NR	NR
CheckMate 057 (Borghaei et al., 2015; Bristol-Myers Squibb, 2015b)		Nivolumab (292)	All-comers NSQ NSCLC: 56 (19.2%) Pooled EGFR mutation-negative/unknown NSCLC: 51 (21%)	All-comers NSQ NSCLC: 0.73 (0.59, 0.89) Pooled EGFR mutation-negative/unknown NSCLC: 0.68 (0.54, 0.83)	For all comers at tau = 13 months: 9.108 (0.273; 8.572, 9.463) For EGFR mutation-negative/unknown at tau = 28 months: 14.976 (0.665; 13.673, 16.28)	All-comers NSQ NSCLC: 0.92 (0.77, 1.11) Pooled EGFR mutation negative/unknown NSCLC: 0.83 (0.59, 0.997)	For all comers at tau = 12 months: 5.116 (0.251; 4.624, 5.696) For EGFR mutation-negative/unknown at tau = 12 months: 6.336 (0.364; 5.622, 7.05)	280 (98%)	NR
		Docetaxel (290)	All-comers NSQ NSCLC: 36 (12.4%) Pooled EGFR mutation-negative/unknown NSCLC: 30 (12%)		For all comers at tau = 13 months: 8.894 (0.251; 8.402, 9.386) For negative/unknown at tau = 28 months: 12.325 (0.599; 11.151, 13.498)		For all comers at tau = 12 months: 5.263 (0.221; 4.831, 5.696) For EGFR mutation-negative/unknown at tau = 12 months: 5.684 (0.303; 5.09, 6.277)	265 (99%)	NR

Study ID (acronym)	Primary reference	Treatment (N)	ORR, n (%)	OS (Reported as HR) (95% CI)	OS (RMST; Mean (SE; 95% CI) (months)	PFS (Reported as HR) (95% CI)	PFS (RMST; months)	Any adverse event	Any grade 3 or 4 adverse event
Studies connected in networks of 'all-comers' NSQ NSCLC									
V-15-32 (Maruyama et al., 2008)		Docetaxel (244)	24 (9.8%)	1.01 (0.87, 1.27)	For all comers at tau = 13 months: 10.323 (0.240; 9.853, 10.793)	0.89 (0.73, 1.09)	NR	236 (99%)	195 (82%)
		Gefitinib (245)	45 (18.4%)		For all comers at tau = 13 months: 9.432 (0.275; 8.893, 9.971)		NR	242 (99%)	99 (41%)

Abbreviations: CI = Confidence Interval, EGFR = Epidermal Growth Factor Receptor, HR = Hazard Ratio, NR = Not Reported, NSCLC = Non-Small Cell Lung Cancer. NSQ = Non-squamous, ORR = Objective response Rate, OS = Overall Survival, PFS = Progression-Free Survival, RMST = Restricted Mean Survival Time, SE = Standard Error. Tau = Truncation Time

A summary of outcomes from all the studies included in the systematic review (n = 33) 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. A summary of results from ITC is provided in Table 28.

An ITC was feasible for nivolumab against nintedanib plus docetaxel and BSC in pre-treated patients with advanced non-squamous NSCLC.

All-comers population

Among the 'all-comers' patient population with non-squamous NSCLC, the results suggested a [redacted] reduction in the risk of death for patients treated with nivolumab compared with nintedanib plus docetaxel (HR: [redacted]; 95% CI: [redacted]; p = [redacted]). Statistically significant benefit in OS with nivolumab was observed against BSC, suggesting a [redacted] reduction in the risk of dying (HR: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted]). However, the results depicted that nintedanib plus docetaxel was numerically better, compared with nivolumab for PFS (HR: [redacted]; 95% CI: [redacted]; p [redacted]); however, statistical significance was not achieved.

Results of RMST difference indicated that nivolumab increases the life expectancy by 0.38 months compared with nintedanib in combination with docetaxel, although this did not reach statistical significance (RMST difference: [redacted] months; 95% CI[redacted]; p = [redacted]). Further, RMST results suggested that there was statistically significant increases in the life expectancy by [redacted] months with nivolumab, compared with BSC (RMST difference: [redacted] months; 95% CI: [redacted]; p [redacted]). However, the results of RMST approach numerically favoured nintedanib plus docetaxel against nivolumab for PFS, although this was not statistically significant (RMST difference: [redacted] months; 95% CI: [redacted]; p = [redacted]).

In terms of ORR, results indicated that response rate was numerically better among patients treated with nivolumab compared with nintedanib in combination with docetaxel, but the difference was not statistically significant (RR: [redacted]; 95% CI: [redacted]; p = [redacted]).

In terms of safety profile, ITC results illustrated that the risk of any grade 3 or 4 adverse event was statistically significantly lower among patients treated with nivolumab, compared with nintedanib plus docetaxel (RR: [redacted]; 95% CI: [redacted]; p [redacted]).

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

Subpopulation of patients with EGFR mutation-negative/unknown status

Among the patient population with EGFR mutation-negative/unknown non-squamous NSCLC, the results suggested a [redacted]% reduction in the risk of death with nivolumab compared with nintedanib in combination with docetaxel, although this did not reach statistical significance (HR: [redacted]; 95% CI: [redacted]; p = [redacted]). Numerical, but not statistically significant benefit in OS with nivolumab was also observed against BSC, suggesting a [redacted] % reduction in the risk of dying (HR: [redacted]; 95% CI: [redacted]; p = [redacted]). No significant differences were observed in PFS between nivolumab and nintedanib in combination with docetaxel in the EGFR mutation-negative/unknown sub-group (HR[redacted]; 95% CI: [redacted]; p = [redacted]). Comparisons with BSC in terms of PFS were not possible, owing to a lack of clinical data on this outcome for patients treated with BSC.

Validity of hazard ratios is dependent upon the proportional hazard (PH) assumption. PH assumption diagnostics suggested that this assumption was violated; therefore, HR analysis results should be interpreted with caution. When the PH assumption was violated, RMST, which is defined as area under the survival curve up to a time *t* (shortened follow-up time), was used as a measure of effectiveness.

Results of the RMST difference indicated a favourable survival with nivolumab compared with nintedanib plus docetaxel, although this did not reach statistical significance. Nivolumab

increased the life expectancy during 13 months of follow-up (the longest minimum follow-up time for the two treatment arms) by nearly [redacted] months (or [redacted] days) compared with nintedanib in combination with docetaxel (RMST difference: [redacted] months; 95% CI: [redacted]; p = [redacted]). No difference was observed between nivolumab and nintedanib in combination with docetaxel for PFS using the RMST approach (RMST difference: [redacted] months; 95% CI: [redacted]; p = [redacted]).

In terms of ORR, results indicated that response rate was numerically better among patients treated with nivolumab, compared with nintedanib in combination with docetaxel (RR: [redacted]; 95% CI: [redacted]; p = [redacted]).

Table 28: Results of the indirect treatment comparison

Outcome	Nivolumab vs. nintedanib plus docetaxel	Nivolumab vs. BSC
Patient population: 'All-comers' NSQ NSCLC		
OS (HR [95% CI]; p value)	[redacted]	
OS (RMST difference (95% CI]; p value)		
PFS (HR([95% CI]; p value)		
PFS (RMST difference [95% CI]; p value)		
ORR (RR [95% CI]; p value)		
Any adverse event (RR [95% CI]; p value)		
Any grade 3/4 adverse event (RR [95% CI]; p value)		
Patient population: EGFR mutation-negative/unknown NSQ NSCLC		
OS (HR [95% CI]; p value)	[redacted]	
OS (RMST difference [95% CI]; p value)		
PFS (HR [95% CI]; p value)		
PFS (RMST difference [95% CI]; p value)		
ORR (RR [95% CI]; p value)		

Abbreviations: BSC = Best Supportive Care; CI = Confidence Interval; HR = Hazard Ratio; NSCLC = Non-Small Cell Lung Cancer; NSQ = Non-squamous; ORR = Objective Response Rate; OS = Overall Survival; PFS = Progression-Free Survival; RMST = Restricted Mean Survival Time; RR = Relative Risk

4.11 Non-randomised and non-controlled evidence

4.11.1 List of relevant non-randomised and non-controlled evidence

In addition to the Phase III RCT (CheckMate 057), a Phase IIIb/IV, open-label study (CheckMate 153) (Hussein et al., 2015) and a single-arm, Phase Ib, dose-escalation non-RCT (CheckMate 003) also evaluated the safety and efficacy of nivolumab in previously treated patients with squamous and non-squamous NSCLC (Table 29).

CheckMate 153 and CheckMate 003 are included in this submission as they provide clinical data that are directly relevant to the NICE decision problem: nivolumab for previously treated patients with locally advanced or metastatic non-squamous NSCLC whose disease had progressed after receiving platinum-based chemotherapy. CheckMate 153 included non-squamous and squamous patients who had received prior treatment with at least one conventional systemic therapy (Hussein et al., 2015). CheckMate 003 also included patients who had received at least one prior systemic therapy, including a platinum-based or taxane-based chemotherapy (although most patients had multiple previous cycles of chemotherapy) (Gettinger et al., 2015).

CheckMate 153 and CheckMate 003 are the only non-controlled nivolumab studies with available data for non-squamous NSCLC. See Section 4.14 below for further information about ongoing RCT and non-RCT nivolumab studies.

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

A summary of the study methodology is provided in Table 29.

Table 29: List of relevant non-randomised controlled trials

Study number (acronym)	Objectives	Population	Intervention	References	Justification for inclusion
CheckMate 153 (CA209-153)	To explore the safety of nivolumab in patients with previously treated metastatic squamous and non-squamous NSCLC	Adult patients with advanced NSCLC or with recurrent or progressive disease following prior conventional systemic treatment	Nivolumab 3 mg/kg Q2W up to 1 year or until disease progression, unacceptable toxicity or withdrawal of informed consent	Primary reference (Hussein et al., 2015).	Examines the safety of nivolumab in a previously treated advanced squamous and non-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 (advanced melanoma [n = 107], NSCLC [n = 129], renal cell carcinoma [n = 34], castration-resistant prostate cancer [n = 17] or colorectal cancer [n = 19]), including a subset of patients with 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 et al., 2015)† Secondary reference (Topalian et al., 2012)‡ Bristol-Myers Squibb (2015h)	Examines the safety and efficacy of nivolumab in a heavily pre-treated (up to five prior treatments) squamous and non-squamous NSCLC population

Sources: Gettinger et al. (2015); Hussein et al. (2015); Topalian et al. (2012).

Abbreviations: NSCLC = Non-Small Cell Lung Cancer; ORR = Objective Response Rate; Q2W = Every 2 Weeks

* Each treatment cycle is composed of four doses of study drug administered on days 1, 15, 29 and 43, with a response assessment between days 52 and 56. Two additional doses of 0.1 mg/kg and 0.3 mg/kg were added as an amendment in the study but are not included in the reported data, as they were not part of the initial dose escalation.

† Gettinger et al. (2015) provided clinical and demographic data for the NSCLC patient subset.

‡ Data in Topalian et al. (2012) included patients with all included cancers (including but not limited to NSCLC). This article was used to obtain methodological characteristics of the study.

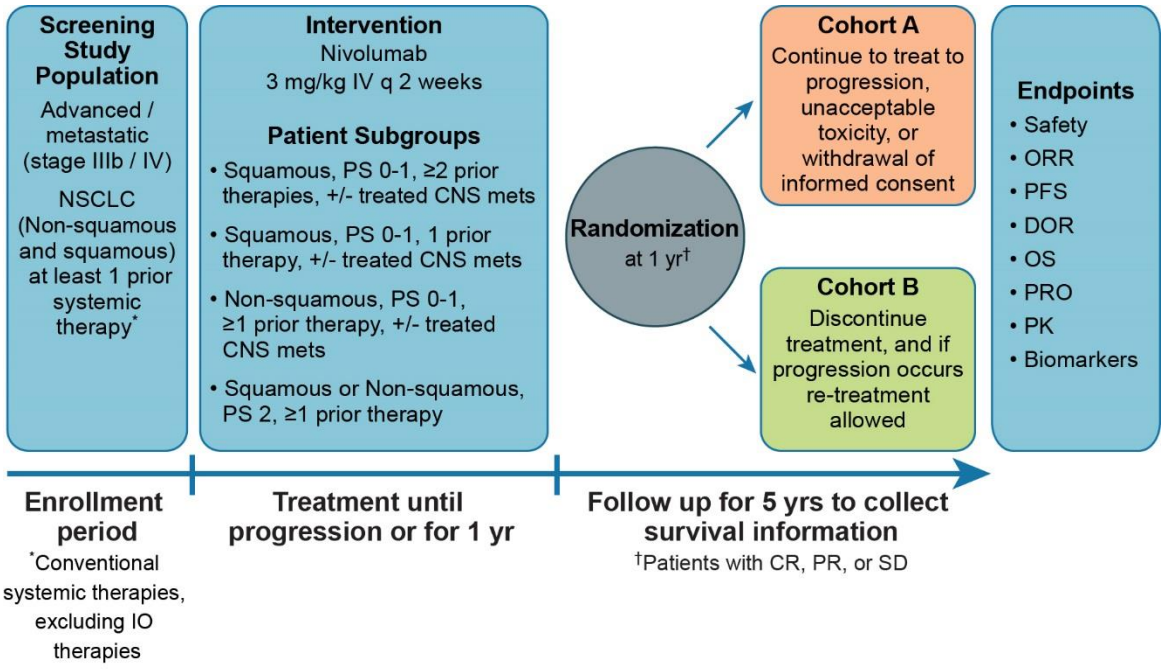
CheckMate 153

CheckMate 153 was a Phase IIIb/IV, multicentre, open-label study conducted at 127 sites in the United States, where most patients were treated at community centres. The study included 824 previously treated patients with locally advanced or metastatic squamous (N = 145) or non-squamous (N = 386) NSCLC (Hussein et al., 2015). To be included in the study, patients had to have experienced disease progression or recurrence during or after at least one systemic therapy for advanced or metastatic disease (Clinicaltrials.gov, 2015). Patients (N = 824) received 3 mg/kg nivolumab as an intravenous infusion over 60 minutes every 2 weeks, until disease progression, or until 1 year. At 1 year, patients with CR, PR or stable disease (SD) were randomised to continue treatment until disease progression, unacceptable toxicity or withdrawal of informed consent (Cohort A) or to discontinue treatment (unless progression occurred, in which re-treatment was allowed) (Cohort B).

The primary endpoint of the study was the incidence for high-grade (Grade 3-4 and Grade 5) treatment-related Select AEs. The secondary endpoints of this study were the incidence of high-grade Select AEs; the median time to onset and median time to resolution (Grade 3-4 AEs); the percentage of patients who received immune-modulating medication or hormonal replacement therapy; the percentage of patients who received ≥ 40 mg prednisone equivalents; and total duration of all immune-modulating medications given for Select AEs (Clinicaltrials.gov, 2015).

The study design of CheckMate 153 is shown in Figure 22.

Figure 22: CheckMate 153 study design



Source: Hussein et al. (2015)

Abbreviations: CNS = Central Nervous System; CR = Complete Response; DOR = Duration of Response; IO = Immuno-Oncology; IV = Intravenous; NSCLC = Non-Small Cell Lung Cancer; NSQ = Non-Squamous; ORR = Objective Response Rate; OS = Overall Survival; PFS = Progression-Free Survival; PK = Pharmacokinetics; PR = Partial Response; PRO = Patient-Reported Outcomes; PS = Performance Status; q = Every; SD = Stable Disease; SQ = Squamous

CheckMate 003

CheckMate 003 was a Phase Ib, open-label, multicentre study across 12 sites in the United States. It was a multi-dose, dose-escalation study of nivolumab in patients with selected advanced or recurrent malignancies and included a cohort consisting of 129 patients with

NSCLC (74 non-squamous patients [of relevance for this submission], 54 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 10 mg/kg Q2W for up to 96 weeks (12 treatment cycles). Each treatment cycle was composed 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).

The efficacy analysis, including OS results for all patients, is reported as of September 2014. Updated OS data based on a database lock of October 2015 also are presented (updated analysis). Baseline characteristics and the safety analysis are reported as of March 2013.

4.11.3 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 Appendix 17.1 and 17.2.

4.11.4 Participant flow

CheckMate 153

As of the 31 December 2014 data cut, 824 patients were treated, of whom 531 had at least one study tumour assessment (386 had non-squamous NSCLC versus 145 with squamous NSCLC). The median follow-up was limited, at 10.4 weeks only (Hussein et al., 2015).

Baseline demographics and disease characteristics were in line with those expected of an NSCLC population. The median age of patients was 66 years, and 90% had an ECOG PS of 0 or 1 (8% PS2, 2% not reported). The patients in this study were all previously treated; 38% had received three or more prior systemic treatments for advanced NSCLC.

Detailed baseline characteristics of this study are provided in Appendix 17.3.1.

CheckMate 003

From November 2008 through January 2012, 129 patients with advanced NSCLC were enrolled, with a median follow-up of 39 months (range: 32 to 66 months). Within the non-squamous NSCLC patient sub-group (n = 74/129), 18, 19 and 37 patients received 1, 3 and 10 mg/kg nivolumab Q2W, respectively.

Baseline demographics and disease characteristics were in line with those expected of an NSCLC population. The median age of patients was 65 years, and 98% had an ECOG PS of 0 or 1. The patients in this study 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 et al., 2015).

Detailed baseline characteristics of this study, for the NSCLC subset are provided in Appendix 17.3.2.

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

Detailed quality assessments of CheckMate 153 and 003 are provided in Appendix 8.

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

CheckMate 153

Tumour response

At the time of first assessment of evaluable patients (week 9; n = 531), the ORR was 12% (responders, n = 63/531); however, the follow-up was only 9 weeks. Median DOR was 3.3 months (95% CI: 2.0, 4.6) for nivolumab and 1.4 months (95% CI: 1.4, 2.1) for docetaxel. The rate of SD was 44% (n = 233) (Hussein et al., 2015).

Clinical response with nivolumab was seen regardless of histology type, performance status, EGFR/ALK mutation status, smoking status and number of prior therapies (Table 30).

Table 30: CheckMate 153: summary of response at first assessment (week 9)

	CR, n (%)	PR, n (%)	SD, n (%)
Total patients overall, N = 531	0	63 (12)	233 (44)
Age			
< 70 (n = 318)	0	35 (11)	135 (43)
≥ 70 (n = 213)	0	28 (13)	98 (46)
Sex			
Male (n = 290)	0	35 (12)	131 (45)
Female (n = 241)	0	28 (12)	102 (42)
Tumour histology			
Squamous (n = 145)	0	19 (13)	73 (50)
Non-squamous (n = 386)	0	44 (11)	160 (42)
Number of prior therapies			
1 (n = 138)	0	15 (11)	60 (44)
2 (n = 160)	0	21 (13)	70 (44)
≥ 3 (n = 220)	0	25 (11)	99 (45)
ECOG performance status			
0-1 (n = 489)	0	54 (11)	214 (44)
2 (n = 35)	0	7 (20)	16 (46)
***EGFR* mutation status**			
Positive (n = 55)	0	9 (16)	26 (47)
Negative (n = 300)	0	34 (11)	123 (41)
***ALK* translocation status**			
Positive (n = 12)	0	1 (8)	7 (58)
Negative (n = 299)	0	35 (12)	123 (41)

Source: Hussein et al. (2015)

Abbreviations: ALK = Anaplastic Lymphoma Kinase; CR = Complete Response; ECOG = Eastern Cooperative Oncology Group; EGFR = Epidermal Growth Factor Receptor; PR = Partial Response; SD = Stable Disease

Patients with ECOG PS 2 had similar levels of response to those with ECOG PS 0-1 in terms of tumour volume change, and the change in target tumour burden from baseline was similar regardless of performance status. This suggests that nivolumab is beneficial in patients with PS 0-2.

There were 23 patients remaining on treatment at 12 months in the nivolumab arm versus only 2 patients in the docetaxel arm.

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 31) (Gettinger et al., 2015). Specifically, for patients with NSCLC treated at the 3 mg/kg Q2W dose, the confirmed ORR was 24.3% (n = 9/37) (Gettinger et al., 2015).

In patients with non-squamous histology who were treated with 3 mg/kg nivolumab (the subset of patients directly relevant to the population defined by the NICE decision problem), the ORR observed was 26.3% (n = 5/19) (Table 31) (Gettinger et al., 2015).

Stable disease (SD) was observed in [redacted] of patients with NSCLC pooled across all doses of nivolumab. The median duration of SD for all treated patients was [redacted], with a range of [redacted] weeks. SD rates and durations were similar across dose levels and NSCLC histologies (Table 31) (Bristol-Myers Squibb, 2013b; Gettinger et al., 2015).

Table 31: CheckMate 003: summary of tumour response outcomes in all treated patients with NSCLC

Efficacy parameter	All NSCLC All doses N = 129	Non-squamous NSCLC All doses N = 74	Non-squamous NSCLC 3 mg/kg N = 19
ORR* n (%) **(95% CI)**	22 (17.1) (11.0, 24.7)	13 (17.6) (9.7, 28.2)	5 (26.3) (9.1, 51.2)
Confirmed BOR† number (%) of responders‡			
CR‡	[redacted]		
PR‡			
PD‡			
SD‡			
Unable to determine‡			

Source: Gettinger et al. (2015); Bristol-Myers Squibb (2013b)

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

* Confirmed PR or CR by the sponsor using RECIST v1.0 criteria based on investigator-assessed tumour measurements.

† 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, 2013b)

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.

Survival outcomes

Median OS was 9.9 months (95% CI: 7.8, 12.4) for all 129 patients with NSCLC (Gettinger et al., 2015). In the 37 patients who received nivolumab 3 mg/kg, the median OS was 14.9 months (95% CI: 7.3, 30.3) (Gettinger et al., 2015). In the total population of patients with NSCLC and across all dose levels, 1-, 2- 3- and 4-year survival rates were 42% (95% CI: 33, 50), 24% (95% CI: 17, 33), 18% (95% CI: 11, 25) and [redacted] respectively (Gettinger et al., 2015) (Bristol-Myers Squibb, 2015h). The results of the OS update from the October 2015 database lock (4-year data) are shown below (Figure 23). This shows that [redacted] were still alive at 4 years, suggesting a long-term benefit from treatment with nivolumab.

Figure 23. CheckMate 003: Kaplan-Meier curve of overall survival for patients with NSCLC (all doses)

Abbreviations: CI = Confidence Interval; NSCLC = Non-Small Cell Lung Cancer.

Source: Bristol-Myers Squibb (2015h).

At the 3 mg/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 rates for non-squamous NSCLC at 3 mg/kg were 62%, 48% and 24%, respectively) (Gettinger et al., 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 event 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 et al., 2015). The results of the PFS analysis from the October 2015 database lock (4-year data) are shown in Figure 24 (Bristol-Myers Squibb, 2015a).

The KM curves for all patients with NSCLC by histology are provided in Appendix 17.4.1.

Figure 24. CheckMate 003: Kaplan-Meier curve of progression-free survival for patients with NSCLC (all doses)

Abbreviations: CI = confidence Interval; NSCLC = Non-Small Cell Lung Cancer.
Source: Bristol-Myers Squibb (2015a).

4.12 Adverse reactions

- Nivolumab has been studied in 1,322 patients in the safety population across the clinical study programme.
- Clinical study data, including 4-year follow-up data, show that nivolumab is generally 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 AEs.
- 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 them have been defined during the nivolumab development programme (see SmPC in Appendix 1).

CheckMate 057

- Nivolumab demonstrated a more favourable safety profile than docetaxel (standard of care) (in both haematologic and non-haematologic AEs). Most first-onset AEs occurred within the first 3 to 6 months.
    - This favourable safety profile over docetaxel was demonstrated in both high and low PD-L1 expressers.
- There were fewer Grade 3-4 AEs (and treatment-related AEs) in the nivolumab arm compared with the docetaxel arm: 46% versus 67% (and 10% vs. 54%).
- Serious AEs that were treatment-related were less frequent in the nivolumab arm compared with the docetaxel arm (7% vs. 20%, respectively).
- Treatment-related AEs leading to discontinuation were less common in the nivolumab arm compared with the docetaxel arm (5% vs. 15%, respectively).
- Immune-related AEs were manageable with established treatment algorithm guidelines (SmPC in Appendix 1).
- One death was attributed to nivolumab toxicity, and one death was attributed to docetaxel toxicity.

Supporting studies

- Similar rates of AEs were seen in CheckMate 153 and CheckMate 003.

4.12.1 Introduction

Select AEs are a category of 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 with the broader group of AEs (including those of immunological and non-immunological origin); however, these are usually manageable and reversible with interruption of drug treatment and/or, for moderate- or high-grade Select AEs, treatment with steroids 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- or 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, which can be found in the SmPC (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:

- Pulmonary toxicity
- Gastrointestinal toxicity
- Endocrinopathy
- Hepatic toxicity
- Renal toxicity
- Skin toxicity
- Infusion reaction

Hypersensitivity and 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 and infusion reactions do not otherwise meet the 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 (Bristol-Myers Squibb, 2015c) (Appendix 1).

4.12.2 Safety of nivolumab

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

In this submission, we present nivolumab safety data from three NSCLC studies (CheckMate 057, CheckMate 153 and CheckMate 003).

4.12.3 Safety in non-squamous non-small cell lung cancer

The overall safety and tolerability of nivolumab in the non-squamous NSCLC population is based on patients who received the licensed dose of nivolumab 3 mg/kg in two NSCLC studies (CheckMate 057 and CheckMate 153) and described below. The safety profile of nivolumab in the Phase Ib dose-escalation CheckMate 003 study is also briefly described.

Overall, nivolumab is a well-tolerated therapy for non-squamous NSCLC.

4.12.4 CheckMate 057

The methodology and baseline characteristics for this study are given in Section 4.3 and Section 4.5, respectively.

Overall safety summary

Comparative safety data from CheckMate 057 demonstrated that nivolumab monotherapy has a more favourable safety profile than docetaxel, including both haematologic and non-

haematologic toxicities, in patients with advanced non-squamous NSCLC. Most first-onset AEs occurred within the first 3 to 6 months.

In patients who received study treatment, there were fewer AEs of Grade 3 or 4 reported with nivolumab than with docetaxel (Table 32) (Borghaei et al., 2015). Overall, a similar incidence was observed for all-causality, all-grade AEs reported within 100 days of the last dose compared with those reported within 30 days for the nivolumab group (Bristol-Myers Squibb, 2015b).

Treatment-related AEs were low in severity with nivolumab and were less frequent with nivolumab than with docetaxel (69% vs. 88% of patients had events of any grade, and 10% vs. 54% had events of Grade 3 or 4) (Borghaei et al., 2015).

Treatment-related serious adverse events (SAEs) were also less frequent in the nivolumab group than in the docetaxel group (7% vs. 20% of patients had events of any grade, and 5% vs. 18% had events of Grade 3 or 4) (Borghaei et al., 2015).

There were fewer treatment-related AEs leading to treatment discontinuation in the nivolumab group compared with the docetaxel group (5% vs. 15% of patients).

The frequencies of treatment-related AEs, SAEs and AEs leading to discontinuation of the study drug were similar in the sub-groups of patients with a PD-L1 expression level of 1% or higher and those with a PD-L1 expression level of less than 1% (Borghaei et al., 2015).

Most Select AEs were low grade, manageable and resolved using the recommended treatment guidelines for early work-up and intervention (Borghaei et al., 2015; Bristol-Myers Squibb, 2015b).

The overall safety profiles of both nivolumab and docetaxel were consistent with expectations based on prior data in terms of the type, frequency and severity of reported events, and no new safety concerns with nivolumab monotherapy treatment were identified (Bristol-Myers Squibb, 2015b).

Table 32: CheckMate 057: summary of deaths (all treated patients) and adverse events

	Nivolumab, n (%) (n = 287)		**Docetaxel, n (%) (n = 268)**	
All deaths	185 (64.5)		204 (76.1)	
Reason for death:				
Disease progression	157 (54.7)‡		179 (66.8)‡	
Study drug toxicity	0*		1 (0.4)†	
Unknown	7 (2.4)‡		13 (4.9)‡	
Other	21 (7.3)‡		11 (4.1)‡	
Deaths within 30 days of last dose	36 (12.5)‡		21 (7.8)‡	
Deaths within 100 days of last dose	93 (32.4)‡		76 (28.4)‡	
	Any grade n (%)	**Grade 3-4 n (%)**	**Any grade n (%)**	**Grade 3-4 n (%)**
All-causality AEs	280 (98)	132 (46)	265 (99)	180 (67)
Treatment-related AEs	199 (69)	30 (10)	236 (88)	144 (54)
All-causality Select AEs				
Endocrine	31 (10.8)‡	2 (0.7)‡	3 (1.1)‡	0‡
Gastrointestinal	45 (15.7)‡	3 (1.0)‡	73 (27.2)‡	3 (1.1)‡

	Nivolumab, n (%) (n = 287)		Docetaxel, n (%) (n = 268)	
Hepatic	29 (10.1)‡	8 (2.8)‡	7 (2.6)‡	2 (0.7)‡
Pulmonary	11 (3.8)‡	4 (1.4)‡	3 (1.1)‡	3 (1.1)‡
Renal	16 (5.6)‡	0‡	3 (1.1)‡	0‡
Skin	76 (26.5)‡	2 (0.7)‡	49 (18.3)‡	1 (0.4)‡
Hypersensitivity/infusion reactions	10 (3.5)‡	0‡	14 (5.2)‡	1 (0.4)‡
All treatment-related Select AEs				
Endocrine	27 (9.4)‡	0‡	1 (0.4)‡	0‡
Gastrointestinal	22 (7.7)‡	2 (0.7)‡	62 (23.1)‡	3 (1.1)‡
Hepatic	15 (5.2)‡	3 (1.0)‡	5 (1.9)‡	2 (0.7)‡
Pulmonary	10 (3.5)‡	4 (1.4)‡	1 (0.4)‡	1 (0.4)‡
Renal	7 (2.4)‡	0‡	1 (0.4)‡	0‡
Skin	51 (17.8)‡	2 (0.7)‡	35 (13.1)‡	0‡
Hypersensitivity/infusion reactions	8 (2.8)‡	0‡	2 (0.7)‡	0‡
All-causality SAEs	134 (46.7)‡	95 (33.1)‡	111 (41.4)‡	91 (34.0)‡
All treatment-related SAEs	21 (7)‡	15 (5)‡	53 (20)‡	48 (18)‡
All-causality AEs leading to discontinuation	48 (16.7)‡	38 (13.2)‡	58 (21.6)‡	34 (12.7)‡
All treatment-related AEs leading to discontinuation	14 (5)	11 (4)	40‡ (14.9)‡	18‡ (6.7)‡

Sources: Borghaei et al. (2015); Bristol-Myers Squibb (2015b)

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

* The association of one death (from encephalitis) in a patient in the nivolumab group was changed from not related to treatment to treatment-related after the database lock.

† A treatment-related death of a patient in the docetaxel group, which occurred before the database lock, was reported as Grade 4 febrile neutropenia. Based on a 18 March 2015 database lock.

‡ All commercial in confidence data are underlined and were obtained from the clinical study report (Bristol-Myers Squibb, 2015b).

Deaths

For all treated patients, there were 185 deaths (64.5%) in the nivolumab treatment arm. In the docetaxel group, there were 204 deaths (76.1%).

Disease progression was the most common cause of death: 157 (54.7%) patients in the nivolumab group and 179 (66.8%) patients in the docetaxel group.

One death in each of the two treatment groups was assessed by the investigator as being related to treatment. One patient in the nivolumab group died from encephalitis (which was reported before the database lock, but the causality was changed after the database lock to be treatment-related), and 1 patient in the docetaxel group died from febrile neutropenia (Table 32) (Borghaei et al., 2015).

Adverse events leading to discontinuation

Discontinuation of the study drug due to treatment-related AEs occurred less frequently with nivolumab than with docetaxel (in 5% vs. 15% of patients). The most common treatment-

related AE leading to discontinuation was pneumonitis in the nivolumab group (in 1% of patients) and fatigue in the docetaxel group (in 3%) (Borghaei et al., 2015).

Overall, treatment-related AEs leading to discontinuation at the PD-L1 ≥ 1% expression level at baseline was comparable to that in PD-L1 (< 1% expression level) patients (Table 33) (Horn et al., 2015)

Table 33: CheckMate 057: safety summary by 1% PD-L1 expression

	Nivolumab				Docetaxel			
	≥ 1% (n = 121*)		< 1 (n = 106*)		≥ 1% (n = 115*)		< 1 (n = 92*)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related AEs leading to discontinuation	5%	4%	3%	2%	17%	8%	15%	8%

Source: Horn et al. (2015)

Abbreviations: AE = Adverse Event; PD-L1 = Programmed Death-Ligand 1

* Safety is reported for patients receiving study drug.

Treatment-related adverse events

Treatment-related AEs were reported less frequently in the nivolumab group (69%) than in the docetaxel group (88%) (Table 34) (Bristol-Myers Squibb, 2015b). The most frequently reported treatment-related AEs of any grade in the nivolumab group were fatigue (in 16% of patients), nausea (in 12%), decreased appetite (in 10%) and asthenia (in 10%). The most frequently reported treatment-related AEs of any grade in the docetaxel group were neutropenia (in 31% of patients), fatigue (in 29%), nausea (in 26%) and alopecia (in 25%) (Borghaei et al., 2015).

Grade 3 and 4 treatment-related AEs and SAEs were also less frequent in the nivolumab group than in the docetaxel group: 10% versus 54% of patients had Grade 3 or 4 treatment-related AEs; 7% versus 20% had treatment-related SAEs of any grade; and 5% versus 18% had SAEs of Grade 3 or 4 (Borghaei et al., 2015).

Similar frequencies were observed for treatment-related SAEs reported during nivolumab treatment or within 100 days of last nivolumab dose (Bristol-Myers Squibb, 2015b). An SAE of Grade 3 encephalitis was reported, which was considered related to nivolumab by the investigator and led to study drug discontinuation. The patient died due to this event. The assessment of causality of death was initially not related to study drug but was changed post-database lock to treatment-related.

Overall, the safety profiles of PD-L1 ≥ 1% expression level at baseline and PD-L1 (< 1% expression level) sub-groups were comparable (Table 35) (Horn et al., 2015).

Table 34: CheckMate 057: summary of treatment-related adverse events, reported in ≥ 5% of treated patients

	Nivolumab n = 287		Docetaxel n = 268	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Event	Number of patients with an event (%)			
Any event	199 (69)	30 (10)	236 (88)	144 (54)
Fatigue	46 (16)	3 (1)	78 (29)	13 (5)
Nausea	34 (12)	2 (1)	70 (26)	2 (1)
Decreased appetite	30 (10)	0	42 (16)	3 (1)
Asthenia	29 (10)	1 (< 1)	47 (18)	6 (2)
Rash	27 (9)	1 (< 1)	8 (3)	0
Pruritus	24 (8)	0	4 (1)	0
Diarrhoea	22 (8)	2 (1)	62 (23)	3 (1)
Hypothyroidism	19 (7)	0	0	0
Arthralgia	16 (6)	0	16 (6)	0
Vomiting	15 (5)	0	20 (8)	0
Constipation	13 (5)	0	21 (8)	2 (1)
Peripheral oedema	8 (3)	0	28 (10)	1 (< 1)
Pyrexia	8 (3)	0	17 (6)	0
Myalgia	7 (2)	1 (< 1)	30 (11)	0
Anaemia	6 (2)	1 (< 1)	53 (20)	7 (3)
Dysgeusia	5 (2)	0	25 (9)	0
Paraesthesia	5 (2)	0	20 (7)	0
Pain	4 (1)	0	14 (5)	0
Peripheral neuropathy	3 (1)	0	25 (9)	3 (1)
Stomatitis	3 (1)	0	23 (9)	2 (1)
Mucosal inflammation	2 (1)	0	20 (7)	5 (2)
Lacrimation increased	1 (< 1)	0	14 (5)	0
Alopecia	1 (< 1)	0	67 (25)	0
Neutrophil count decreased	1 (< 1)	1 (< 1)	19 (7)	16 (6)
Neutropenia	1 (< 1)	0	83 (31)	73 (27)
Febrile neutropenia	0	0	27 (10)	26 (10)
Leukopenia	0	0	27 (10)	22 (8)
White blood cell count decreased	0	0	22 (8)	12 (4)

Source: Borghaei et al. (2015).

Note: A patient may be recorded as having more than one adverse event within a category.

Table 35: CheckMate 057: safety summary by 1% PD-L1 expression

	Nivolumab				Docetaxel			
	≥ 1% (n = 121)		< 1 (n = 106)		≥ 1% (n = 115)		< 1 (n = 92)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related AEs	74%	13%	61%	8%	90%	53%	85%	58%
Treatment-related SAEs	7%	5%	7%	3%	22%	19%	18%	17%

Source: Horn et al. (2015)

Abbreviations: AE = Adverse Event; PD-L1 = Programmed Death-Ligand 1; SAE = Serious Adverse Event

Select adverse events

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

Most Select AEs were of low grade. In the nivolumab group, all-causality Select AEs were most frequently reported (≥ 15% of patients) in the skin and gastrointestinal categories (Table 36) (Bristol-Myers Squibb, 2015b).

Table 36: CheckMate 057: all-causality Select adverse events*

	Nivolumab (n = 287)	Docetaxel (n = 268)
Skin and gastrointestinal		
Rash	9%	3%
Pruritus	8%	1%
Erythema	1%	4%
Diarrhoea	8%	23%
Hypothyroidism	7%	0%
Other		
Increased alanine aminotransferase level	3%	1%
Increased aspartate aminotransferase level	3%	1%
Infusion-related reaction	3%	3%
Pneumonitis	3%	< 1%

Source: Borghaei et al. (2015)

* Includes events reported between first dose and 30 days after last dose of study drug.

The most frequently reported (> 10% of patients) treatment-related Select AE category with nivolumab treatment was skin (17.8%). The most frequently reported (≥ 1% of patients) Grade 3-4 treatment-related Select AE categories with nivolumab treatment were pulmonary (1.4%) and hepatic (1.0%) (Bristol-Myers Squibb, 2015b).

Time to onset and time to resolution of Select AEs were also analysed. The median time to the onset of treatment-related Select AEs of any grade in the nivolumab group ranged from 0.9 to 31.1 weeks versus 1.0 to 113 weeks with docetaxel (Borghaei et al., 2015). Across categories, 44% to 100% of the treatment-related Select AEs resolved with nivolumab; the median time to resolution ranged from 0.1 to 12.1 weeks. Correspondingly, 0% to 100% of

the treatment-related Select SAEs resolved with docetaxel across categories; the median time to resolution ranged from 0.1 to 9.0 weeks (Borghaei et al., 2015).

Most nivolumab Select AEs were manageable, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered.

Table 37: CheckMate 057: Summary of treatment-related Select adverse events

	Nivolumab n = 287		**Docetaxel n = 268**	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Select adverse event category	**Number of patients with an event (%)**			
Skin				
Rash	27 (9)	1 (< 1)	8 (3)	0
Pruritus	24 (8)	0	4 (1)	0
Rash maculopapular	5 (2)	0	1 (< 1)	0
Erythema	4 (1)	0	11 (4)	0
Eczema	3 (1)	0	0	0
Rash pruritic	3 (1)	0	1 (< 1)	0
Urticaria	3 (1)	0	2 (1)	0
Rash erythematous	2 (1)	0	1 (< 1)	0
Rash macular	2 (1)	0	2 (1)	0
Skin exfoliation	2 (1)	0	2 (1)	0
Dermatitis	1 (< 1)	1 (< 1)	0	0
Drug eruption	1 (< 1)	0	0	0
Rash generalised	1 (< 1)	0	1 (< 1)	0
Palmar-plantar erythrodysesthesia syndrome	0	0	3 (1)	0
Photosensitivity reaction	0	0	1 (< 1)	0
Pruritus generalised	0	0	1 (< 1)	0
Rash papular	0	0	1 (< 1)	0
Gastrointestinal				
Diarrhoea	22 (8)	2 (1)	62 (23)	3 (1)
Colitis	2 (1)	1 (< 1)	0	0
Endocrine				
Hypothyroidism	19 (7)	0	0	0
Blood thyroid-stimulating hormone increased	6 (2)	0	0	0
Hyperthyroidism	4 (1)	0	0	0
Blood thyroid-stimulating hormone decreased	1 (< 1)	0	0	0
Thyroiditis	1 (< 1)	0	0	0
Diabetes mellitus	0	0	1 (< 1)	0

Select adverse event category	Nivolumab n = 287		Docetaxel n = 268	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
	Number of patients with an event (%)			
Hepatic				
Alanine aminotransferase increased	9 (3)	0	4 (1)	1 (< 1)
Aspartate aminotransferase increased	9 (3)	1 (< 1)	2 (1)	0
Blood alkaline phosphatase increased	2 (1)	0	4 (1)	1 (< 1)
Gamma-glutamyl transpeptidase increased	2 (1)	2 (1)	0	0
Transaminases increased	2 (1)	1 (< 1)	0	0
Blood bilirubin increased	1 (< 1)	0	0	0
Hepatotoxicity	1 (< 1)	0	0	0
Hyperbilirubinemia	1 (< 1)	0	1 (< 1)	0
Hypersensitivity/infusion reaction				
Infusion-related reaction	8 (3)	0	8 (3)	1 (< 1)
Hypersensitivity	1 (< 1)	0	4 (1)	0
Bronchospasm	0	0	2 (1)	0
Pulmonary				
Pneumonitis	8 (3)	3 (1)	1 (< 1)	1 (< 1)
Interstitial lung disease	2 (1)	1 (< 1)	0	0
Renal				
Blood creatinine increased	5 (2)	0	1 (< 1)	0
Renal failure	1 (< 1)	0	0	0
Renal failure acute	1 (< 1)	0	0	0

Source: Borghaei et al. (2015).

4.12.5 CheckMate 153

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

Overall safety summary

This open-label, randomised study demonstrated that nivolumab monotherapy (3 mg/kg) has a reasonably well-tolerated safety profile in patients with locally advanced or metastatic non-squamous NSCLC (Table 38).

One death was attributed to nivolumab, which occurred in a patient with multiple comorbidities and in the setting of progressive disease (PD).

Approximately half of patients reported a treatment-related AE of any grade. The nature, frequency and severity of treatment-related AEs, SAEs, Select AEs and AEs leading to discontinuation are consistent across the PS0-1 and PS2 populations, as well as consistent with prior nivolumab studies in non-squamous NSCLC. The treatment-related pneumonitis rate was low (0.8%) and consistent with that reported in prior nivolumab studies.

Table 38: CheckMate 153: summary of adverse events

	Nivolumab 3 mg/kg N = 824		
	Any Grade n (%) patients	**Grade 3-4 n (%) patients**	**Grade 5 n (%) patients**
All AEs	762 (93)	311 (38)	158 (19)
All SAEs	309 (38)	223 (27)	158 (19)
All Select AEs	282 (34)	37 (5)	5 (1)
All treatment-related AEs	439 (53)	59 (7)	1 (< 1)
All treatment-related SAEs	23 (3)	19 (2)	1 (< 1)*
All treatment-related Select AEs	199 (24)	20 (2)	0
All AEs leading to discontinuation	87 (11)	53 (6)	34 (4)
All treatment-related SAEs leading to discontinuation	14 (2)	12 (2)	1 (< 1)
All treatment-related Select AEs leading to discontinuation	12 (2)	11 (1)	0

Source: Hussein et al. (2015)

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

* Fatal event

Deaths

One fatal event was reported as treatment-related respiratory failure, with known comorbidities of lymphangitic spread of tumour, recurrent pulmonary embolism, G-bacteraemia, pleural effusion, pneumothorax or tumour progression. The death occurred in the setting of PD (Hussein et al., 2015).

Adverse events leading to discontinuation

Adverse events led to discontinuation for 87 (11%) of 824 patients. However, treatment-related SAEs only led to discontinuation for 14 (2%) of 824 patients.

Treatment-related adverse events

A total of 439 (53%) patients experienced a treatment-related AE. Most were Grade 1 or 2 in severity; 59 (7%) patients experienced a Grade 3 or 4 treatment-related AE. Similarly, 23 (3%) patients experienced a treatment-related SAE with nivolumab; only 19 (2%) patients experienced a Grade 3 or 4 treatment-related SAE and 14 (2%) patients experienced a Grade 3 or 4 treatment-related SAE leading to discontinuation.

Select adverse events

Most Select AEs were of low grade, with only 37 (5%) patients experiencing Grade 3 or 4 Select AEs in the nivolumab arm. Approximately a quarter of patients (199 [24%]) experienced treatment-related Select AEs, with 20 (2%) experiencing Grade 3 or 4 treatment-related Select AEs.

Only 12 (2%) patients had treatment-related Select AEs leading to discontinuation.

The rates of treatment-related Select AEs were similar in patients of PS 0-1 and those with PS 2.

4.12.6 CheckMate 003

Following the nivolumab dose-escalation portion of this study, the 1, 3 and 10 mg/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 et al., 2015).

Overall safety summary

Among the treated patients with NSCLC across all doses and histologies, 71% had experienced a treatment-related AE of any grade (Gettinger et al., 2015). The most common treatment-related AEs were fatigue (24%), decreased appetite (12%) and diarrhoea (10%) (Gettinger et al., 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 et al., 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 study before AE management guidelines were established, and the third occurred after the March 2013 safety analysis (Gettinger et al., 2015).

Treatment-related adverse events and serious adverse events

Among the treated patients with NSCLC, 71% had experienced treatment-related AEs of any grade (Appendix 18.2). The most common AEs were fatigue (24%), decreased appetite (12%) and diarrhoea (10%) (Table 14 in Appendix 17) (Gettinger et al., 2015). Eighteen patients (14%) experienced Grade 3 or 4 treatment-related AEs, and the most common was fatigue (3%) (Appendix 18.2) (Gettinger et al., 2015).

Select adverse events

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 39). Four patients (3%) had treatment-related Grade 3 or higher pneumonitis, including one with Grade 5 pneumonitis (Table 39). No clear relationships between the occurrence of pneumonitis and dose level or treatment duration were noted.

Table 39: CheckMate 003: Summary of Select adverse events

	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
Gastrointestinal	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 et al. (2015).

Abbreviations: AE = Adverse Event

Note: Select AEs were those requiring more frequent monitoring or intervention with immune suppression or hormone replacement, based on a pre-specified list of Medical Dictionary for Regulatory Activities terms. Data are from the 16 March 2013 data analysis.

* 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 the date of the 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 but was not included because the event occurred after the date of the safety analysis.

4.12.7 Summary

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

Docetaxel, the current standard of care in this NSCLC patient population, is poorly tolerated.

- The most frequently reported nivolumab treatment-related AEs across studies were fatigue and decreased appetite. Most Select AEs were mild, transient and generally manageable using the established safety management algorithm guidelines outlined in the SmPC (Appendix 1).
- In CheckMate 057, the rate of treatment-related AEs of any grade in the nivolumab and docetaxel arms was 69% and 88%, respectively (Borghaei et al., 2015). The rate of treatment-related Grade 3-4 AEs was significantly lower in the nivolumab group (10%) compared with the docetaxel group (54%). Five percent of patients discontinued because of drug toxicity in the nivolumab group compared with 15% in the docetaxel group. There was one treatment-related death in the nivolumab treatment group, and one in the docetaxel treatment group (Borghaei et al., 2015).
- Similar rates of AEs were seen in CheckMate 153. The rate of treatment-related AEs in nivolumab-treated patients was 53%, and the rate of Grade 3-4 treatment-related AEs was 7% (Hussein et al., 2015).
- Nivolumab was generally well tolerated by patients with locally advanced or metastatic non-squamous NSCLC.

4.13 Interpretation of clinical effectiveness and safety evidence

Non-squamous NSCLC is a disease associated with a poor prognosis. Docetaxel, the current standard of care, offers only limited efficacy and a poor toxicity profile. CheckMate 057 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 non-squamous NSCLC after prior chemotherapy.

4.13.1 Principal findings of the clinical evidence base

- Nivolumab offers a clinically significant survival benefit in patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy, in an area of unmet medical need:
- Nivolumab resulted in a 27% lower risk of death in CheckMate 057 at the interim analysis, as compared with docetaxel in the previously treated setting after platinum-based chemotherapy. Nivolumab significantly increased 1-year OS (51% vs. 39%; HR: 0.73; p = 0.002), with a median OS benefit of 12.2 months versus 9.4 months, despite patients treated with docetaxel experiencing longer than anticipated OS.
    - With additional follow-up in CheckMate 057, the OS rate at 18 months in CheckMate 057 was 39% (95% CI: 34, 45) with nivolumab versus 23% (95% CI: 19, 28) with docetaxel (Table 16), and there was a 28% reduction in risk of death (HR: 0.72; 95% CI: 0.60, 0.88; p = 0.0009).
    - In CheckMate 153, a Phase IIIb/IV, open-label study that included patients with PS2 as well as PS0-1, nivolumab demonstrated efficacy and safety consistent with the pivotal study, although follow-up was limited.
    - CheckMate 003, a Phase Ib study of nivolumab in heavily pre-treated patients with NSCLC, also showed consistency, where 1-year and 3-year survival of patients with NSCLC was 56% and 27%, respectively, in those patients treated with 3 mg/kg nivolumab.
- Four-year follow-up data from CheckMate 003 indicate that there may be a long-term survival benefit from nivolumab in NSCLC.
- Nivolumab demonstrates durable response:
    - In CheckMate 057, patients treated with nivolumab had an ORR of 19% vs. 12% in the docetaxel group (p = 0.02). Median DOR was 17.2 months in the nivolumab group compared with 5.6 months in the docetaxel group. This pattern was also seen in CheckMate 153, with an overall ORR of 12%, and median DOR was 3.3 months (95% CI: 2.0, 4.6) for nivolumab and 1.4 months (95% CI: 1.4, 2.1) for docetaxel. The rate of SD was 44% overall.
    - In high PD-L1 expressors, superior efficacy with nivolumab was observed for all endpoints (OS, PFS, ORR) regardless of expression level. In low expressors, clinical efficacy for nivolumab was similar to that for docetaxel, and tolerability was favourable, regardless of expression level.
    - Further, the OS benefit observed for nivolumab compared with docetaxel in the whole study population was observed when a sub-group analysis examined patients known to have EGFR mutation-negative/unknown status. No meaningful differences in median PFS were observed across the pre-defined EGFR mutation status sub-groups. A statistically significant benefit was not observed in patients with EGFR mutation-positive status; however, the CIs in this sub-group were wide owing to its small size, and the study was not powered to identify significant

differences in this sub-group. Further, it is unlikely that nivolumab would be used in this population in clinical practice.

- In CheckMate 057, a total of 71 patients were treated beyond progression. Of these, 16 patients continued to benefit from treatment beyond disease progression ("non-conventional" benefiters). This is typically seen in nivolumab studies and is owing to the immunological mechanism of action of nivolumab.

- Nivolumab is generally 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.
  - The most frequently reported nivolumab treatment-related AEs in CheckMate 057 were fatigue, nausea, decreased appetite and asthenia.
  - Most nivolumab Select AEs were mild, transient and generally manageable using the established safety management algorithm guidelines outlined in the SmPC (Appendix 1).
  - In CheckMate 057, the rate of treatment-related Grade 3-4 AEs was significantly lower in the nivolumab group (10%) compared with the docetaxel group (54%). There were 5% discontinuations due to treatment-related AEs in the nivolumab group compared with 15% in the docetaxel group. There was one treatment-related death in the nivolumab treatment group, and one in the docetaxel treatment group.
  - Similar rates of treatment-related AEs were seen in CheckMate 153; the rate of treatment-related Grade 3-4 AEs was 7% with nivolumab.
  - The AE profile of nivolumab is well understood and is consistent across the body of nivolumab studies.

4.13.2 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, RCTs—CheckMate 017 (squamous) and CheckMate 057 (non-squamous).

2. CheckMate 057 is a well-designed Phase III RCT that provides comparative evidence of nivolumab against the recognised UK standard of care:

   - When CheckMate 057 was first designed, docetaxel was the recognised standard of care for patients in the UK with previously treated advanced NSCLC.
     - Although the use of nintedanib is increasing, docetaxel is still the current standard of care—making the results of this study directly relevant to current UK clinical practice.
   - CheckMate 057 was stopped early, as the assessment conducted by the independent data monitoring committee (DMC) concluded that nivolumab had met its endpoint demonstrating superior OS in patients treated with nivolumab compared with patients treated with docetaxel.
   - CheckMate 153 is a single-arm Phase IIIb/IV study and CheckMate 003 is a Phase Ib expansion study. Although these are not RCTs, they provide useful data in addition to the CheckMate 057 RCT.

- CheckMate 153 shows that clinical response to nivolumab is observed regardless of performance status (0, 1 or 2)
- CheckMate 003 provides longer-term (4-year) survival data for nivolumab.

- All studies were or 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. The study endpoints are clinically relevant to UK clinical practice:

- The CheckMate 057 RCT has endpoints that are most relevant to patients and physicians in the UK:
  - The study was powered for OS as the primary endpoint—the most important and robust clinical endpoint for patients and clinicians.
  - OS is most important for immuno-oncology treatments, as ORR does not capture the true benefit of these drugs.
  - HRQoL data were collected as secondary endpoints.

4.13.3 Limitations of the current evidence base

- CheckMate 057
  - The minimum follow-up time of patients at the interim analysis was 13.2 months and for the additional analysis it was 17.1 months. Follow-up data continue to be collected and will further support the survival benefit of nivolumab beyond 18 months.
  - The independent DMC stopped this study early because nivolumab already showed superior survival benefit over docetaxel. Although this may be seen as a limitation, planned enrolment was complete before the study was stopped and this showed that nivolumab had already demonstrated superior survival benefit over docetaxel (the UK current SOC) by a minimum follow-up of 13.2 months.
  - 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 studies, some features may not be typical of real-world patients with lung cancer. The median age in the study was 62 years, and the proportion of patients with PS1 was 69%, which may not reflect the real-world UK clinical population, although it is typical of clinical studies in lung cancer.
  - There was insufficient power and patient numbers in sub-group analysis to identify whether there is a statistical relative benefit in some patients (e.g. those older than 75 years).
  - Determination of EGFR mutation status was not mandatory per the protocol (it was reported by the investigator and collected from case-report forms if the test was performed as part of the patient's routine care prior to study entry), which meant that no definitive data were available for many patients. Therefore, results should be interpreted with caution.
  - Further, EGFR and ALK mutation status was evaluated by individual centres as part of patients' clinical management, rather than via a centralised laboratory, which represents a limitation of the study.

- The benefit/risk profile of nivolumab compared with docetaxel was favourable across all PD-L1 expression sub-groups, and PD-L1 expression was predictive of an improved OS benefit with nivolumab in comparison to docetaxel. However, there are limitations to these data that need to be recognised, meaning that sub-group analyses by PD-L1 status should be interpreted with caution:
    - Patients were not prospectively stratified by PD-L1 expression level
    - Although tissue was required for study entry, ascertainable PD-L1 expression level status was not required, and so only 78% of all study patients had an expression level available.
    - Many of the samples used were taken before patients received first-line chemotherapy (i.e., archival).
  - Docetaxel was used as the comparator, and it is the current standard of care in the UK. Nintedanib in combination with docetaxel has recently been approved for use in the UK; however, there is no direct comparison with this agent in RCTs.
- Whilst an indirect comparison with nintedanib in combination with docetaxel 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 153
  - This is a single-arm Phase IIIb/IV study conducted in the US that included 386 patients with non-squamous NSCLC (and 145 patients with squamous NSCLC). Currently, data are available only from the first planned assessment, at 9 weeks' follow-up.
  - Despite these limitations, CheckMate 153 provides initial data for patients with ECOG PS2 and also will provide data regarding the efficacy of stopping treatment after 1 year (2016).
- CheckMate 003
  - This is a Phase Ib 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 4-year follow-up and long-term safety data for nivolumab when interpreted appropriately, bearing in mind that this is a large Phase Ib study.
  - Further, 1-year OS was similar in CheckMate 057 and 003, suggesting conserved clinical efficacy across studies.

4.13.4 End-of-life criteria

CheckMate 057 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 mean survival extrapolated from the clinical study data for the economic model (with a 20-year time horizon) was 26.8 months for nivolumab and 13.09 months for docetaxel, resulting in an increase of more than 3 months of survival benefit. Because patient life expectancy is less than 24 months (Health and Social Care Information Centre, 2015) and the licensed population is likely to include low patient numbers (estimated 1,413), we believe that nivolumab will fulfil NICE's end-of-life criteria (Table 40).

Table 40: 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, 2015).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The proportional hazards assumption used in the published OS analysis has been shown not to hold (refer to Section 4.10). Therefore, mean OS from the cost-effectiveness model may be considered more appropriate. This estimates mean OS, over the model time horizon of 20 years, to be 26.8 months for nivolumab compared with 13.09 months for docetaxel. This means that nivolumab is anticipated to extend life by greater than 3 months compared with docetaxel.
The treatment is licensed or otherwise indicated for small patient populations	The non-squamous NSCLC patient population potentially eligible for nivolumab treatment is expected to be very small (estimated 1,413 patients) (please see Section 3.3 for estimation method). Nivolumab is also indicated for the treatment of advanced (unresectable or metastatic) squamous NSCLC in adults. The expected number of eligible patients for which nivolumab is being appraised in that submission is 853.* 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.†

Abbreviations: NHS = National Health Service; NSCLC = Non-Small Cell Lung Cancer

* Advanced or metastatic NSCLC estimates (n = 19,138) (Health and Social Care Information Centre, 2014) and proportion of patients with squamous NSCLC (Powell et al., 2013) combined with estimates of proportion of patients receiving treatment (NICE, 2010a), and of those, patients who relapse (Sculier and Moro-Sibilot, 2009).

† Office for National Statistics population estimates (n = 201,385) (Office for National Statistics, 2014a) and melanoma incidence estimates (Office for National Statistics, 2014b) extrapolated using increased incidence rate of 3.5% previously used in melanoma submissions (NICE, 2012a; NICE, 2012b; NICE, 2014c).

4.14 Ongoing studies

Study	Study description	Data availability
CheckMate 057	RCT study described in this submission	
CheckMate 003	Non-RCT study described in this submission	
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) This study is primarily a (Phase IIIb/IV) safety study, although it also will include comparative outcome data examining patients who were randomised to stop treatment after 1 year. Study includes Cohort A that is treated until disease progression, unacceptable toxicity or withdrawal of informed consent and Cohort B treated until 1 year (52 weeks).	Initial safety data were presented in June 2015, and further safety data were presented third quarter 2015. [redacted]
Indirect Treatment Comparison	Indirect Treatment Comparison comparing nivolumab with nintedanib in combination with docetaxel	[redacted]

Abbreviations: RCT = Randomised Controlled Trial

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 non-squamous NSCLC from a UK NHS and PSS perspective.
- The health economic model was a standard three-health-state cohort model (progression-free [PF], progressed disease [PD] 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. This model is consistent with the model submitted for nivolumab in squamous NSCLC but with additional modifications to address specific critiques raised by the ERG on the squamous model.
- 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. Therefore, the economic analysis was consistent with the NICE reference case.
- In line with the NICE decision problem, the base-case comparator was docetaxel using study data and nintedanib plus docetaxel using an ITC.
- Efficacy, resource use, costs and utilities were estimated based on information from CheckMate 057, previous technology appraisals to NICE, published sources and clinical experts. EQ-5D–based utilities were collected in CheckMate 057 and applied in the model.
- In the base-case analysis, OS and treatment duration from CheckMate 057 was modelled using the generalised gamma distribution for nivolumab and comparators.
- The base-case ICER is £[redacted] per QALY gained versus docetaxel and £[redacted] per QALY gained versus nintedanib plus docetaxel.
- 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 were also undertaken, which resulted in ICERs versus docetaxel of £[redacted] and £[redacted], respectively. In comparison to nintedanib plus docetaxel, the ICERs for a 1-year and 2-year treatment-stopping rule resulted in ICERs of £[redacted] and £[redacted], respectively. This suggests that as duration on treatment 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 OS, treatment efficacy (HR on OS applied to docetaxel), body weight, discount rate and utility of PF and PD health states. 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

5.1.1 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. Although the decision problem is relevant to a non-squamous-only NSCLC population, the published economic literature is often reported as NSCLC; therefore, the focus of the review was to identify evidence in previously treated locally advanced or metastatic NSCLC.

Literature was searched in biomedical electronic literature databases recommended by HTA agencies (CADTH, 2014; IQWIG, 2008; NICE, 2015a; NICE, 2015c). MEDLINE® In-process was searched to ensure that non-indexed citations were retrieved. Table 41 presents the databases that were searched.

Table 41: 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 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	

Abbreviations: HTA = Health Technology Assessment

Appendix 11 presents the search strategy. 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.

Table 42 summarises the inclusion/exclusion criteria for the systematic review. The range of comparators included in the search was broader than the scope of the decision problem; this was to allow additional analysis outside the scope of the decision problem in the future. Table 43 presents the studies assessed to have met the inclusion criteria.

Table 42: Inclusion/exclusion criteria for the economic review in NSCLC

	Inclusion criteria	Exclusion criteria	Rationale
Patient population (P)	• Adults diagnosed with locally advanced or metastatic NSCLC previously treated with at least one previous line of chemotherapy	• Patients aged < 18 years • Patients with stage I-IIIa disease • Chemotherapy treatment-naïve patients	• To ensure that evidence related to economic evaluations of NSCLC will be captured, as the studies specifically in non-squamous NSCLC may be limited
Intervention (I)	• Nivolumab	• Studies investigating first-line treatment for NSCLC • Studies assessing included intervention as an adjuvant or neoadjuvant 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	• Nivolumab is the intervention of interest within the decision problem
Comparator (C)	• Any pharmacological intervention • Placebo • BSC • Afatinib • Docetaxel • Erlotinib • Gefitinib • Nintedanib (in combination with docetaxel) • Pemetrexed monotherapy	• Non-pharmacological interventions, other than BSC	• The included treatment options are broader than the scope but are included to allow further analysis in the future if required

	Inclusion criteria	Exclusion criteria	Rationale
	• Ceritinib • Crizotinib • Platinum-based chemotherapy in combination with gemcitabine, vinorelbine, pemetrexed, or a taxane		
Outcome (O)	• All reported outcomes	• 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	• Studies reporting only cost and resource use data where no formal economic analysis has been undertaken	• 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	• Animal/in vitro studies • Single-arm studies • Studies with no sub-group data for disease and adult population • Reviews, letter to the editors and editorials • Conference abstracts prior to 2012	• The aim of the review was to identify relevant studies that reported quality of life data • Studies are published within 3 years of results presentation in conference abstracts. Studies that are terminated or are of poor quality are generally not published within this time frame, and conference abstracts prior to 2012 thus were excluded
Line of therapy	• Second- or further-line of therapy	• First-line of therapy	• Second- or further-line are the relevant lines of treatment

	Inclusion criteria	Exclusion criteria	Rationale
Search timeframe	• 2000 to 2015 (last 15 years)	• Prior to 2000	• 2000-2015 was deemed relevant to reflect models that are representative of the current NSCLC landscape
Language	• Only studies with the full-text published in English will be included	• Studies with the full-text published in languages other than English	• It is expected that most evidence in this disease area will be available in English

Abbreviations: BSC = Best Supportive Care; NSCLC = Non-Small Cell Lung Cancer

* 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.

5.1.2 Description of identified studies

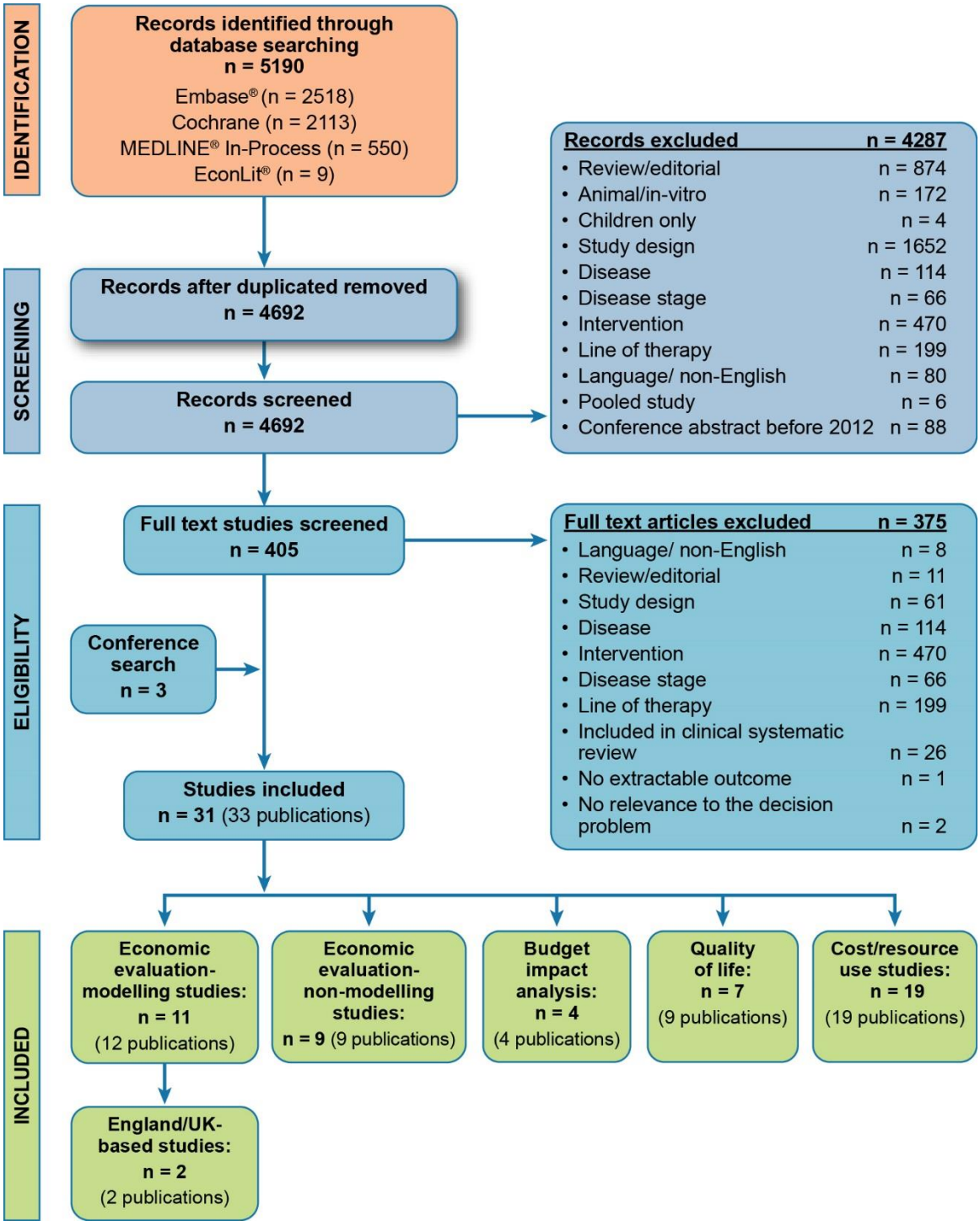
The literature search yielded a total of 5,190 studies, of which 31 met the inclusion/exclusion criteria. Of these, 11 studies were modelling studies (Figure 25). Table 43 presents an overview of the two UK-based studies. Both of these studies were in a broad NSCLC population. No study evaluated the cost-effectiveness of treatments in a non-squamous-only population, and no study evaluated nivolumab.

A review was also undertaken of published NICE technology appraisals to identify appraisals in previously treated NSCLC with the aim of identifying the structure of previous models in this area and potential sources of resource use or utility values. Table 44 presents an overview of the four relevant appraisals identified in this review.

The two UK-based publications (Table 43) compared docetaxel and BSC or erlotinib and docetaxel in a previously treated population of patients with NSCLC. Holmes et al. (2004) reported an incremental cost per LYG for docetaxel versus BSC of £13,863. Lewis et al. (2010) reported 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 PF, PD and death.

Appendix 12 presents a quality assessment for each of the cost-effectiveness studies.

Figure 25: Identification of economic evaluations identified in the systematic literature review



Abbreviation: UK: United Kingdom

Table 43: Summary list of UK-based published cost-effectiveness studies

Author	Patient population (mean age in years [range])	NSCLC type (NSQ, SQ, or NR)	Disease stage	Line of therapy	Treatments being compared	Evaluation type, cost year	Perspective	Model design	QALYs	Total costs	ICER
Holmes et al. (2004)	Previously treated with platinum-based chemotherapy, taxane-naïve, with PS ≤ 2 Age: NR	NR	NR	Second	D vs. BSC	Cost-effectiveness analysis Costs: 2000/2001	UK NHS	Difference in weighted mean survival estimated by calculating the area under the survival curves	LYG vs. BSC: 3.82 months (0.32 years)	Net incremental cost: £4,432	Incremental cost per LYG for D vs. BSC: £13,863
Lewis et al. (2010)	Previously treated stage IIIB-IV NSCLC with PS ≤ 3 E: 62 (34-87); D: 61 (37-73)	NR	IIIB, IV	Second	E vs. D	Cost-utility analysis 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; D = Docetaxel; E = Erlotinib; ICER = Incremental Cost-Effectiveness Ratio; LYG = life-year gained; NHS = National Health System; NSCLC = Non-Small Cell Lung Cancer; NR = Not Reported; NSQ = Non-Squamous; PS = performance status; SQ = Squamous; UK = United Kingdom

Table 44: 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 (2013b)	Second-line ALK+ patients with advanced NSCLC	NR	D and BSC	CUA	Semi-Markov model	3 state: PF, PD, death	15 years	30 days	C: 1.949 D: 0.981 BSC: 0.592	C: £54,149 D: £13,922 BSC: £6,021	C vs. D: £41,544 C vs. BSC: £35,455
Erlotinib TA 162 NICE (2008)	Second-line patients with NSCLC	R	D	CUA	Markov model	3 state: PF, PD, death	2 years	Per month	E: 0.201 D: 0.176	E: £12,707 D: £12,621	E vs. D: £3,354
Nintedanib (in combination with docetaxel) GID-TAG449* NICE (2015f)	Second-line patients with locally advanced, metastatic or locally recurrent NSCLC	R (final appraisal determination)	D	CUA	Partitioned survival (area under curve) approach	3 state: PF, 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 (2015g)	Second-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: PF after second-line chemotherapy, post-progression, death	5 years	21 days	EGFR– population D: 0.5939 E: 0.4863 EGFR unknown population BSC: 0.3452 E: 0.4484 No Assessment Group analysis for gefitinib	EGFR– 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– population D vs. E: £15,359 EGFR unknown population E vs. BSC: £61,132 No Assessment Group analysis for gefitinib

Abbreviations: ALK = Anaplastic Lymphoma Kinase; BSC = Best Supportive Care; C = Crizotinib; CUA = Cost-utility Analysis; D = Docetaxel; E = Erlotinib; EGFR = Epidermal Growth Factor Receptor; ERG = Evidence Review Group; ICER = Incremental Cost-effectiveness Ratio; MTA = Multiple Technology Appraisal; N = Nintedanib; NICE = National Institute for Health and Care Excellence; NR = Not recommended; NSCLC = Non-Small Cell Lung Cancer; PD = Progressive Disease; PF = Progression Free; QALY = Quality-Adjusted Life-Year; R = Recommended; TA = Technology Appraisal

* Final appraisal determination.

5.2 De novo analysis

5.2.1 Patient population

The economic evaluation considers previously treated adult patients with advanced or metastatic non-squamous NSCLC, which is consistent with the study population of CheckMate 057. This population is also consistent with the marketing authorisation for nivolumab and the decision problem (see Section 1.4).

5.2.2 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 26). The model structure is in line with the clinical pathway of care for the treatment of previously treated non-squamous NSCLC in the UK and is consistent with previous economic evaluations submitted to NICE in advanced NSCLC (including for nivolumab in squamous NSCLC) and other metastatic cancers (NICE, 2010b; NICE, 2012c; NICE, 2015d; NICE, 2015f).

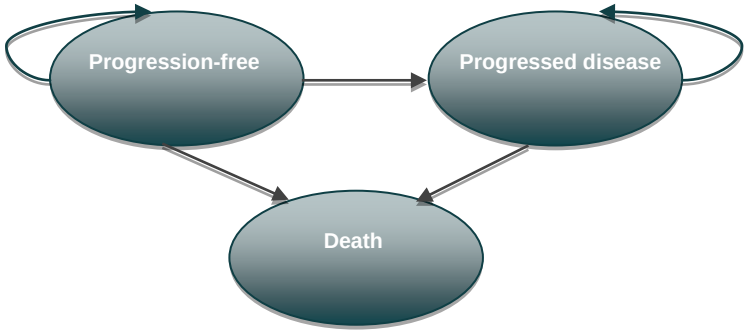
The base-case evaluates the cost-effectiveness of nivolumab compared with docetaxel and nintedanib plus docetaxel. These two comparators represent the current standard of care in the second-line setting in the UK (for non-squamous NSCLC) and are the treatments most likely to be displaced from UK clinical practice following the introduction of nivolumab. CheckMate 057 evaluated the efficacy, safety and tolerability of nivolumab in previously treated patients with non-squamous NSCLC; docetaxel was the comparator in this study (Borghaei et al., 2015). Clinical parameters in the economic evaluation are derived from the CheckMate 057 clinical study and the ITC outlined in Section 4.10, 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. To address ERG comments on the model in squamous NSCLC, in this model (NICE, 2015d), the PF health state occupancy is modelled using time to treatment discontinuation (TTD), rather than PFS. This means that drug costs and utility benefit are based on actual treatment duration and that patients who are treated beyond radiological progression, as they are gaining some benefit from treatment, continue to accrue utility benefit for this period.

The number of patients in each health state was estimated using the partitioned survival method.[14] The proportion of patients in the PD health state is calculated as the difference between OS and TTD. The partitioned survival approach allows for modelling of OS and TTD based on study-observed events, which is expected to accurately reflect disease progression and the long-term expected survival profile of patients treated with nivolumab.

[14] The number of patients occupying each state in the model is derived directly from the cumulative survival probabilities for treatment discontinuation and OS. The proportion of patients occupying the progressed disease state was calculated as the proportion alive (OS) minus the on treatment proportion alive (PF).

Figure 26: Health states in the economic model



Note: as described above, the “progression-free” health state is modelled using time to treatment discontinuation. Nonetheless, the health state is named “progression-free” in line with previous models.

Patients with locally advanced or metastatic non-squamous NSCLC who have failed platinum-based chemotherapy enter the model in the PF health state. Patients who remain PF are treated with either nivolumab, docetaxel or nintedanib plus docetaxel. At the end of each cycle, a patient remains in the same health state or transitions to PD or death (see Figure 26). A restriction is that patients cannot transition to an improved health state; this is consistent with previous economic modelling in NSCLC (NICE, 2010b; NICE, 2012c; NICE, 2015d; NICE, 2015f).

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 (Q2W) and docetaxel (Q3W). A half-cycle correction is implemented to mitigate bias.

All patients are treated until treatment discontinuation, which may be beyond progression, consistent with CheckMate 057 protocol. 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 45: 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; 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 life-years)	NICE Reference Case
Discount of 3.5% for utilities and costs	Yes	NICE Reference Case
Perspective (NHS/PSS)	Yes	NICE Reference Case

Abbreviations: 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; STA = Single Technology Appraisal

5.2.3 Intervention technology and comparators

In line with the decision problem (Section 1.4), the base-case comparator in the economic analysis is docetaxel and nintedanib plus docetaxel. Docetaxel is the current standard of care in previously treated patients with non-squamous NSCLC in the UK, with approximately 85% market share, and is the treatment most likely to be displaced by the introduction of nivolumab (Bristol-Myers Squibb, 2015d). It is anticipated that uptake of nintedanib in combination with docetaxel will increase over the next couple of years, as a result of the recent positive NICE opinion; however, there is currently limited use. The dosing and administration frequencies for all treatments in the evaluation are in line with their marketing authorisations.

5.3 Clinical parameters and variables

5.3.1 Overall method of modelling survival

The primary data source for the economic model was patient-level data from the CheckMate 057 clinical study. The follow-up period in CheckMate 057 was shorter than the required length of the economic analysis (a lifetime equivalent), and extrapolation of the TTD and OS data from CheckMate 057 was required for the partitioned survival (area under the curve) approach. This involved identifying parametric survival models for both OS and TTD.

The guidance from the NICE DSU and from Royston and colleagues was followed to identify the best-fitting parametric survival model for OS and TTD (Latimer, 2013; Royston and

Parmar, 2002). Figure 27 presents 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 057 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 was explored. These included the standard exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma models, as well as a series of flexible models such as spline-based models (additional details around flexible-based models are given in Appendix 19).[15]
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. Finally, the choice of parametric model was validated for clinical plausibility of both short-term and long-term extrapolations.

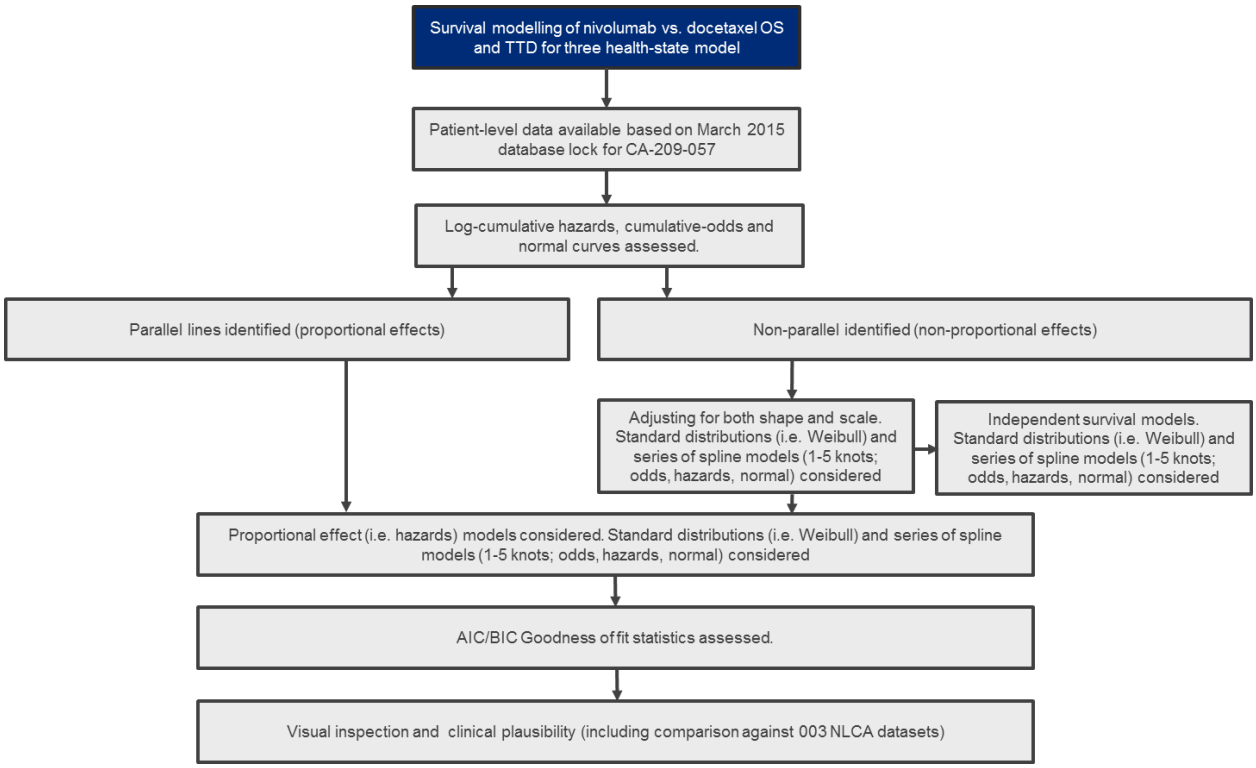
The final choice of parametric survival model adopted for the base-case model was a balance between statistical fit (as per AIC/BIC values) within the period when patient-level data were available and long-term clinical plausibility of the extrapolated model, based on clinical opinion. Specifically, the long-term clinical plausibility of the extrapolated model was based on validation against available nivolumab clinical study data with longer follow-up than CheckMate 057 (in-study validation), RWD where available and the input from UK clinicians.

The following data sets were available for validation:

- Clinical study data: survival data were available for nivolumab-treated patients from CheckMate 003 (Phase Ib study) for up to 4 years (Section 4.11.5).
- RWD: the NLCA registry (UK): survival data were available for patients diagnosed with stage IV NSCLC from 2008 to 2012. The survival data represent current standard of care in the UK. Further details on the NLCA registry are given later in this section (Health and Social Care Information Centre, 2014; Howlader et al., 2015).

[15] Whilst flexible models, such as 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 flexible models provided the best fit to the data, they were explored in full to determine their appropriateness to the economic model.

Figure 27: Identifying parametric survival models based on NICE DSU guidelines



Source: Latimer (2013)

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CA-209-017 = CheckMate 057; 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

5.3.2 Extrapolation model for OS

Figure 28 shows the cumulative survival plot for OS based on CheckMate 057 interim (12-month) data cut. Due to the crossing of the OS curves seen at approximately 7 months, it is evident that proportional hazards do not hold for OS. Therefore, steps 3 to 5 above were followed to identify the best-fitting curves. In addition, it is evident that no single survival model adjusted for shape and scale could capture this relationship because a single parametric curve could not model cross-over in OS survival curves. Therefore, independent parametric survival models fitted separately to the docetaxel and nivolumab arms were considered.

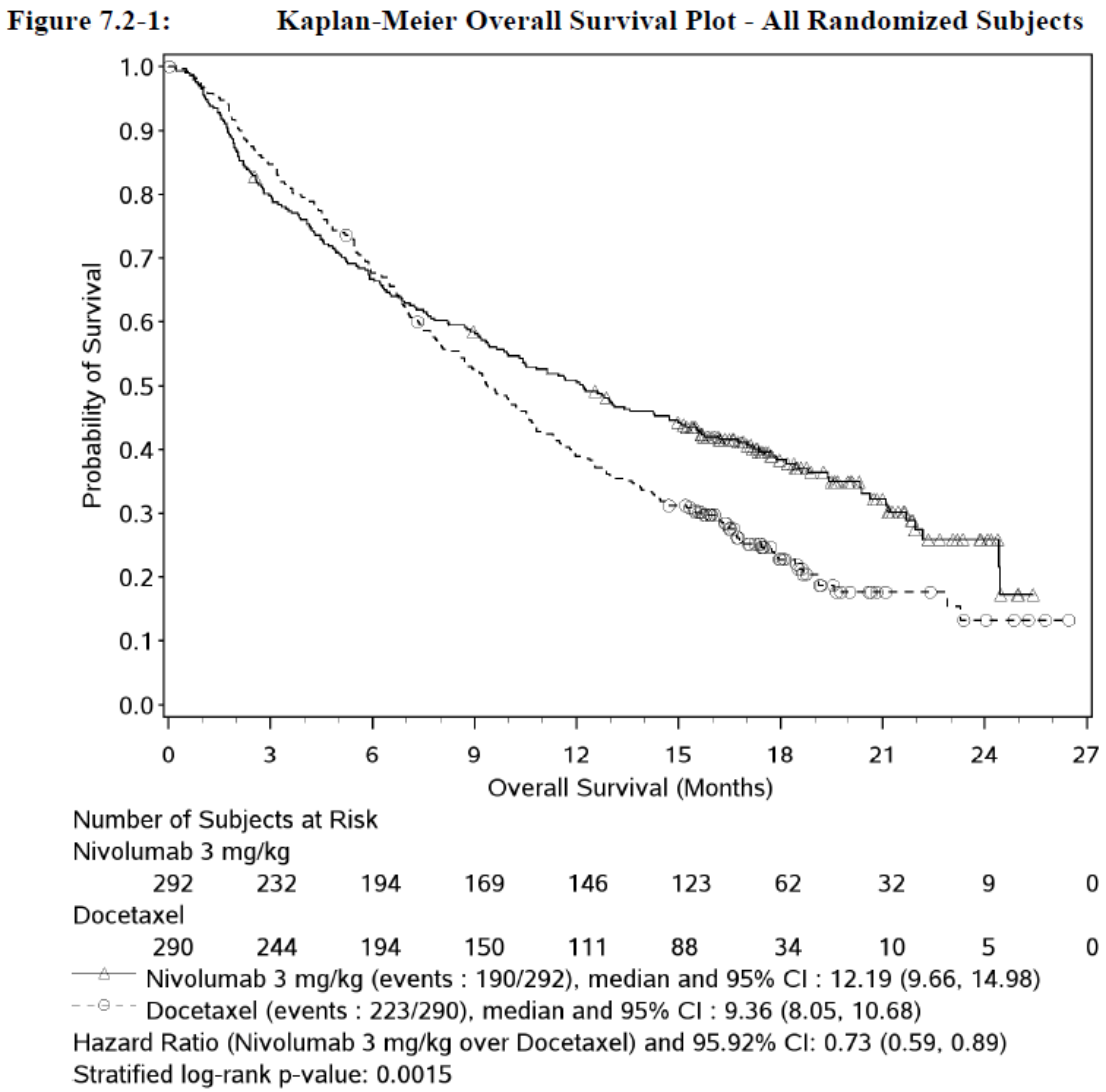
Table 46 summarises the AIC/BIC values for the variety of independent parametric distributions explored for OS for docetaxel and nivolumab. Flexible models can increase in complexity depending on the number of intermediate knots defined within the distribution (See Appendix 19). The implicit assumption within these models is that the number of knots represents the number of potential heterogeneous sub-groups of patients—that is, 2-knot, 3-knot, 4-knot models represent 3, 4 and 5 sub-groups, 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 flexible 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 used. In light of this, although up to 5-knot models were tested, only 1-knot and 2-knot models were explored within the economic model.

Table 46 suggests that, in terms of statistical fit, the three best-fitting parametric survival models are the gamma, generalised gamma and 1-knot spline distributions for docetaxel. Correspondingly, the three best-fitting survival models for nivolumab are the 2-knot spline, log-normal and generalised gamma distributions.

Figure 29 and Figure 30 show the fit of each distribution to the CheckMate 057 OS data for docetaxel and nivolumab, respectively. Figure 31 and Figure 32 show the long-term extrapolation of each distribution.

Figure 28: Cumulative survival plot for overall survival based on CheckMate 057



Source: (Bristol-Myers Squibb, 2015b)

Abbreviations: OS = Overall Survival

Table 46: Summary of goodness-of-fit data for independent survival models for overall survival

Docetaxel

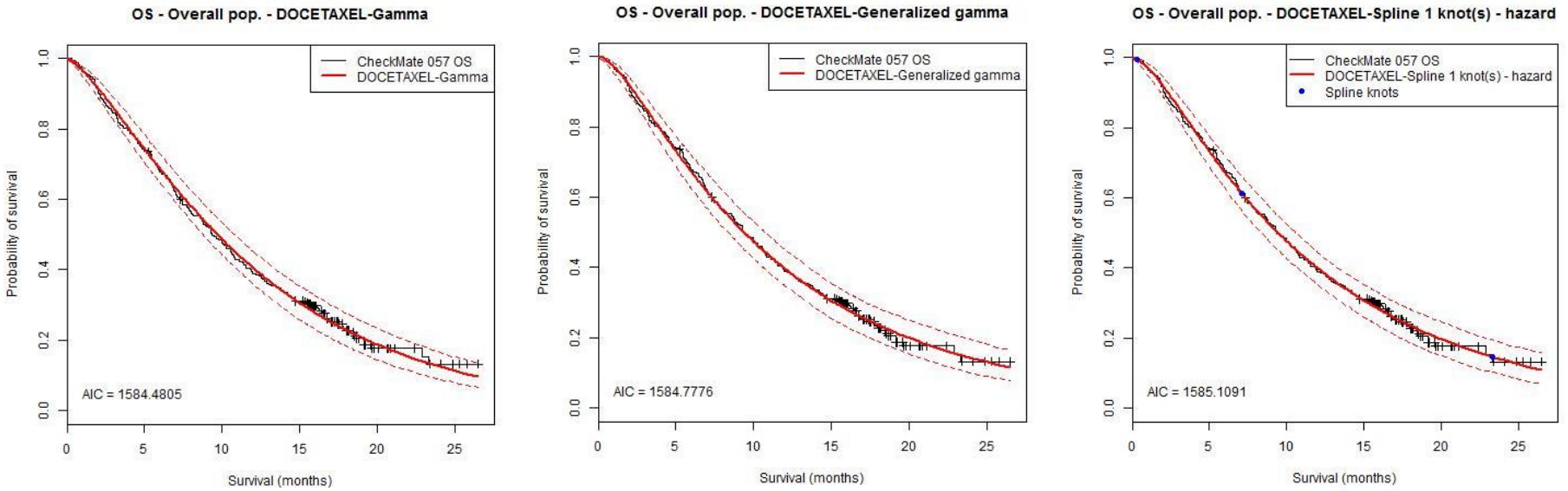
Distribution	AIC	BIC
Gamma	**1,584.480**	**1,591.820**
Generalised gamma	**1,584.778**	**1,595.787**
Spline 1 knot(s): hazard	**1,585.109**	**1,596.119**
Log-logistic	1,586.094	1,593.434
Weibull	1,586.523	1,593.863
Spline 2 knot(s): hazard	1,586.951	1,601.630
Spline 3 knot(s): hazard	1,587.661	1,606.011
Spline 4 knot(s): hazard	1,587.888	1,609.908
Log-normal	1,588.131	1,595.471
Spline 5 knot(s): hazard	1,589.584	1,615.273
Gompertz	1,594.365	1,601.705
Exponential	1,599.007	1,602.676

Nivolumab

Distribution	AIC	BIC
Spline 2 knot(s): hazard	**1,457.602**	**1,472.309**
Spline 3 knot(s): hazard	1,458.793	1,477.176
Spline 4 knot(s): hazard	1,459.951	1,482.012
Spline 5 knot(s): hazard	1,461.753	1,487.491
Log-normal	**1,461.828**	**1,469.181**
Generalised gamma	**1,463.826**	**1,474.856**
Spline 1 knot(s): hazard	1,464.365	1,475.395
Log-logistic	1,467.749	1,475.103
Exponential	1,469.660	1,473.337
Weibull	1,471.354	1,478.707
Gamma	1,471.611	1,478.964
Gompertz	1,472.125	1,479.478

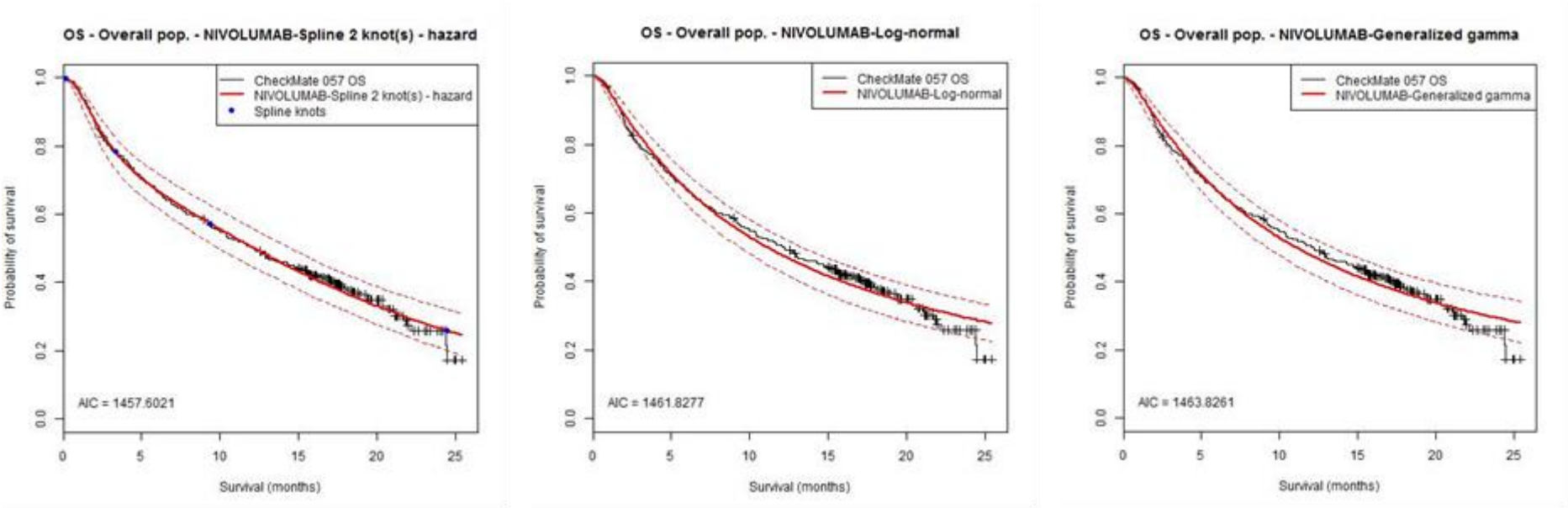
Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = Overall Survival

Figure 29. Plots of gamma, generalised gamma and 1-knot spline hazards distribution for docetaxel overall survival



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

Figure 30. Plots of 2-knot spline, log-normal and generalised gamma distributions for nivolumab overall survival



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

Figure 31: Plot of long-term extrapolation of three best-fitting parametric models for docetaxel overall survival extrapolation

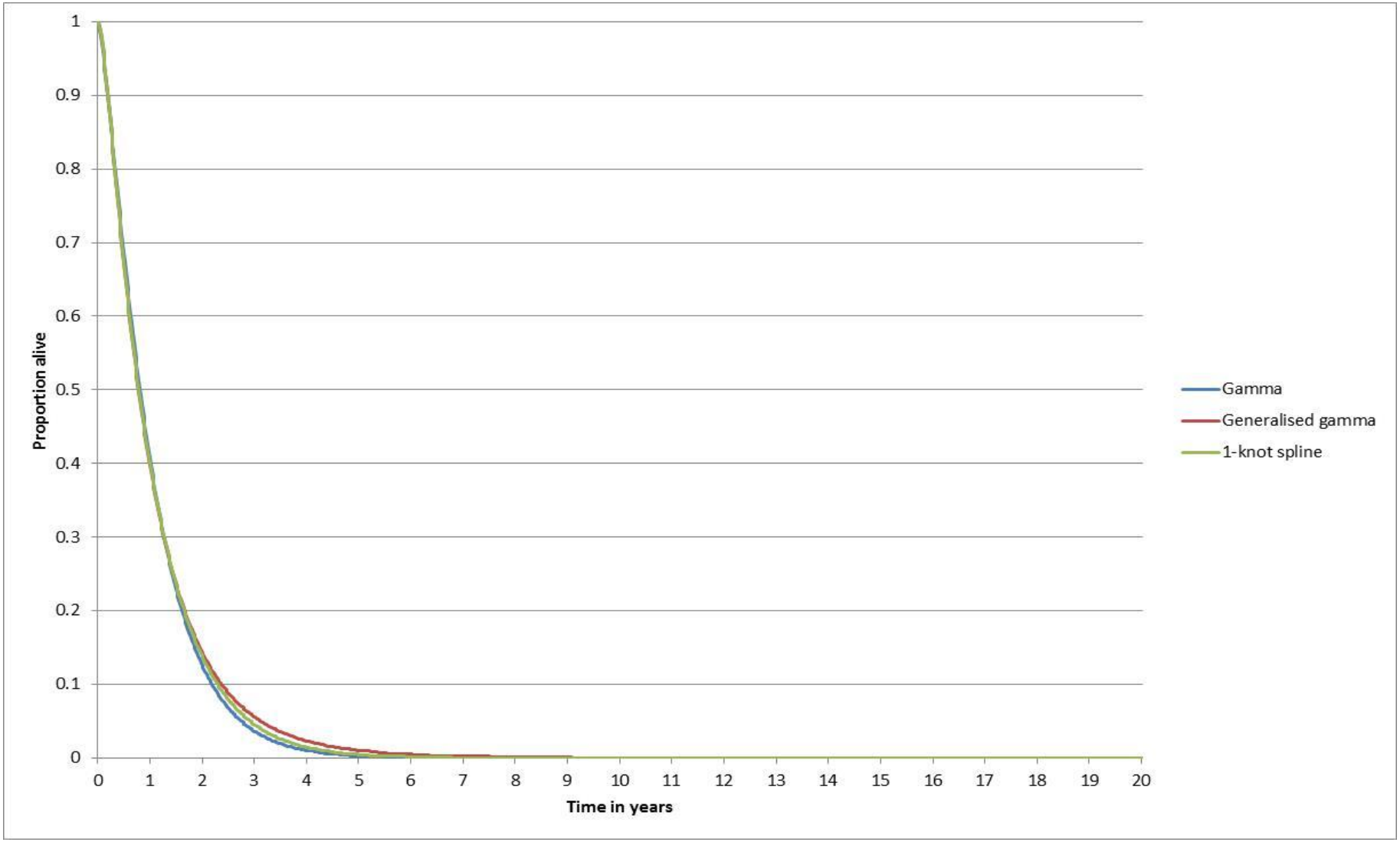
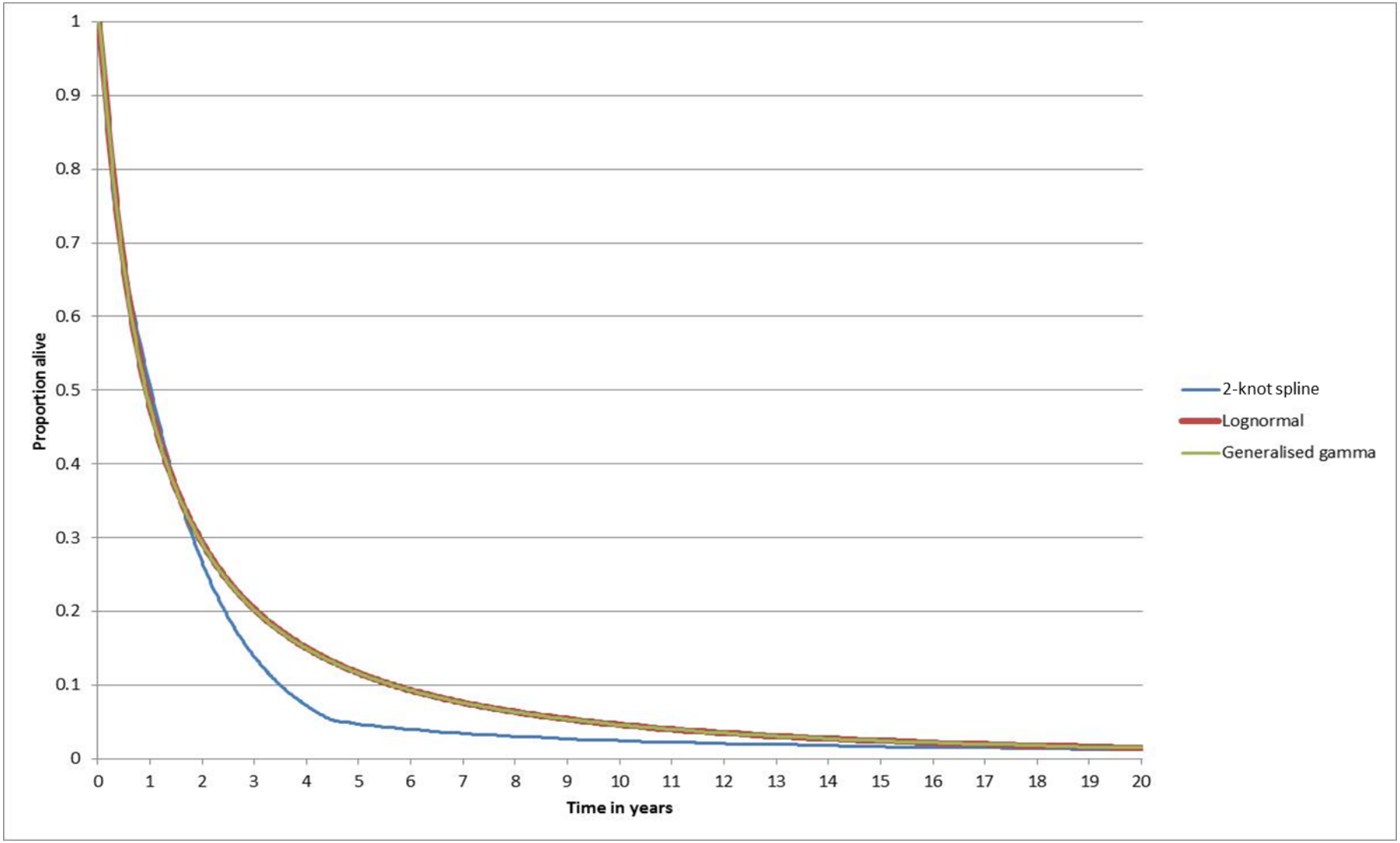


Figure 32: Plot of long-term extrapolation of three best-fitting parametric models for nivolumab overall survival extrapolation



5.3.3 Selection of base-case OS parametric distribution

Determining the base-case parametric model for OS was based on validating the best-fitting curves against both clinical study data and RWD to ensure the clinical plausibility of the extrapolation.

Table 47 provides a comparison of the OS extrapolations for docetaxel and nivolumab against CheckMate 057 and the CheckMate 003 study, which provides the longest term follow-up of patients on nivolumab[16]. Table 47 suggests that, for docetaxel, the three distributions provide comparable survival rates to CheckMate 057 at both 1 year and 18 months. In addition, within the docetaxel extrapolations, the proportion alive over time is not significantly different between the three distributions. This is also evident in Figure 31, which shows that the distributions are very similar in terms of proportion alive over the time horizon of the model.

Table 47 suggests that, for nivolumab, the three distributions provide comparable survival rates to CheckMate 057 at both 1 year and 18 months. However, beyond 18 months, the log-normal and generalised gamma distributions are more consistent with the survival rates seen within CheckMate 003 than the 2-knot spline distribution. For example, 4-year survival estimated from the log-normal and generalised gamma distributions and CheckMate 003 are all 15% in comparison to 7% estimated from the 2-knot spline model.

It should be noted that the survival rates reported from the CheckMate 003 study are for a population of patients that stopped receiving treatment at 96 weeks (Section 4.11.2). Therefore, it would be clinically plausible to expect that the future survival rates of patients in CheckMate 057—which is based on a treat-to-progression protocol—would at a minimum be in line with the survival rates measured in patients who stopped treatment at 96 weeks. In addition, it is important to note that, although the patients enrolled in CheckMate 003 may be different than those enrolled in CheckMate 057, the 1-year and 18-month survival rates between the two studies are similar. Furthermore, there is very little difference in OS rates at 1, 2 and 3 years for squamous versus non-squamous patients in CheckMate 003 (Gettinger et al., 2015). Therefore, it is assumed that nivolumab patients in CheckMate 057 will follow a similar survival profile to patients in CheckMate 003.

[16] CheckMate 003 included patients with both squamous and non-squamous NSCLC, but no significant differences were seen between squamous and non-squamous patients; other baseline demographics and disease characteristics, such as age, level of pre-treatment and performace status were similar to those in Checkmat 057.

Table 47: Overall survival estimates from nivolumab studies compared with extrapolations

Data source	Curve	Proportion alive				
		1 year	1.5 years	2 years	3 years	4 years
Model estimates for docetaxel OS	Gamma	41%	23%	13%	4%	1%
	Generalised gamma	40%	24%	14%	6%	2%
	1-knot spline	40%	24%	14%	5%	1%
Model estimates for nivolumab OS	2-knot spline	51%	37%	27%	14%	7%
	Log-normal	48%	37%	29%	20%	15%
	Generalised gamma	48%	37%	29%	20%	15%
CheckMate 057	Nivolumab OS	51%	39%	NA	NA	NA
	Docetaxel OS	39%	23%	NA	NA	NA
CheckMate 003	Nivolumab OS	42%	31%	24%	18%	15%

Sources: Horn et al. (2015); Bristol-Myers Squibb (2013b)

Abbreviations: OS = Overall Survival; NA = not available

Beyond 4 years, there is no clinical survival evidence on nivolumab to facilitate long-term validation. Therefore, RWD from a non-nivolumab pre-treated cohort up to 5 years from the NLCA were used. The NLCA looks at the care delivered for people diagnosed with lung cancer and mesothelioma in England, Wales and Scotland; therefore, survival estimates reported in NLCA can be considered representative of UK clinical practice (Health and Social Care Information Centre, 2014). The NLCA provided 1-year conditional survival data from data of diagnoses for patients with advanced stage IV NSCLC from 2008 to 2012 (Health and Social Care Information Centre, 2014; Howlader et al., 2015). Please note that data from the SEER programme have not been used in this appraisal, as it was included within the nivolumab in squamous NSCLC appraisal and discounted by the ERG and NICE committee because it was US based and cannot be validated in UK clinical practice (NICE, 2015d).

In CheckMate 057, patients were nearly 1 year from diagnosis when entering the study; median duration of time from initial diagnosis to randomisation was 0.82 years for patients on nivolumab and docetaxel (Bristol-Myers Squibb, 2015b). Therefore, predicted OS rates from the economic model were compared against NLCA OS rates for the following year. 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.

Table 48 presents a comparison of the conditional survival estimates from CheckMate 057 and the NLCA. It is evident from Table 48 that the log-normal and generalised gamma model for nivolumab OS provides a closer estimate to the conditional survival seen in the NLCA. With regards to the docetaxel arm, the conditional survival from the NLCA is above what is predicted for docetaxel within the economic model. As the NLCA data represent conditional survival across all existing treatments for stage IV NSCLC and not just docetaxel, the differences in conditional survival could be driven by different types of treatments and patient characteristics. Although the same could be said about the comparison for nivolumab, it is evident from Table 48 that the conditional survival predicted from the model is still marginally

below that from the NLCA. Therefore, it is assumed that, at a minimum, nivolumab has comparable survival to current therapies for NSCLC. In addition, the survival predicted from the docetaxel arm in the model was validated with clinicians, as outlined in Section 5.11, and it was determined that survival from the model was more appropriate than that of the NLCA for docetaxel patients.

Table 48: Comparison of conditional survival estimates predicted from overall survival parametric distributions versus real-world data

OS parametric distributions	**Curve**	**Conditional survival**	
	Start year	**2**	**3**
	End year	**3**	**4**
Docetaxel	Gamma	29%	28%
	Generalised gamma	39%	41%
	1-knot spline	33%	31%
Nivolumab	2-knot spline	52%	52%
	Log-normal	69%	74%
	Generalised gamma	69%	74%
RWD (NLCA)*	**Start year**	**3**	**4**
	End year	**4**	**5**
NLCA stage IV	Treatment not specified	78.6%	90.9%

Sources: Health and Social Care Information Centre (2014); Howlader et al. (2015); Bristol-Myers Squibb (2015b)

Abbreviations: NLCA = National Lung Cancer Audit; NSCLC = Non-Small Cell Lung Cancer; OS = Overall Survival; RWD = Real-World Data

* The NLCA dataset measures absolute survival rates of patients diagnosed with NSCLC; therefore, it inherently captures “all-cause” mortality. The dataset also includes squamous and non-squamous NSCLC.

Beyond 5 years, there are no clinical or RWD to facilitate the validation of the OS extrapolation. In this context, the validation of the OS extrapolation was based on input from clinical experts (see Appendix 20). Therefore, two one-to-one telephone interviews were conducted with clinical oncologists with experience in treating patients with advanced NSCLC in the UK. During the interview, the long-term extrapolation for OS for nivolumab and docetaxel was presented in a graphical and tabular format from 0 to 20 years. In addition, these were compared against the survival rates from CheckMate 057 and CheckMate 003. The clinicians were asked between the different extrapolations explored which model would be considered the most clinically plausible in terms of the proportion of patients being alive from 1 to 20 years. Specifically, it was estimated by the clinicians that, for docetaxel, the percentage alive at 3, 5 and 10 years would be < 5%, 1% and 0%, respectively. For nivolumab, it was estimated that the 2-knot spline model appeared to be too pessimistic considering the survival rates in CheckMate 003. In addition, it was acknowledged that

predicting survival for nivolumab patients would be difficult without more data, although an estimated approximation of the OS rates that might be seen at 3, 5, 10 and 20 years was 20%, 10%, 5% and 2%, respectively.

Upon consideration of all of the evidence (statistical and visual fit, validation against CheckMate 003 and NLCA and clinical input), it was recommended that the gamma/generalised gamma distribution be used for docetaxel OS extrapolation and the log-normal/generalised gamma survival model be used for the nivolumab OS extrapolation. The NICE DSU guidance states when using independent parametric models for extrapolation that, if possible, the same functional form should be adopted for intervention and comparators. In light of this, the generalised gamma model was used in the base-case for OS extrapolation, as it met the following criteria:

- Goodness-of-fit statistics
- Clinical plausibility
- Visual inspection of fit
- Internal validation against all available nivolumab clinical study data
- External validation using conditional survival estimates available from NLCA
- Interviews with clinical experts

NLCA registry data

The economic analysis uses the NLCA registry data to assess the clinical plausibility and validity of the short- to intermediate-term extrapolation methods for OS.

Baseline characteristics of patients registered in CheckMate 057 were compared with those of patients in the NLCA (Table 49). For median age, age range and male to female ratios, study data appear well aligned with RWD from NLCA. 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 study patients match those seen in the routine clinical practice.

Table 49: Comparison of baseline characteristics from CheckMate 057 and NLCA

		CheckMate 057*	NLCA
Median age (years)		62	72†
Age range (years)		21-85	40-90‡
	Age categorisation (years)		
≤ 55		NR	9.2%‖
< 65		NR	35.8%‖
≥ 70		NR	44.7%‖
≥ 75		7%	24.5%‖
% males		55% male	58% male†
	Disease stage		
Stage IIIb		8%	NR
Stage IV		92%	32%†

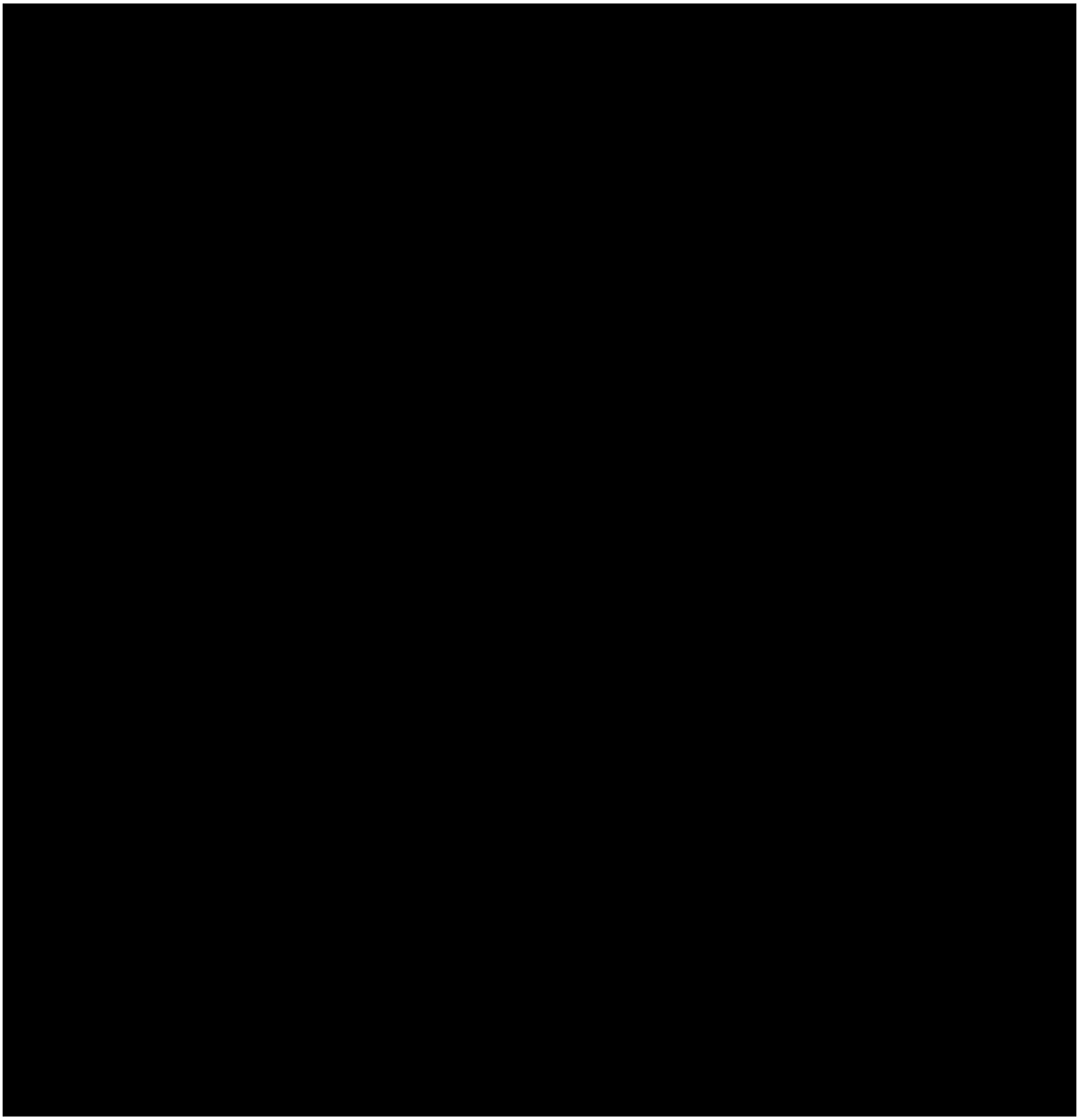
Sources:
* Borghaei et al. (2015).
† Based on 120,745 patients with NSCLC in NLCA database seen from 2004 to 2014 in Khakwani et al. (2013).
‡ Health and Social Care Information Centre (2014).
‖ Data from 10,991 patients with NSCLC operated on from 2004 to 2010 from NLCA database in Powell et al. (2013).
Abbreviations: NLCA = National Lung Cancer Audit; NR = Not Reported; NSCLC = Non-Small Cell Lung Cancer

5.3.4 Selection of the base-case PFS/TTD parametric distribution

As stated in Section 5.2.2, the proportion of patients in the PF health state receive treatment with either nivolumab or docetaxel until discontinuation. Within CheckMate 057, data on both PFS and TTD were collected. There could be instances where PFS is not equal to TTD as patients may discontinue treatment prior to progression due to toxicity. In addition, per the study protocol for CheckMate 057 nivolumab patients may be given treatment beyond progression based on the investigators assessment of whether the patient would continue to receive clinical benefit. A comparison of PFS and TTD for nivolumab and docetaxel was undertaken (

Figure 33).

Figure 33: CheckMate 057: progression-free survival versus time to treatment discontinuation: nivolumab and docetaxel



Abbreviations: PFS = Progression-Free Survival.

This analysis showed that, for nivolumab, the Kaplan-Meier (KM) curve for TTD was slightly above PFS; in comparison for docetaxel, the KM curve for TTD was slightly below PFS. Because of the differences in PFS and TTD, the model used TTD data to estimate the proportion of patients in the PF health state, as recommended by the ERG in the recent submission for squamous NSCLC (NICE, 2015d). For the nivolumab treatment group in CheckMate 057, a total of 71 patients were treated beyond progression, 16 of whom demonstrated a non-conventional pattern of benefit (Bristol-Myers Squibb, 2015b), further detail can be found in Section 4.7.1. If TTD is used in the model, instead of PFS drug treatment costs will be higher for nivolumab, and benefit will be accrued for longer. Overall, this is likely to result in higher ICERs. To be conservative in the assumptions used in the

model and to accommodate ERG comments on the nivolumab model (NICE, 2015d) in squamous NSCLC, TTD was used to model the PF health state occupancy in the model.

Similar to the OS extrapolation, the choice of a parametric survival model for TTD was informed by assessment of whether the assumption of proportional effects holds. This was done by visual inspection of the TTD KM, log-cumulative hazards, log-cumulative odds and standardised normal curve plots (Figure 34). 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 ($p < 0.05$), indicating that the null hypothesis for proportional hazards should be rejected.

Figure 34: CheckMate 057: time to treatment discontinuation Kaplan-Meier, log-cumulative hazards, log-cumulative odds and standardised normal curve plots

Visual inspection suggested that the TTD curve and the proportional-hazards assumption were heavily influenced by the steep drop observed within the 4 months of follow-up. In the absence of further clinical information, non-proportional hazards was assumed and curve fitting options explored.

Table 50 summarises the AIC/BIC values for the variety of independent parametric distributions explored for TTD for docetaxel and nivolumab. Similar to OS, flexible models with more than 2 knots were not considered clinically plausible for TTD. Table 50 suggests that, in terms of statistical fit, the two best-fitting parametric survival models are the generalised gamma and gamma distribution for docetaxel. Correspondingly, the two best-fitting survival models for nivolumab are the 1-knot spline odds and generalised gamma.

Figure **35** and

Figure **36** show the fit of each distribution to the CheckMate 057 TTD data for docetaxel and nivolumab, respectively.

Figure 37 and Figure 38 show the long-term extrapolation of each distribution.

Table 50: Summary of goodness-of-fit data for independent survival models for time to treatment discontinuation

Docetaxel

Distribution	AIC	BIC
Generalised gamma	**1235.098**	**1245.871**
Gamma	**1235.428**	**1242.610**
Spline 1 knot(s) - normal	1235.887	1246.660
Spline 2 knot(s) - normal	1237.479	1251.843
Log-logistic	1241.672	1248.854
Weibull	1243.891	1251.073
Log-normal	1245.250	1252.432
Gompertz	1270.522	1277.704

Nivolumab

Distribution	AIC	BIC
Spline 1 knot(s) - odds	**1355.805**	**1366.784**
Generalised gamma	**1367.654**	**1378.632**
Log-normal	1393.789	1401.108
Log-logistic	1395.246	1402.565
Weibull	1462.893	1470.212
Exponential	1469.173	1472.832
Gamma	1469.773	1477.092
Gompertz	1476.032	1483.351

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

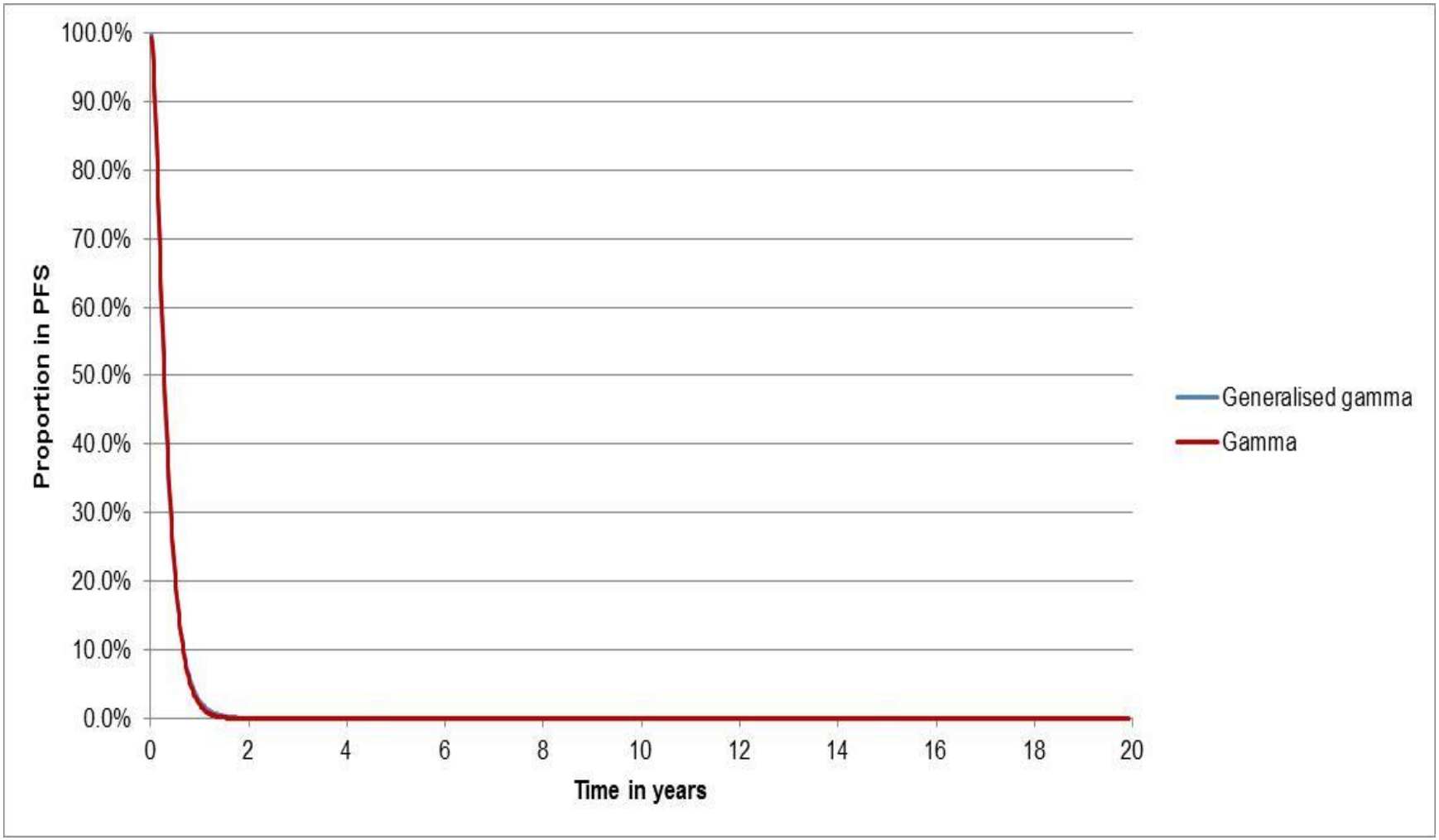
Figure 35. Plot of generalised gamma and gamma distribution for docetaxel time to treatment discontinuation

Abbreviations: AIC = Akaike Information Criterion; TTD = Time to Treatment Discontinuation.

Figure 36. Plot of 1-knot spline and generalised gamma distributions for nivolumab time to treatment discontinuation

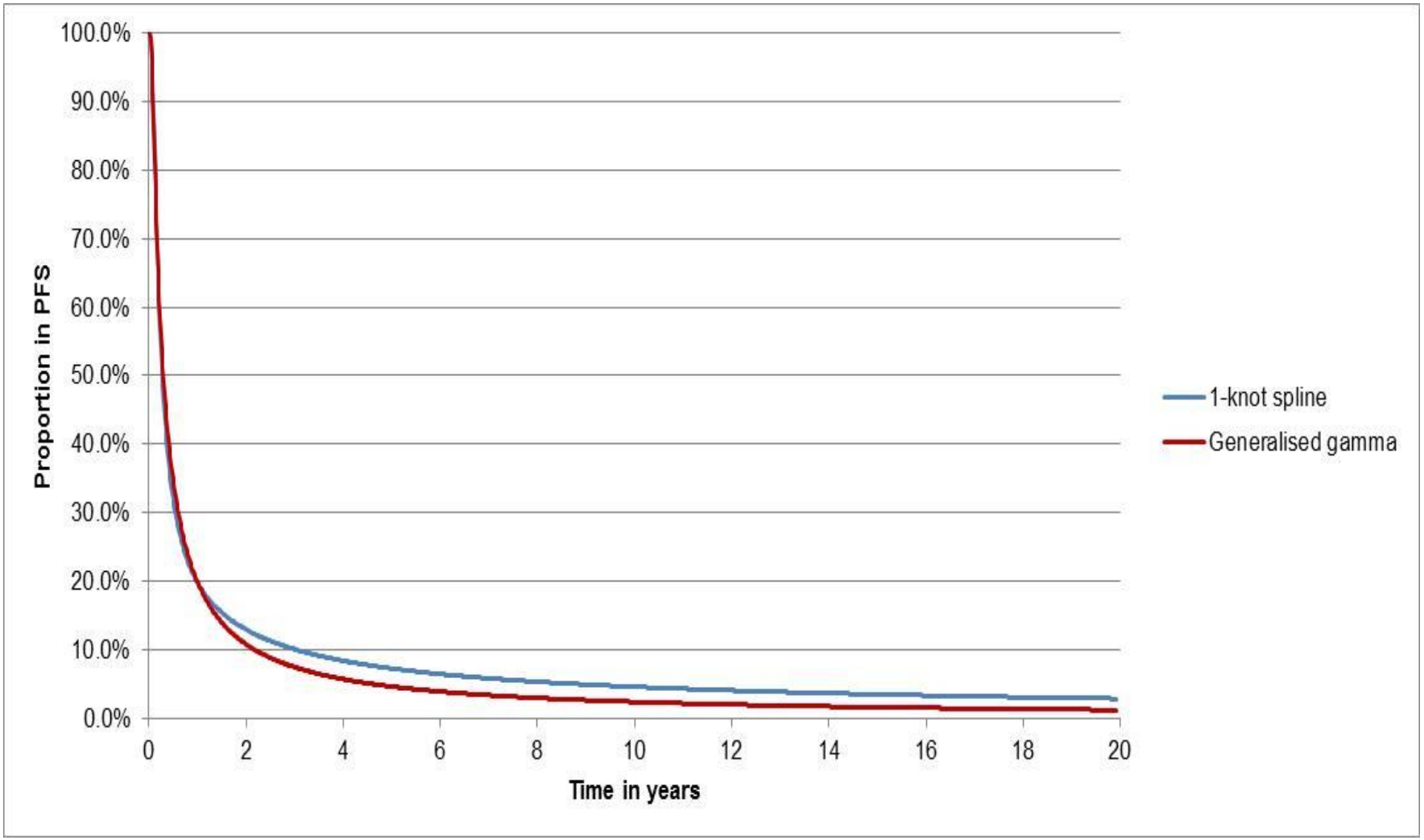
Abbreviations: AIC = Akaike Information Criterion; TTD = Time to Treatment Discontinuation.

Figure 37: Plot of long-term extrapolation of two best-fitting parametric models for docetaxel time to treatment discontinuation extrapolation



Abbreviations: PFS = Progression-Free Survival

Figure 38: Plot of long-term extrapolation of two best-fitting parametric models for nivolumab time to treatment discontinuation extrapolation



Abbreviations: PFS = Progression-Free Survival

Visual inspection of the TTD curves (see

Figure 35 and

Figure 36) revealed that both distributions provided a good fit to the data. Table 51 provides a comparison of the TTD extrapolations for docetaxel and nivolumab against CheckMate 057 and the PFS data from CheckMate 003, which provides the longest term follow-up of patients on nivolumab. Table 51 suggests that, for docetaxel, the two distributions provide comparable survival rates to CheckMate 057 at 1 year. In addition, the proportion in TTD is not significantly different between the generalised gamma and gamma distribution.

Table 51 suggests that, for nivolumab, the two distributions considered provide comparable TTD rates to CheckMate 057 at 1 year. Beyond 1 year, only PFS data from CheckMate 003 are available that estimate that 5% of patients are in PFS by year 3. The TTD predictions for nivolumab from the model are slightly higher than this, as might be expected when comparing TTD with PFS. Long-term RWD on PFS are not available to compare extrapolations over a longer period.

Table 51: In-study survival estimates for time to treatment discontinuation survival functions

Data source	Curve	Proportion on treatment				
		6 months	1 year	1.5 years	2 years	3 years
Model estimates for docetaxel	Generalised gamma	21%	2%	0%	0%	0%
	Gamma	20%	3%	0%	0%	0%
Model estimates for nivolumab	1-knot spline	32%	20%	16%	13%	8%
	Generalised gamma	35%	20%	14%	11%	6%
CheckMate 057	Nivolumab TTD	NA	20%	NA	NA	NA
	Docetaxel TTD	NA	3%	NA	NA	NA
CheckMate 003	Nivolumab PFS	33%	22%	NA	9%	5%

Abbreviations: NA = Not Available; PFS = Progression-Free Survival; TTD = Time to Treatment Discontinuation

5.3.5 Selection of the base-case parametric distribution for TTD

Based on all of the evidence considered, it was determined that the generalised gamma model should be used as the base-case for TTD extrapolation for nivolumab and docetaxel. This was decided based on that the generalised gamma distribution provides a good fit for both treatment arms, provided the best model in terms of goodness-of-fit statistics and internal validation against the long-term nivolumab clinical study data and it allowed the fitting of the same functional form across treatments. In addition, using the generalised gamma model for PFS maintains consistency between the functional forms used for OS and TTD extrapolation. To summarise, these curves were selected as the base-case survival function for TTD based on the following criteria:

- Goodness-of-fit statistics
- Clinical plausibility
- Visual inspection of fit
- Internal validation against all available nivolumab clinical study data

5.3.6 Summary of survival analysis

Table 52 summarises the survival functions that were selected for the base-case, per the descriptions in Sections 5.3.3 and 5.3.5, as well as the alternative choice of distributions considered based on goodness of fit and thus included in scenario analyses.

Table 52: Summary of survival distributions for time to treatment discontinuation and overall survival

Survival models explored	Best-fitting parametric curve
TTD	
Base-case	Docetaxel: Generalised gamma Nivolumab: Generalised gamma
Scenario analysis	Docetaxel: Gamma Nivolumab: 1-knot spline odds
OS	
Base-case	Docetaxel: Generalised gamma Nivolumab: Generalised gamma
Scenario analysis	Docetaxel: Gamma Nivolumab: 2-knot spline hazards

Abbreviations: OS = Overall Survival; TTD = Time to Treatment Discontinuation

5.3.7 Adverse events

The incidence of AEs was taken from CheckMate 057 (Table 53). The inclusion criteria for AEs in the economic model were any Grade 3 or 4 AE with a ≥ 2% incidence in either treatment arm (Bristol-Myers Squibb, 2015b). This AE criteria differed from that selected for nivolumab in squamous NSCLC where a ≥ 5% incidence in either treatment arm was used. The reason for this difference was that when adopting these criteria for CheckMate 057, it was clear that no all-cause Grade 3 or 4 AEs for nivolumab had a ≥ 5% incidence. Therefore, to be conservative, the incidence threshold was reduced in order to capture the toxicity of nivolumab. The inclusion criteria for AEs were produced with the help of clinical experts (Appendix 20).

Table 53: Grade 3 and 4 severity adverse events included in the economic model based on CheckMate 057 data

Type of AE	Rate for nivolumab	Rate for docetaxel
Fatigue	3.10%	6.70%
Asthenia	3.50%	4.10%
Pain	2.10%	1.90%
Dyspnoea	4.90%	3.70%
Pleural effusion	2.40%	0.70%
Hyperglycemia	2.40%	1.90%
Pneumonia	3.50%	5.20%
Neutrophil count decreased	0.00%	6.00%
White blood cell count decreased	0.00%	4.50%
Anaemia	1.70%	4.50%
Neutropenia	0.30%	28.00%
Febrile neutropenia	0.00%	10.80%
Leukopenia	0.00%	8.60%
Diarrhoea	1.00%	1.10%
Increased ALT	0.30%	0.40%
Increased AST	0.00%	0.00%
Hyponatraemia	0.00%	0.00%

Source: Bristol-Myers Squibb (2015b)

Abbreviations: AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Transaminase

According to the CSR, most patients who experienced a specific Select AE only experienced one episode of that event (Bristol-Myers Squibb, 2015b); therefore, this approach can be justified. Thus, the cost and disutility per AE were applied in the first cycle of the model for all patients. This method of calculation is to ensure that the full cost and HRQoL impact associated with AEs is captured for both treatment arms (i.e. without discounting).

5.3.8 Transition probabilities

The economic model is defined on three health states: PF, PD and death (see Figure 26). The proportion of patients in each health state per cycle is determined by the area under the curve or partitioned survival approach, based on parametric survival functions for TTD and OS. The proportion of patients in PD per cycle is defined as the difference between OS and TTD for that cycle. As OS and TTD are defined by different parametric survival models, in instances where there is cross-over of curves—that is, TTD is greater than OS—the model has an adjustment factor to ensure that OS is equal to TTD.

In addition, the model is structured so that neither OS nor TTD can be above the UK all-cause mortality rate for a cohort of patients starting in the model, who are aged 62 years, in line with the mean age in CheckMate 057.

5.3.9 Subsequent treatment

Progressive disease is represented by a single health state; however, to reflect the treatment of patients after disease progression and to ensure that the full cost of treatment is accurately represented, patients in the PD health state were assumed to incur costs of subsequent (post-progression) treatment that were calculated based on the proportion of patients who received subsequent systemic therapy as reported in CheckMate 057 (Table 54). 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. However, CheckMate 057 did not provide details on duration of subsequent treatment, and the duration of third-line therapy was derived from RWD, 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, 2015i). The time until treatment discontinuation in patients in a third-line setting for the overall population was [redacted] (Bristol-Myers Squibb, 2015i). Cost of subsequent treatment was calculated by weighting the costs by the distribution of the different third-line treatments received by patients in CheckMate 057 (Table 54), assuming an average duration of treatment of [redacted]. This weighted cost was applied as a one-off cost to all patients who transitioned out of the PF health state.

Table 54: Type and distribution of subsequent (third-line) therapy based on CheckMate 057

	Nivolumab arm	Docetaxel arm
Docetaxel	[redacted]	
Gemcitabine		
Pemetrexed		
Carboplatin		
Erlotinib		
Best supportive care		

Source: adapted from CheckMate 057 data (Bristol-Myers Squibb (2015b)).

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality of life data from clinical studies

Health-related quality of life data were collected in CheckMate 057 using the EQ-5D preference-based health state utility questionnaire (EQ-5D utility index). 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 is scaled from 0-1; higher scores indicate better health status. The MID has been estimated to be 0.08 for the EQ-5D utility index (Pickard et al., 2007).

All randomised patients from CheckMate 057 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 (82.2% and 76.6% for nivolumab and docetaxel, respectively, at baseline); however, for baseline and at least one post-baseline visit,

completion rates decreased to 70.5% and 69.7% for nivolumab and docetaxel, respectively (see Section 4.7.1). No adjustments were made for missing data when analysing the EQ-5D index. Data from screening visits (up to 28 days before) were used in place of missing baseline data.

Table 55 presents the schedule of assessments. Assessments were taken every other treatment cycle (every 4 weeks) on day 1 for the first 6 months of the study for nivolumab and every treatment cycle (Q3W) 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 study period for both treatment arms.

The use of utilities as captured in CheckMate 057 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 study 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 56.

The strength of this approach is that it is based on patient-level data from the pivotal CheckMate 057 clinical study, making it directly relevant to the economic analysis. The results are in line with those from CheckMate 017, suggesting that they reflect current utility for patients with NSCLC.

Table 55: EQ-5D assessment schedule in CheckMate 057

EQ-5D assessment schedule	**On-study assessment**			**Follow-up assessment (visit 1 and 2)**	**Survival assessment (beyond 100 days from the last study dose)**
	Every 4 weeks for the first 6 months	Every 3 weeks for the first 6 months	Every 6 Weeks thereafter	Within the first 100 days from the last dose of study	Every 3 months for the first 12 months, and every 6 months thereafter
Nivolumab	✓		✓	✓	✓
Docetaxel		✓	✓	✓	✓

Table 56: UK-specific mean EQ-5D values by health state

Tumour Response Category (N= number of assessments)	**UK (Mean)**	**Standard deviation**	**95% CI**
Overall (N = 1,132)	0.728	NA	NA
PD (N = 219)	0.688	0.298	0.665, 0.712
PF (including SD/PR/CR) (N = 913)	0.739	0.233	0.729, 0.748

Sources: Dolan (1997); Bristol-Myers Squibb (2015b); Bristol-Myers Squibb (2015f)

Abbreviations: CI = Confidence Interval; CR = Complete Response; NA = Not Available; PD = Progressive Disease; PF = Progression-Free; PR = Partial Response; SD = Stable Disease; UK = United Kingdom

5.4.2 Health-related quality of life studies

A 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 42 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, none were performed in a UK population and none used EQ-5D in an appropriate population. For these reasons, HRQoL data from CheckMate 057 were used in this submission.

5.4.3 Adverse events

The economic model includes the quality of life impact of AEs of Grade 3 or 4 severity, which occurred in ≥ 2% of patients in CheckMate 057. Table 57 presents the disutility per episode for each of the included AEs; this disutility 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 of more than one AE at a time; in the absence of better information, the disutility of each AE is applied separately. This may introduce an element of double-counting. However, this approach is routinely used in economic evaluations.

Disutility values could not be identified for all AEs; therefore, in the base-case, where information was not available, a disutility of 0 was assumed. This should be considered a conservative assumption, as the AEs for which utility data were not available occurred more frequently overall in docetaxel or nintedanib plus docetaxel than in nivolumab patients. Therefore, it may be that the AE impact for comparators is underestimated.

Table 57: Disutilities of adverse events

Adverse event	Disutility	Reference
Fatigue	-0.07346	Nafees et al. (2008)
Asthenia	-0.07346	Nafees et al. (2008)
Pain	0	Assumption
Dyspnoea	-0.050	Doyle et al. (2008)
Pleural effusion	0	Assumption
Hyperglycemia	0	Assumption
Pneumonia	-0.008	Marti et al. (2013)
Neutrophil count decreased	0	Assumption
White blood cell count decreased	-0.05	(NICE, 2015f)
Anaemia	-0.07346	Nafees et al. (2008)
Neutropenia	-0.08973	Nafees et al. (2008)
Febrile neutropenia	-0.09002	Nafees et al. (2008)
Leukopenia	-0.08973	Nafees et al. (2008)
Diarrhoea	-0.0468	Nafees et al. (2008)
Increased ALT	-0.05	(NICE, 2015f)
Increased AST	0	Assumption
Hyponatraemia	0	Assumption

Sources: Nafees et al. (2008); Doyle et al. (2008); Marti et al. (2013)

Abbreviations: ALT = Alanine Aminotransferase; AST = Aspartate Transaminase

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

Table 58 summarises the utility values used in the economic model. The mean utility values derived from patients with advanced NSCLC based on the CheckMate 057 analysis (for the UK) are 0.728 (overall across all categories), 0.688 (PD) and 0.739 (PF). 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, based on a population with a mean age of 50 years (Anokye et al., 2012), which demonstrates that the HRQoL of patients with advanced NSCLC is lower than that of the general population.

Table 58: Summary of utility values used in the cost-effectiveness analysis

	Utility value: mean (SD)	95% confidence interval	Reference in submission	Justification
Progression-free	0.739 (0.233)	0.729, 0.748	Section 5.4	Derived from EQ-5D data collected in CheckMate 057 (BMS data on file)
Progressed disease	0.688 (0.298)	0.665, 0.712	Section 5.4	
Death	0	—	Section 5.4	Assumption
	Disutility value: mean (SE)			
Fatigue	-0.07346 (0.01849)	—	Section 5.4	Based on societal preferences for health states of patients with advanced NSCLC in England and Wales
Asthenia	-0.07346 (0.01849)	—	Section 5.4	Assumed to be same as fatigue based on medical opinion
Pain	0	—	Section 5.4	Assumption
Dyspnoea	-0.05	—	Section 5.4	Based on recent NICE appraisal of nintedanib in NSCLC
Pleural effusion	0	—	Section 5.4	Assumption
Hyperglycemia	0	—	Section 5.4	Assumption
Pneumonia	-0.008	—	Section 5.4	Assumption that disutility is applicable to patients with advanced NSCLC
Neutrophil count decreased	0	—	Section 5.4	Assumption
White blood cell count decreased	-0.05	—	Section 5.4	Based on recent NICE appraisal of nintedanib in NSCLC
Anaemia	-0.07346 (0.01849)	—	Section 5.4	Assumed to be same as fatigue based on medical opinion
Neutropenia	-0.08973 (0.01543)	—	Section 5.4	Based on societal preferences for health states of patients with advanced NSCLC in England and Wales

	Utility value: mean (SD)	95% confidence interval	Reference in submission	Justification
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
Leukopenia	0.08973 (0.01543)	—	Section 5.4	Assumed to be same as neutropenia based on medical opinion
Diarrhoea	-0.0468 (0.01553)	-	Section 5.4	Based on societal preferences for health states of patients with advanced NSCLC in England and Wales
Increased ALT	-0.05	-	Section 5.4	Based on recent NICE appraisal of nintedanib in NSCLC
Increased AST	0	-	Section 5.4	Assumption
Hyponatraemia	0	-	Section 5.4	Assumption

Source: Bristol-Myers Squibb (2015b)

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

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 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 42 and the search strategy presented in Appendix 9. Two UK-based modelling studies contained resource use assumptions (Table 43), 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 three relevant appraisals is provided in Table 59. These were used to inform the resource use assumptions in the nivolumab model (Table 43): erlotinib (TA162), erlotinib and gefitinib MTA (rev TA162, TA175; [ID620]) and nintedanib (GID-TAG449; information taken from the draft appraisal consultation document) (NICE, 2008; NICE, 2015f; NICE, 2015g).

Where applicable, all resource costs are the same as those in the recent squamous submission to NICE, which were accepted by the ERG (NICE, 2015d). Resource use data reported in the nintedanib draft appraisal consultation document (NICE, 2015f) provide 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 MTA (rev TA162, TA175; [ID620]) were used to inform resource use not reported in the nintedanib consultation document (NICE, 2008; NICE, 2015f; NICE, 2015g). Resource use inputs were validated through one-on-one discussions with clinicians and health economists (Appendix 20).

Table 59: Summary of cost and resource use studies identified within the systematic review

Study, year	Country	Population	Study type	Resource use and costs included
Holmes et al. (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 et al. (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 (2008)	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 (2015f)	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 (2015g)	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

Sources: Holmes et al. (2004); Lewis et al. (2010); NICE (2008); NICE (2015g); NICE (2015f)

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

5.5.2 Intervention and comparator costs and resource use

This section presents the costs of drug acquisition, administration, monitoring, AEs and health states. 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 60 and Table 61, respectively. Based on the nivolumab in squamous NSCLC Evidence Review Group (ERG) report, the discounted costs of some comparators were made available. These unit costs were used where possible. All other unit costs of comparators and subsequent treatments were sourced from the British National Formulary 2015 (Joint Formulary Committee, 2015).

The cost per dose of nivolumab and comparators is based on the weight and body surface area calculator provided by the ERG during the review of the nivolumab in squamous NSCLC model. This calculator takes the distribution of weight and body surface area and estimates the vials required for each treatment to minimise wastage and cost. The net cost per dose is a weighted cost across the distribution of weight and body surface area (Sacco et al., 2010).

Table 60: 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	£7.45 (£0.37/mg)	NICE (2015d)
		8 ml	£25.73 (£0.32/mg)	
		16 ml	£35.35 (£0.22/mg)	
Dexamethasone	-	100 tablets	£5.16 cost per 21-day cycle	NICE (2015d)
Nintedanib	150 mg	60 tablets	£2,151.10	PharmaTimes (2015)

Source: Joint Formulary Committee (2015)

Abbreviations: BNF = British National Formulary

Note: All BNF prices were retrieved in June 2015.

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

Drug	Total dose per administration	No. of vials per packs	Method of administration	Total drug cost per dose	Frequency of administration
Nivolumab	3 mg/kg	1.19 × 10-ml vial*+ 1.84 × 4-ml vial	IV; no vial sharing (i.e. round up to nearest full vials)	£2,538.25	Every 2 weeks
Docetaxel	75 mg/m^2	1.79 × 2 ml + 0.65 × 8 ml + 0.35 × 16 ml* + dexamethasone	IV; no vial sharing (i.e. round up to nearest full vials)	£47.59	Every 3 weeks
Nintedanib + docetaxel	-	2 tablets per day × 21 days plus the cost per dose of docetaxel	Oral	£1,553.29	2 tablets a day for 21 days = 1 dose

Source: Joint Formulary Committee (2015)

Abbreviations: IV = Intravenous

*The 4-ml vial (nivolumab) and 16-ml 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 (see Table 54) based on the distribution of subsequent therapy observed in CheckMate 057. Table 62 presents drug acquisition costs for these subsequent treatments.

Table 62: Drug acquisition costs (subsequent treatments)

Drug	Tablet dose/vial concentration	Pack size/vial volume	Cost per vial/pack	Source
Pemetrexed	1 mg/ml	100 ml	£160.00	BNF 2015
		500 ml	£800.00	
Carboplatin	10 mg/ml	5 ml	£3.43	NICE (2015d)
		15 ml	£7.69	
		45 ml	£20.17	
Gemcitabine	200 mg/vial	200 mg	£3.35	NICE (2015d)
	1,000 mg/vial	1,000 mg	£9.13	
Docetaxel	10 mg/ml	2 ml	£7.45	NICE (2015d)
		8 ml	£25.73	
		16 ml	£35.35	
Erlotinib	150 mg	30 tablets	£1,631.53	BNF 2015

Source: Joint Formulary Committee (2015)

Abbreviations: BNF = British National Formulary

Table 63 presents the cost of each subsequent treatment per dose and the frequency of administration. The treatment duration for all subsequent therapies is [redacted], 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, 2015i). An assumption was made that the pooled RWD collected from European countries was applicable to clinical practice in the UK.

Table 63: 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
Pemetrexed	500 mg/m^2	2.15 × 500-ml vials	IV; no vial sharing (i.e. round up to nearest full vials)	£1,723.02	Every 3 weeks
Carboplatin	400 mg/m^2	0.80 × £3.43 + 1.22 × £7.69 + 1.15 × £20.17	IV; no vial sharing (i.e. round up to nearest full vials)	£35.42	Every 4 weeks
Gemcitabine	1,000 mg/m^2	1.44 × 200 mg + 5.63 1,000 mg	IV; no vial sharing (i.e. round up to nearest full vials)	£56.20	Every 4 weeks (once per week for 3 weeks, followed by 1 week off treatment)
Docetaxel	75 mg/m^2	1.79 × 2 ml + 0.65 × 8 ml+ 0.35 × 16 ml + dexamethasone	IV; no vial sharing (i.e. round up to nearest full vials)	£47.59	Every 3 weeks
Erlotinib	150 mg	1/30 pack (30 × 150 mg)	Oral; vial sharing is N/A	£54.38	Daily

Source: Joint Formulary Committee (2015)

Abbreviations: IV = Intravenous; N/A = Not Applicable

Treatment administration costs

The costs of treatment administration for nivolumab and docetaxel are shown in Table 64 as applied in the model. The administration costs for platinum-based therapy, gemcitabine, vinorelbine and nintedanib plus docetaxel 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 simple chemotherapy in line with the ERG recommendation in squamous NSCLC (NICE, 2015d).

Table 64: Cost per administration

Treatment*	Type of administration		Currency code	Cost per administration†	Source
Nivolumab	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z	£167.34	NHS reference costs 2013-2014
Docetaxel	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z	£167.34	NHS reference costs 2013-2014

Source: Department of Health (2014)

Abbreviations: NHS = National Health Service

*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.

†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.

Monitoring costs

Table 65 presents the cost of monitoring for a patient in the PF health state. 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 65: 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, docetaxel or nintedanib plus docetaxel	Outpatient visit (consultant-led)	£151.89	Medical oncology code 370, Consultant-led outpatient appointment	1	£151.89

Source: Liverpool Reviews and Implementation Group (2006)

*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 66 shows the assumed resource use for disease management in the PF health state. 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 66: 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%	£46.71	£42.97	Erlotinib and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE, 2015g).
Palliative care (days)	2.00	100%	£86.42	£172.83	Nintedanib NICE submission (NICE, 2015f). The values were updated following clinician validation.
Radiotherapy (bone)—per fraction	0.31	100%	£128.11	£39.71	Nintedanib NICE submission (NICE, 2015f). The values were adjusted following clinician validation.
CT scan (thorax or abdominal/brain)	0.31	100%	£94.26	£29.22	Nintedanib NICE submission (NICE, 2015f). The values were adjusted following clinician validation.
X-ray	0.67	100%	£43.01	£28.81	Nintedanib NICE submission (NICE, 2015f). 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

*Sources of unit costs are in Table 68. All unit costs are inflated to June 2015 values.

Table 67 presents the resource use in the PD health state; the associated unit costs of each resource are shown in Table 68. 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 67: 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%	£46.71	£46.71	Erlotinib and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620] (Fiala et al., 2013a).
Routine GP visit (at patient's home)	0.31	100%	£119.43	£37.02	Erlotinib and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE, 2015g). The values were adjusted following expert clinician validation.
Palliative care (per day)	4.00	100%	£86.42	£345.67	Nintedanib NICE submission (NICE, 2015f).The values were adjusted following expert clinician validation.
Oxygen	1.33	100%	£14.04	£18.67	Nintedanib NICE submission (NICE, 2015f). The values were adjusted following expert clinician validation.
Blood transfusion	0.46	100%	£155.58	£71.57	Nintedanib NICE submission (NICE, 2015f). The values were adjusted following expert clinician validation.
CT scan (thorax or abdominal/brain)	0.31	100%	£94.26	£29.22	Nintedanib NICE submission (NICE, 2015f). 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%	£43.01	£19.78	Nintedanib NICE submission (NICE, 2015f). The values were adjusted following expert clinician validation.
Radiotherapy—per fraction	1.00	100%	£128.11	£128.11	Nintedanib NICE submission (NICE, 2015f). The values were adjusted following expert clinician validation.
Oncologist visit	0.46	100%	£151.89	£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; TA = Technology Appraisal

*Sources of unit costs are in Table 68. All cost were inflated to June 2015 values.

Table 68: Unit costs (progression-free and progressed disease health states)*

Resource	Unit cost	Source
Routine GP visit (surgery)	£46.71	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)	£119.43	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)	£86.42	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	£14.04	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	£128.11	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	£155.58	NHS reference costs 2013-2014 (Department of Health, 2014) Blood and marrow transplant (currency code: 308); non–consultant-led outpatient attendance.

Resource	Unit cost	Source
CT scan (thorax or abdominal/brain)	£94.26	NHS reference costs 2013-2014 (Department of Health, 2014) CT scan, one area, pre- and post-contrast (currency code: RA10A).
X-ray	£43.01	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	£151.89	NHS reference costs 2013-2014 (Department of Health, 2014) Medical oncology code 370, consultant-led outpatient appointment.

Abbreviations: CT = Computerised Tomography; GP = General Practitioner; NHS = National Health Service; PSSRU = Personal Social Services Research Unit

*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. Table 69 presents resource use in each care setting and the weightings applied. The overall weighted end-of-life cost is £3,628.70 (Table 70).

Table 69: 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 and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE, 2015g)	55.8%	Erlotinib and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE, 2015g)
Macmillan Nurse (home setting)	50.00	Marie Curie Cancer Care	27.3%	
Hospice care	1.00	Erlotinib and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE, 2015g)	16.9%	

Abbreviations: ID = In Development; MTA = Multiple Technology Appraisal; TA = Technology appraisal

Table 70: 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 cytoreduction score 11+ (currency code: DZ17E), non-elective inpatient stays - long stay	£2,353.15 (+ £152.64 for 0.84 excess bed days) = £2,505.79	£2,481.37
Macmillan Nurse (home setting)	£44.68 (assumed two-thirds the cost of a community nurse)	Erlotinib and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620] and PSSRU 2014 Curtis (2014); (NICE, 2015g)	£12.20	£609.84
Hospice care	£5,699.68 (25% increase on hospitalisation setting)	Erlotinib and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE, 2015g)	£573.49	£573.49
Total cost				£3,628.70

Abbreviations: ID = In development; MTA = Multiple Technology Appraisal; NHS = National Health Service; 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 ≥ 2% incidence in the nivolumab or docetaxel arms of CheckMate 057 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 71). 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 CheckMate 057 data.

Table 71: Cost of adverse events*

AEs from CheckMate 057	Cost per episode	Mean number of episodes per AE treatment course	Source
Fatigue	£3,015.13	1	Department of Health (2014)
Asthenia	£3,015.13	1	Department of Health (2014)
Pain	£122.00	1	Department of Health (2014)
Dyspnoea	£0.00	1	Assumption based on ipilimumab NICE STA submission for melanoma (NICE, 2014a)
Pleural effusion	£553.00	1	Department of Health (2014)
Hyperglycemia	£652.00	1	Department of Health (2014)
Pneumonia	£1,822.85	1	Department of Health (2014)
Neutrophil count decreased	£0.00	1	Assumption
White blood cell count decreased	£423.00	1	NICE (2015f)
Anaemia	£978.00	1	NICE (2015f)
Neutropenia	£354.72	1	Department of Health (2014)
Febrile neutropenia	£5,489.94	1	Erlotinib and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620] (NICE, 2015g)
Leukopenia	£354.72	1	Assumed to be same as neutropenia based on medical opinion
Diarrhoea	£1,796.00	1	NICE (2015f)
Increased ALT	£587.00	1	NICE (2015f)
Increased AST	£336.00	1	NICE (2015f)
Hyponatraemia	£652.00	1	Assumed to be same as hyperglycaemia based on medical opinion

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

5.6.1 Summary of base-case de novo analysis inputs

Appendix 23 lists details of all values used in the economic model. Table 72 presents a summary of the key variables.

Table 72: 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 45
	Model cycle length	1 week	Section 5.2, Table 45
	Discount rate	3.5%	Section 5.2, Table 45
	Average body weight	70 kg*	Drug acquisition costs in Section 5.5
	Average BSA	1.78 m^2*	Drug acquisition costs in Section 5.5
Subsequent treatment	Patients moving to third-line therapy following nivolumab	Docetaxel: [redacted] Gemcitabine: [redacted] Pemetrexed: [redacted] Carboplatin[redacted] Erlotinib: [redacted] BSC: [redacted]	Section 5.3, Table 54
	Patients moving to third-line therapy following docetaxel	Docetaxel: [redacted] Gemcitabine: [redacted] Pemetrexed: [redacted] Carboplatin: [redacted] Erlotinib: [redacted] BSC: [redacted]	Section 5.3, Table 54
	Average duration of subsequent treatment	[redacted]days	Subsequent therapy in Section 5.3
Costs	Cost of nivolumab per dose	£2,538.25	Section 5.5, Table 61
	Cost of docetaxel per dose	£47.59	Section 5.5, Table 61
	Cost of nintedanib in combination with docetaxel per dose	£1,553.29	Section 5.5, Table 61

Area	Variable	Value	Reference to section in submission
	Administration cost per dose (nivolumab)	£167.34	Section 5.5, Table 64
	Administration cost per dose (docetaxel)	£167.34	Section 5.5, Table 64
	Monitoring cost per 4 weeks	£151.89	Section 5.5, Table 65
	PF cost per 4 weeks	£313.55	Section 5.5, Table 66
	PD cost per 4 weeks	£766.62	Section 5.5, Table 67
	End of life cost	£3,628.70	Section 5.5, Table 70
AEs	Frequency of AE with nivolumab	Fatigue: 3.10% Asthenia: 3.50% Pain: 2.10% Dyspnoea: 4.90% Pleural effusion: 2.40% Hyperglycemia: 2.40% Pneumonia: 3.50% Neutrophil count decreased: 0% While blood cell count decreased: 0% Anaemia: 1.70% Neutropenia: 0.30% Febrile neutropenia: 0% Leukopenia: 0% Diarrhoea: 1.00% Increased ALT: 0.30% Increased AST: 0% Hyponatraemia: 0%	Section 5.3, Table 53
	Frequency of AE with docetaxel	Fatigue: 6.70% Asthenia: 4.10%% Pain: 1.90%% Dyspnoea: 3.70% Pleural effusion: 0.70% Hyperglycemia: 1.90% Pneumonia: 5.20% Neutrophil count decreased: 6.00% While blood cell count decreased: 4.50% Anaemia: 4.50% Neutropenia: 28.00% Febrile neutropenia: 10.80% Leukopenia: 8.60% Diarrhoea: 1.10% Increased ALT: 0.40%	

Area	Variable	Value	Reference to section in submission
		Increased AST: 0% Hyponatraemia: 0%	
	Cost of fatigue	£3,015.13	Section 5.5, Table 71
	Cost of asthenia	£3,015.13	
	Cost of pain	£122.00	
	Cost of dyspnoea	£0.00	
	Cost of pleural effusion	£553.00	
	Cost of hyperglycaemia	£652.00	
	Cost of pneumonia	£1,822.85	
	Cost of neutrophil count decreased	£0.00	
	Cost of white blood cell count decreased	£423.00	
	Cost of anaemia	£978.00	
	Cost of neutropenia	£354.72	
	Cost of febrile neutropenia	£5,489.94	
	Cost of leukopenia	£354.72	
	Cost of diarrhoea	£1,796.00	
	Cost of increased ALT	£587.00	
	Cost of increased AST	£336.00	
	Cost of hyponatraemia	£652.00	
Utility	PF	0.739	Section 5.4, Table 56
	PD	0.688	
Disutility of AEs	Fatigue	-0.07346	Section 5.4, Table 57
	Asthenia	-0.07346	
	Pain	0	
	Dyspnoea	-0.05	
	Pleural effusion	0	
	Hyperglycemia	0	
	Pneumonia	-0.008	
	Neutrophil count decreased	0	
	White blood cell count decreased	-0.05	
	Anaemia	-0.07346	
	Neutropenia	-0.08973	
	Febrile neutropenia	-0.09002	

Area	Variable	Value	Reference to section in submission
	Leukopenia	0.08973	
	Diarrhoea	-0.0468	
	Increased ALT	-0.05	
	Increased AST	0	
	Hyponatraemia	0	

Abbreviations: AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Transaminase; BSA = Body Surface Area; BSC = Best Supportive Care; NSCLC = Non-Small Cell Lung Cancer; OS = Overall Survival; PD = Progressed Disease; PF = Progression Free

* These are the mean values for weight and BSA, although the cost of treatment is based on the distribution around the mean.

5.6.2 Assumptions

Table 73 presents a list of the main parameters and assumptions used in the economic analysis.

Table 73: Key parameters in base-case model

Parameter	Base-case assumption	Justification
Comparator	Docetaxel	Based on UK clinical practice and consistent with CheckMate 057 data
Time horizon	20 years	Lifetime equivalent consistent with NICE reference case
Survival: OS	Base-case: • Docetaxel: generalised gamma • Nivolumab: generalised gamma Sensitivity analysis: • Docetaxel: gamma • Nivolumab: spline 2-knots hazards	Choice of extrapolation technique was based on statistical goodness-of-fit, clinical plausibility and validation with RWE
Survival: TTD	Base-case: • Docetaxel: generalised gamma • Nivolumab: generalised gamma Sensitivity analysis: • Docetaxel: gamma • Nivolumab: spline 1-knot odds	
End-of-life cost	Based on previous NICE TAs	Applied as a one-off cost for all patients who die to take into consideration the added expense of terminal care
HRQoL	Based on EQ-5D data collected in CheckMate 057. Utility values are allocated by health state and not differentiated by treatment arm	Consistent with NICE recommendations

Parameter	Base-case assumption	Justification
Safety	Grade 3 or higher severity adverse events experienced by ≥ 2% of patients in CheckMate 057 are included in the analysis	Conservative approach given safety profile of nivolumab
Subsequent treatment	Treatment type is based on CheckMate 057, 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; OS = Overall Survival; RWE = Real-World Evidence; TTD = Time to Treatment Discontinuation; UK = United Kingdom

5.7 Nintedanib plus docetaxel comparison

As outlined in Section 4.10, an ITC was undertaken to identify data for nivolumab versus nintedanib plus docetaxel—specifically, the ITC identified data on the HR for OS and PFS between nintedanib in combination with docetaxel versus docetaxel. However, the ERG report for nintedanib in combination with docetaxel highlights that the proportional hazards assumption does not hold for OS or PFS (NICE, 2015b). Thus, it was determined that it would not be appropriate to use the HRs from the ITC in the economic analysis

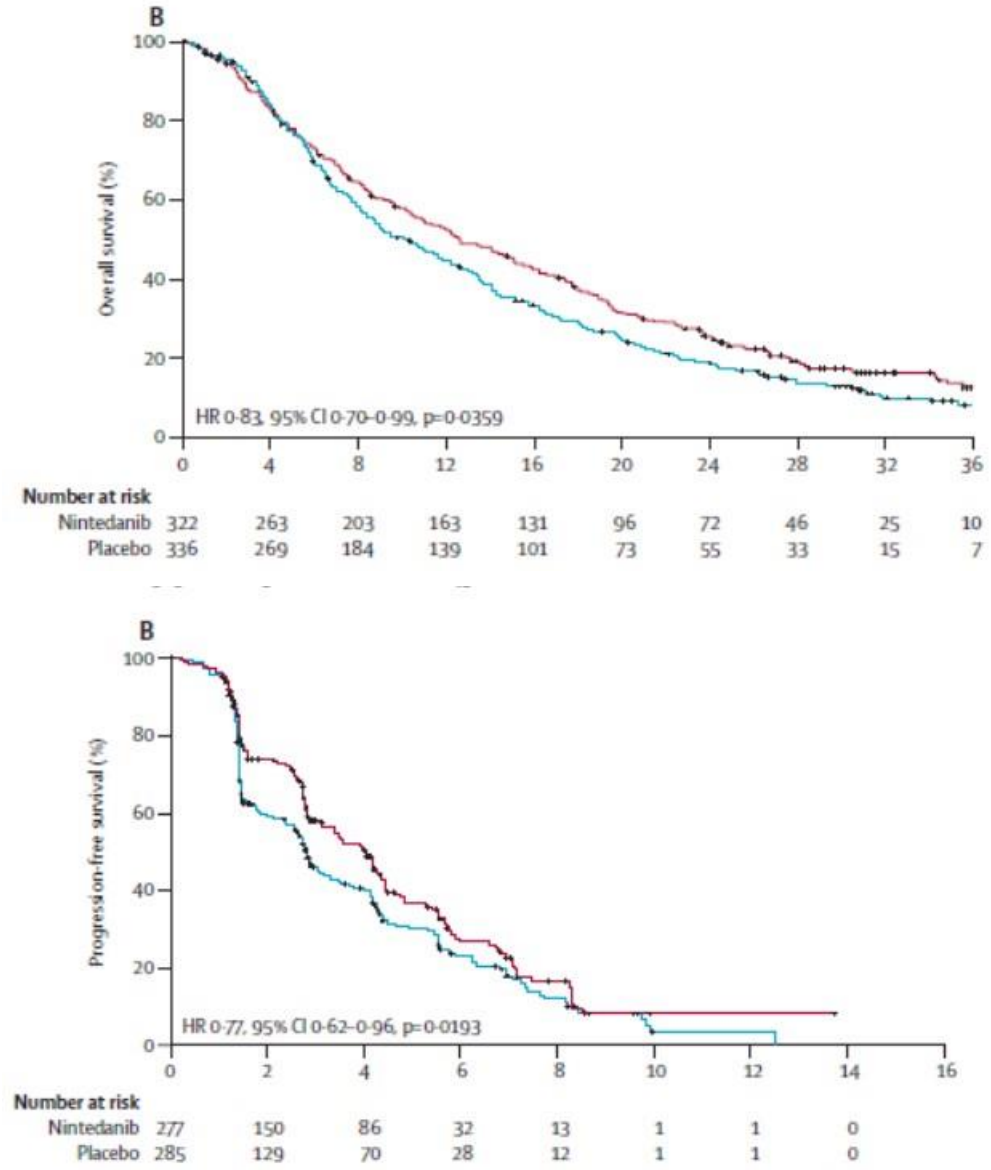
Therefore, KM graphs from the primary publication for nintedanib in combination with docetaxel (Reck et al., 2014) were digitised to estimate proxy patient-level data. Specifically, data for the adenocarcinoma population (sub-group B) were used in the analysis. It is evident from Figure 39 that, for OS, there is almost no difference between the two treatments up to 6 months, and for PFS there is almost no difference between the two treatments up to 2 months. Therefore, it is assumed that the HR for OS and PFS is 1 for these time points. Following this, an HR was estimated that is specific to ≥ 6 months for OS and ≥ 2 months for PFS. Table 74 summarises the output of this analysis.

Table 74: Summary of overall survival and progression-free survival hazard ratios for nintedanib plus docetaxel

Efficacy	HR	95% CI
OS after 6 months	0.75	(0.60, 0.93)
PFS after 2 months	0.98	(0.73, 1.33)

Abbreviations: CI = Confidence Interval; HR = Hazard Ratio; OS = Overall Survival; PFS = Progression-Free Survival

Figure 39: Overall survival and progression-free survival data for the adenocarcinoma sub-group from the LUME-Lung 1 study



Source: Reck et al. (2014)

Abbreviations: CI = Confidence Interval; HR = hazard ratio

In the economic model, it is assumed that the nintedanib in combination with docetaxel data for OS is equal to the docetaxel arm up to 6 months; following this, the HR outlined in Table 74 is applied to the docetaxel arm to estimate the nintedanib plus docetaxel patient flow. Likewise, for TTD the nintedanib plus docetaxel data is equal to the docetaxel arm up to 2 months; following this, the HR outlined in Table 74 is applied to the docetaxel arm to estimate the nintedanib plus docetaxel patient flow.

This approach has two key limitations:

- The nintedanib in combination with docetaxel data are based on proxy patient-level data using a digitised KM curve for OS and PFS. As direct patient-level data were not available, this was the second best option.

- In the economic model, the HR estimated for PFS is being applied to docetaxel TTD data. Due to lack of TTD data for nintedanib plus docetaxel, it is assumed that the relationship between PFS and TTD seen with docetaxel is also maintained for nintedanib plus docetaxel.

Due to the limitations outlined above, the results of the analysis were validated against the manufacture submission for nintedanib plus docetaxel (NICE, 2015b). In the manufacture submission, it was estimated that nintedanib plus docetaxel was associated with a 4.7-month gain in OS and a 28.6-day gain in PFS. When applying the HR outlined in Table 74 in the economic model, it is estimated that nintedanib plus docetaxel is associated with a 4.13-month gain in OS and a 2-day gain in TTD. Therefore, the model appears to be predicting the anticipated OS gain appropriately but may be underestimating TTD, which is a proxy for PFS. Considering that treatment costs are being driven by TTD and that this is a key driver of the model, it is likely that treatment costs for nintedanib plus docetaxel are being underestimated; therefore, the approach is conservative.

Finally, the AE data in the economic model for nintedanib plus docetaxel (Table 75) were taken directly from the primary publication. As with nivolumab and docetaxel, all AEs with a ≥ 2% incidence were included.

Table 75: Grade 3 and 4 severity adverse events included in the economic model based on LUME-Lung 1

Type of AE	Rate for nintedanib plus docetaxel
Fatigue	5.5%
Asthenia	2.0%
Pain	0.0%
Dyspnoea	4.9%
Pleural effusion	1.0%
Hyperglycemia	1.1%
Pneumonia	2.6%
Neutrophil count decreased	32.0%
White blood cell count decreased	16.4%
Anaemia	1.1%
Neutropenia	12.1%
Febrile neutropenia	7.0%
Leukopenia	2.9%
Diarrhoea	6.5%
Increased ALT	7.8%
Increased AST	3.4%
Hyponatraemia	2.1%

Source: Reck et al. (2014)

Abbreviations: AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Transaminase

5.8 Base-case results

5.8.1 Base-case incremental cost-effectiveness analysis results

Table 76 presents total costs, LYG, QALYs and incremental cost per QALY for nivolumab versus docetaxel and nintedanib plus docetaxel. The base-case analysis was based on the generalised gamma curves for all extrapolations (OS and TTD). Life-years were undiscounted. In comparison to docetaxel, nivolumab generated 0.73 incremental QALYs and 1.15 incremental life-years, and the nivolumab-treated cohort had higher total lifetime costs. The incremental cost-effectiveness ratio (ICER) was £103,589 per QALY gained. In comparison to nintedanib plus docetaxel, nivolumab generated 0.49 incremental QALYs and 0.80 incremental life-years, and the nivolumab-treated cohort had higher total lifetime costs. The ICER was £126,861 per QALY gained.

Table 76: Base-case results

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	93,306	2.24	1.42				
Docetaxel	17,854	1.09	0.70	75,452	1.15	0.73	103,589
Nintedanib plus docetaxel	30,708	1.44	0.93	62,598	0.80	0.49	126,861

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

5.8.2 Clinical outcomes from the model

Table 77: Model predictions of median time to treatment discontinuation and overall survival compared with CheckMate 057

Outcome	Nivolumab		Docetaxel		Nintedanib plus docetaxel	
	Checkmate 057	Economic model	Checkmate 057	Economic model	LUME-Lung 1	Economic model
TTD, months (95% CI)	[redacted]					
OS, months (95% CI)						

Abbreviations: CI = Confidence Interval; OS = Overall Survival; TTD = Time to Treatment Discontinuation

Note: although median OS is longer for nintedanib than nivolumab, median OS is considerably longer for nivolumab, due to a small number of patients high OS.

Table 77 presents a comparison of TTD and OS observed in the CheckMate 057 and LUME-Lung 1 studies and model extrapolation. The difference in median TTD was 0.83 months and 0.54 months for nivolumab and docetaxel, respectively. The median TTD was not available for nintedanib plus docetaxel. The difference in median OS was 1.14 months for nivolumab, 0.55 months for nintedanib plus docetaxel and 0.14 months for docetaxel. The economic model overestimated median TTD for nivolumab and docetaxel compared with the study, resulting in high treatment costs. The economic model underestimated median OS for all

three treatments compared with the study. This was not unexpected given the longer time horizon of the model. The median OS estimates from the model were within the 95% CIs from CheckMate 057 and LUME-Lung 1. The 95% CIs for median TTD from the studies were not available. No adjustment was made for cross-over because no patients in the docetaxel arm had received nivolumab prior to the interim database lock.

The difference in median OS between nivolumab and docetaxel was 1.83 months based on the model and 2.83 months based on study data. The difference in median OS between nivolumab and nintedanib plus docetaxel was -1.0 months based on the model and -0.41 months based on study data. There was almost no difference in median TTD in the study or predicted in the model for docetaxel and nintedanib plus docetaxel. These numbers suggested consistency across model and study predicted values.

Figure 40,

Figure 41, and Figure 42 present the distribution of patients between health states for nivolumab, docetaxel and nintedanib plus docetaxel, respectively. These cohort traces are for the second-line indication using base-case assumptions.

Figure 40: Cohort trace for nivolumab up to 20 years (base-case analysis)

Abbreviations: PD = Progressed Disease; PF = Progression Free.

Figure 41: Cohort trace for docetaxel up to 20 years (base-case analysis)

Abbreviations: PD = Progressed Disease; PF = Progression Free.

Figure 42: Cohort trace for nintedanib plus docetaxel up to 20 years (base-case analysis)

Abbreviations: PD = Progressed Disease; PF = Progression Free.

In the base-case, 1.5% of patients in the nivolumab arm and 0% of patients in the docetaxel and nintedanib plus docetaxel arms were alive at 20 years, suggesting that the time horizon of the model was 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 057 ranged from 39 to 85 years, it was clinically plausible to expect that a small proportion of this cohort would be alive at 20 years of follow-up (the younger patients primarily).

5.8.3 Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 78 and Table 79 present expected QALYs for nivolumab, docetaxel and nintedanib plus docetaxel disaggregated by health state. The main source of the benefits from nivolumab came from extending the time in PF health states, rather than time in the PD health state or a reduction in the disutility of AEs, which was consistent with results from CheckMate 057. In CheckMate 057, nivolumab had a favourable AE profile compared with docetaxel (Section 4). This benefit was not fully captured in the economic model because of the limitation to include only Grade ≥ 3 AEs occurring in ≥ 2% of the study population. In addition, it is evident from the LUME-Lung 1 publication that nintedanib plus docetaxel is associated with a higher incidence and frequency of AEs. Overall, 67.6% and 25.6% of the QALY gains for nivolumab compared with docetaxel came from the PF and PD health states, respectively. In comparison, 99.2% of the QALY gains for nivolumab compared with nintedanib plus docetaxel came from the PF health state.

Table 78: Summary of QALY gain per patient by health state—nivolumab versus docetaxel

Health state	QALY intervention (nivolumab)	QALY comparator (docetaxel)	Incremental QALYs	% absolute incremental QALYs
PF				
PD				
AE disutility				
Total				

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year
Note: No utility is assigned to the death state.

Table 79: Summary of QALY gain per patient by health state—nivolumab versus nintedanib plus docetaxel

Health state	QALY intervention (nivolumab)	QALY comparator (nintedanib plus docetaxel)	Incremental QALYs	% absolute incremental QALYs
PF				
PD				
AE disutility				
Total				

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year
Note: No utility is assigned to the death state.

Expected costs disaggregated by health state and by type of cost are shown in Table 80 and Table 81. 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 40,

Figure 41 and Figure 42 illustrate the longer health state occupancy in patients treated with nivolumab.

Table 80: Summary of costs—nivolumab versus docetaxel

Health state	Cost intervention (nivolumab)	Cost comparator (docetaxel)	Incremental costs	% absolute incremental costs
Disease management cost: PF	[redacted]			
Disease management cost: PD*				
Drug acquisition cost				
Administration cost				
Monitoring cost				
Subsequent treatment				
AEs				
Total treatment cost				

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free;

*PD includes the costs of managing patients who have progressed and end-of-life and terminal care. No costs are assigned to the death state.

Table 81: Summary of costs—nivolumab versus nintedanib plus docetaxel

Health state	Cost intervention (nivolumab)	Cost comparator (nintedanib plus docetaxel)	Incremental costs	% absolute incremental costs
Disease management cost: PF				
Disease management cost: PD*				
Drug acquisition cost				
Administration cost				
Monitoring cost				
Subsequent treatment				
AEs				
Total treatment cost				

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free

*PD includes the costs of managing patients who have progressed and end-of-life and terminal care. No costs are assigned to the death state.

5.9 Sensitivity analyses

5.9.1 Probabilistic sensitivity analysis

A second-order Monte Carlo simulation was run for 1,000 iterations. The parameters included in the probabilistic sensitivity analysis (PSA) are shown in Table 82 through Table 101.

General inputs

Average body weight and BSA were included in the PSA assuming a normal distribution (Table 82). These parameters were used to calculate treatment dosage and drug acquisition costs.

Table 82: Average body weight and body surface area

Parameter	Mean deterministic	Distribution	Alpha	Beta
Average body weight	70 kg	Gamma	100	0.69
BSA	1.78 m^2	Gamma	100	0.0179

Abbreviations: BSA = Body Surface Area

Overall survival parameters

In the base-case analysis, a generalised gamma distribution was fitted to all treatments—nivolumab, docetaxel and nintedanib plus docetaxel. In the probabilistic analysis, uncertainty

in OS was represented through the parameters of the survival function. For the OS survival functions for nivolumab and docetaxel, a multivariate normal distribution with correlation between shape and scale parameters was applied (Table 83 and Table 84). As the nintedanib plus docetaxel arm was estimated by applying an HR to the docetaxel arm, after 6 months, a log-normal distribution was applied (Table 85).

Table 83: Generalised gamma distribution parameters fit to docetaxel included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition		
		OS alpha (shape)	OS beta (scale)	OS (Q)
OS alpha (shape)	[redacted]			
OS beta (scale)				
OS (Q)				

Abbreviations: OS = Overall Survival

Table 84: Generalised gamma distribution parameters fit to nivolumab included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition		
		OS alpha (shape)	OS beta (scale)	OS (Q)
OS alpha (shape)	[redacted]			
OS beta (scale)				
OS (Q)				

Abbreviations: OS = Overall Survival

Table 85: Hazard ratio applied to docetaxel overall survival for nintedanib plus docetaxel comparison included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition	
		OS alpha (shape)	OS beta (scale)
HR	[redacted]		

Abbreviations: HR = Hazard Ratio; OS = Overall Survival

To explore uncertainty in the choice of survival function, a scenario analysis was undertaken separately where OS was modelled via separate distributions that included a gamma and 2-knot spline hazard distribution for docetaxel and nivolumab, respectively (extrapolation details are given in Section 5.1). The PSA included survival parameters for this extrapolation technique; these are presented in Table 86 and Table 87.

Table 86: Gamma distribution parameters fit to docetaxel included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition	
		OS alpha (shape)	OS beta (scale)
OS alpha (shape)	[redacted]		
OS beta (scale)			

Abbreviations: OS = Overall Survival

Table 87: 2-knot spline hazards distribution parameters fit to nivolumab included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition			
		Spline parameters: gamma 0	Spline parameters: gamma 1	Spline parameters: gamma 2	Spline parameters: gamma 3
Spline parameters: gamma 0	[redacted]				
Spline parameters: gamma 1					
Spline parameters: gamma 2					
Spline parameters: gamma 3					

Time to treatment discontinuation survival parameters

In the base-case analysis, a generalised gamma distribution was fitted to all treatments—nivolumab, docetaxel and nintedanib plus docetaxel. In the PSA, uncertainty in TTD was represented through the parameters of the survival function. The PSA included survival parameters for this extrapolation technique; these are presented in Table 88, Table 89 and Table 90.

Table 88: Generalised gamma distribution parameters fit to docetaxel included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition		
		OS alpha (shape)	OS beta (scale)	OS Q
OS alpha (shape)	[redacted]			
OS beta (scale)				
OS Q				

Abbreviations: OS = Overall Survival

Table 89: Generalised gamma distribution parameters fit to nivolumab included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition		
		OS alpha (shape)	OS beta (scale)	OS Q
OS alpha (shape)	[redacted]			
OS beta (scale)				
OS Q				

Abbreviations: OS = Overall Survival

Table 90: Hazard ratio applied to docetaxel time to deterioration for nintedanib plus docetaxel comparison included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition	
		OS alpha (shape)	OS beta (scale)
HR	[redacted]		

Abbreviations: HR = Hazard Ratio; OS = Overall Survival

To explore uncertainty in the choice of survival function, a scenario analysis was undertaken separately where TTD was modelled via a gamma and 1-knot spline hazards distribution for docetaxel and nivolumab, respectively (extrapolation details are given in Section 5.1). The PSA included survival parameters for this extrapolation technique; these are presented in Table 91 and Table 92.

Table 91: Gamma distribution parameters fit to docetaxel included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition	
		OS alpha (shape)	OS beta (scale)
OS alpha (shape)	[redacted]		
OS beta (scale)			

Abbreviations: OS = Overall Survival

Table 92: 1-Knot spline hazards distribution parameters fit to nivolumab included in probabilistic sensitivity analysis

Parameter	Mean deterministic	Cholesky decomposition		
		Spline parameters: gamma 0	Spline parameters: gamma 1	Spline parameters: gamma 2
Spline parameters: gamma 0	[redacted]			
Spline parameters: gamma 1				
Spline parameters: gamma 2OS Q				

Abbreviations: OS = Overall Survival

Adverse event disutility

Adverse event disutilities were included in the PSA, and the parameters are shown in Table 93. A gamma distribution was used for disutilities because the values lie between minus infinity and zero.

Table 93: Adverse event disutilities included in probabilistic sensitivity analysis

AE	Mean deterministic disutility (per event)	Distribution	Alpha	Beta
Fatigue	-0.07346	Gamma	100	0.0007346
Asthenia	-0.07346	Gamma	100	0.0007346
Pain	0	-	-	-
Dyspnoea	-0.050	Gamma	100	0.0005
Pleural effusion	0	-	-	-
Hyperglycemia	0	-	-	-
Pneumonia	-0.008	Gamma	100	0.00008
Neutrophil count	0	-	-	-

AE	Mean deterministic disutility (per event)	Distribution	Alpha	Beta
decreased				
White blood cell count decreased	-0.05	Gamma	100	0.0005
Anaemia	-0.07346	Gamma	100	0.0007346
Neutropenia	-0.08973	Gamma	100	0.0008973
Febrile neutropenia	-0.09002	Gamma	100	0.0009002
Leukopenia	-0.08973	Gamma	100	0.0008973
Diarrhoea	-0.0468	Gamma	100	0.000468
Increased ALT	-0.05	Gamma	100	0.0005
Increased AST	0		-	-
Hyponatraemia	0	-	-	-

Abbreviations: AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Transaminase

Adverse event incidence

The incidence of AEs (all-cause) was varied in the PSA for nivolumab and its comparators. A beta distribution was applied to the incidence data because incidence was in the range of 0 to 1 (0%-100%). Table 94, Table 95 and Table 96 present the parameters used in the PSA.

Table 94: Incidence of adverse events included in probabilistic sensitivity analysis: nivolumab

AE	Mean deterministic incidence	Distribution	Alpha	Beta
Fatigue	3.10%	Beta	96.869	3027.937
Asthenia	3.50%	Beta	96.465	2659.678
Pain	2.10%	Beta	97.879	4563.026
Dyspnoea	4.90%	Beta	95.051	1844.765
Pleural effusion	2.40%	Beta	97.576	3968.091
Hyperglycemia	2.40%	Beta	97.576	3968.091
Pneumonia	3.50%	Beta	96.465	2659.678
Neutrophil count decreased	0.00%	-	-	-
White blood cell count decreased	0.00%	-	-	-
Anaemia	1.70%	Beta	98.283	5683.070
Neutropenia	0.30%	Beta	99.697	33132.636
Febrile neutropenia	0.00%	-	-	-
Leukopenia	0.00%	-	-	-
Diarrhoea	1.00%	Beta	98.990	9800.010
Increased ALT	0.30%	Beta	99.697	33132.636
Increased AST	0%	-	-	-
Hyponatraemia	0%	-	-	-

Abbreviations: AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Transaminase

Table 95: Incidence of adverse events included in probabilistic sensitivity analysis: docetaxel

AE	Mean deterministic incidence	Distribution	Alpha	Beta
Fatigue	6.70%	Beta	93.233	1298.304
Asthenia	4.10%	Beta	95.859	2242.165
Pain	1.90%	Beta	98.081	5064.077
Dyspnoea	3.70%	Beta	96.263	2505.440
Pleural effusion	0.70%	Beta	99.293	14085.421
Hyperglycemia	1.90%	Beta	98.081	5064.077
Pneumonia	5.20%	Beta	94.748	1727.329
Neutrophil count decreased	6.00%	Beta	93.940	1471.727
White blood cell count decreased	4.50%	Beta	95.455	2025.767
Anaemia	4.50%	Beta	95.455	2025.767
Neutropenia	28.00%	Beta	71.720	184.423
Febrile neutropenia	10.80%	Beta	89.092	735.834
Leukopenia	8.60%	Beta	91.314	970.477
Diarrhoea	1.10%	Beta	98.889	8891.020
Increased ALT	0.40%	Beta	99.596	24799.404
Increased AST	0.00%	-	-	-
Hyponatraemia	0.00%	-	-	-

Abbreviations: AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Transaminase

Table 96: Incidence of adverse events included in probabilistic sensitivity analysis: nintedanib plus docetaxel

AE	Mean deterministic incidence	Distribution	Alpha	Beta
Fatigue	5.5%	Beta	94.445	1622.737
Asthenia	2.0%	Beta	97.980	4801.020
Pain	0.0%	Beta	-	-
Dyspnoea	4.9%	Beta	95.051	1844.765
Pleural effusion	1.0%	Beta	98.990	9800.010
Hyperglycemia	1.1%	Beta	98.889	8891.020
Pneumonia	2.6%	Beta	97.374	3647.780
Neutrophil count decreased	32.0%	Beta	67.680	143.820
White blood cell count decreased	16.4%	Beta	83.436	425.320
Anaemia	1.1%	Beta	98.889	8891.020
Neutropenia	12.1%	Beta	87.779	637.667
Febrile neutropenia	7.0%	Beta	92.930	1234.641
Leukopenia	2.9%	Beta	97.071	3250.205
Diarrhoea	6.5%	Beta	93.435	1344.027
Increased ALT	7.8%	Beta	92.122	1088.929
Increased AST	3.4%	Beta	96.566	2743.610
Hyponatraemia	2.1%	Beta	97.879	4563.026

Abbreviations: AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Transaminase

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 97 through Table 101.

Table 97: Progression-free health state resource use and treatment costs included in probabilistic sensitivity analysis

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	-	-	-
Palliative care (per day)	2	Gamma	1.00E+02	2.00E-02
Oxygen	0	-	-	-
Radiotherapy (bone) per fraction	0.31	Gamma	1.00E+02	3.10E-03
Blood transfusion	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

Table 98: Progressed disease health state resource use and treatment costs included in the probabilistic sensitivity analysis

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

Table 99: End-of-life/terminal care resource use and treatment costs included in the probabilistic sensitivity analysis

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

Table 100: Administration and monitoring resource use and costs included in the probabilistic sensitivity analysis

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
Nintedanib plus docetaxel	1	Gamma	1.00E+02	1.00E-02
Erlotinib	0	-	-	-
BSC	0	-	-	-
Carboplatin	1	Gamma	1.00E+02	1.00E-02
Gemcitabine	1	Gamma	1.00E+02	1.00E-02
Pemetrexed	1	Gamma	1.00E+02	1.00E-02
Administration costs				
Nivolumab	£167.34	Gamma	1.00E+02	1.67E+00
Docetaxel	£167.34	Gamma	1.00E+02	1.67E+00

Parameter	Mean deterministic value	Distribution	Alpha	Beta
Nintedanib plus docetaxel	£167.34	Gamma	1.00E+02	1.67E+00
Erlotinib	0	-	-	-
BSC	0	-	-	-
Carboplatin	£167.34	Gamma	1.00E+02	1.67E+00
Gemcitabine	£167.34	Gamma	1.00E+02	1.67E+00
Pemetrexed	£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
Nintedanib plus 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
Carboplatin	1	Gamma	1.00E+02	1.00E-02
Gemcitabine	1	Gamma	1.00E+02	1.00E-02
Pemetrexed	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
Nintedanib plus 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
Carboplatin	£151.89	Gamma	1.00E+02	1.52E+00
Gemcitabine	£151.89	Gamma	1.00E+02	1.52E+00
Pemetrexed	£151.89	Gamma	1.00E+02	1.52E+00

Abbreviations: BSC = Best Supportive Care

Table 101: Adverse event costs included in the probabilistic sensitivity analysis

AE	Mean deterministic cost	Distribution	Alpha	Beta
Fatigue	£3,015.13	Gamma	100	30.151
Asthenia	£3,015.13	Gamma	100	30.151
Pain	£122.00	Gamma	100	1.220
Dyspnoea	£0.00	-	-	-
Pleural effusion	£553.00	Gamma	100	5.530
Hyperglycemia	£652.00	Gamma	100	6.520
Pneumonia	£1,822.85	Gamma	100	18.228
Neutrophil count decreased	£0.00	-	-	-
White blood cell count decreased	£423.00	Gamma	100	4.230
Anaemia	£978.00	Gamma	100	9.780
Neutropenia	£354.72	Gamma	100	3.547
Febrile neutropenia	£5,489.94	Gamma	100	54.899
Leukopenia	£354.72	Gamma	100	3.547
Diarrhoea	£1796.00	Gamma	100	17.960
Increased ALT	£587.00	Gamma	100	5.870
Increased AST	£336.00	Gamma	100	3.360
Hyponatraemia	£652.00	Gamma	100	6.520

Abbreviations: AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Transaminase

Results of the probabilistic sensitivity analysis on the base-case model

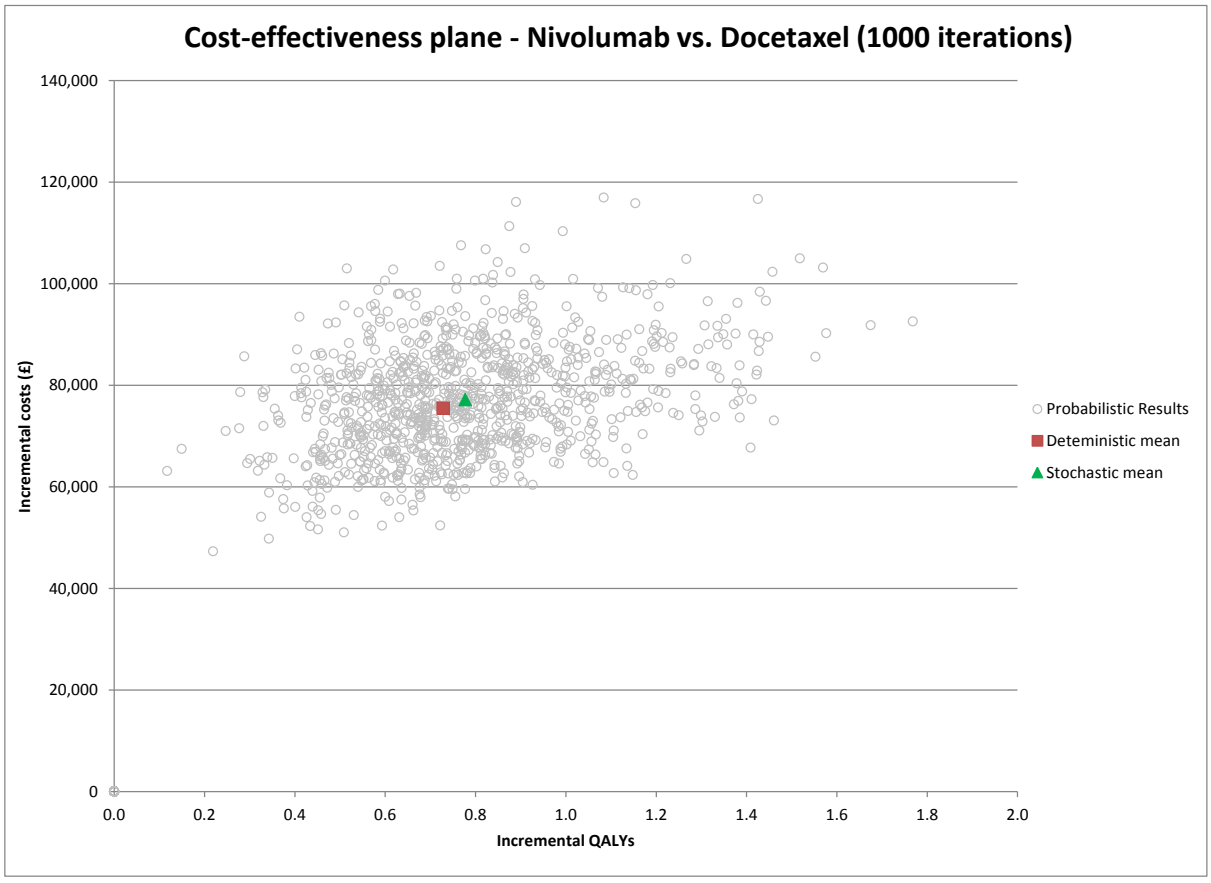
Results of the PSA are shown in Table 102, which also shows results from the deterministic analysis for comparison. The probabilistic ICER versus docetaxel is £99,291 per QALY gained compared with £103,589 per QALY gained in the deterministic analysis. The probabilistic ICER versus nintedanib plus docetaxel is £111,934 per QALY gained compared with £126,861 per QALY gained in the deterministic analysis. The uncertainty in the ICER appears to be driven by the variation on treatment efficacy, resource utilisation, body weight and utility weights, given the high impact they have overall on the results of the model. The cost-effectiveness scatterplots are shown in Figure 43 and Figure 44 and the cost-effectiveness acceptability curve in Figure 45.

Table 102: Probabilistic sensitivity analysis results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Nivolumab	94,83	1.50	-	-	-
Docetaxel	17,666	0.72	77,166	0.78	99,291
Nintedanib plus docetaxel	31,070	0.96	63,761	0.54	117,934
Deterministic values vs. docetaxel			75,452	0.73	103,589
Deterministic values vs. nintedanib plus docetaxel			62,598	0.49	126,861

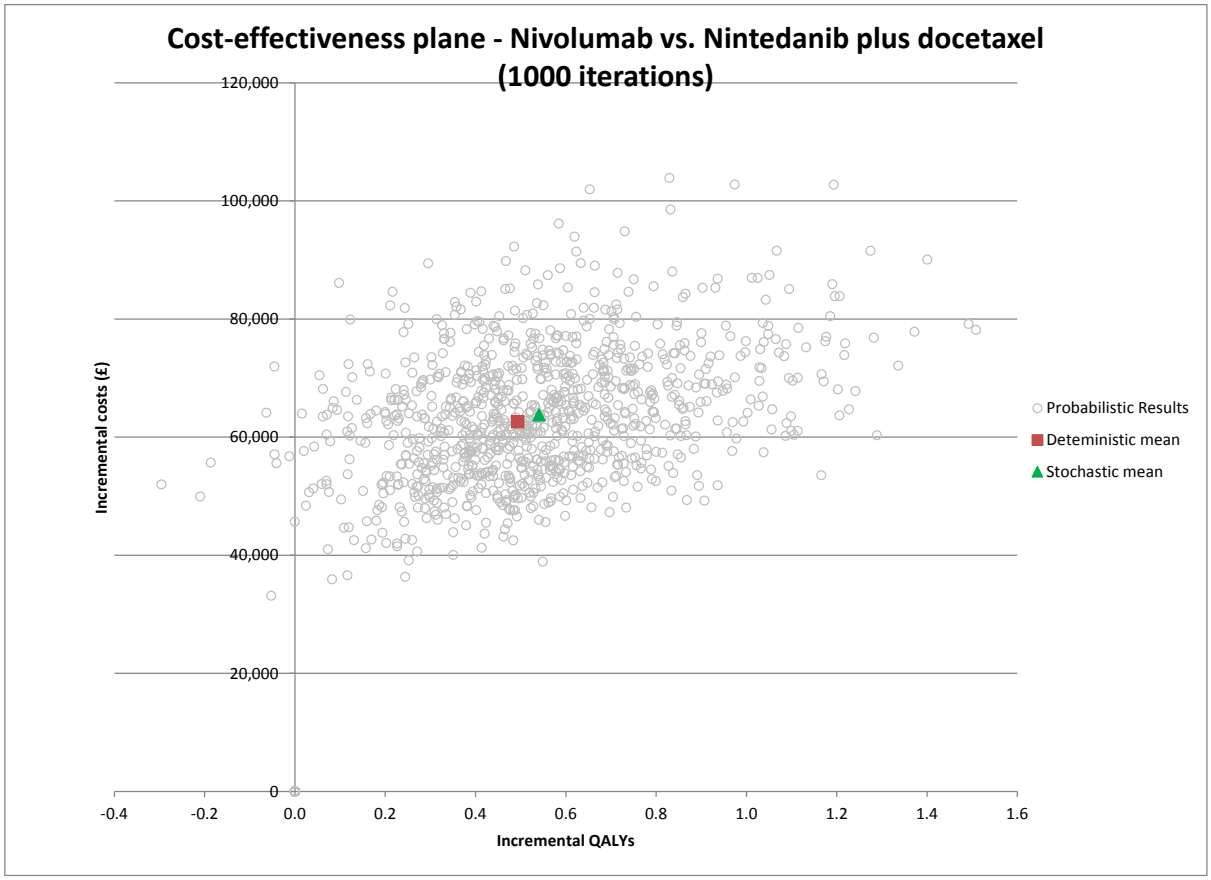
Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life-Year

Figure 43: Scatter plot for cost-effectiveness of nivolumab versus docetaxel (1,000 iterations)



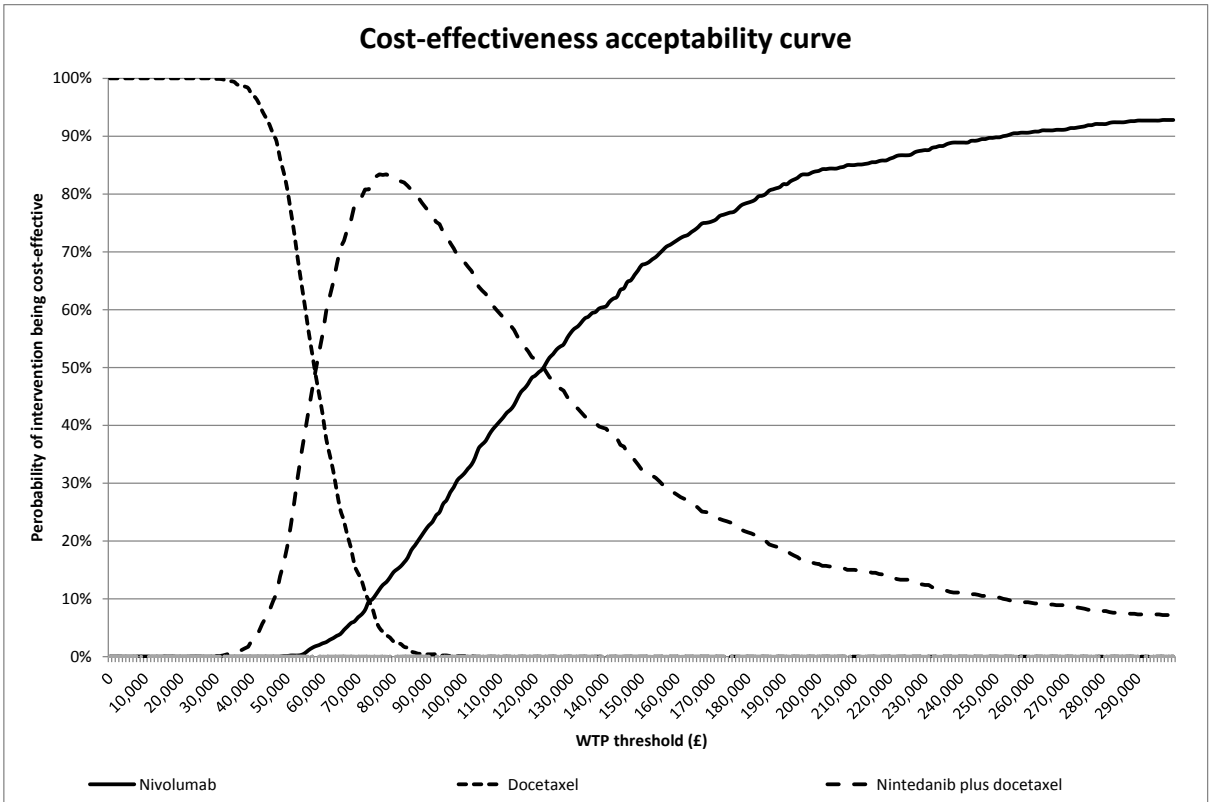
Abbreviations: QALY = Quality-Adjusted Life-Year.

Figure 44: Scatter plot for cost-effectiveness of nivolumab versus nintedanib plus docetaxel (1,000 iterations)



Abbreviations: QALY = Quality-Adjusted Life-Year.

Figure 45: Cost-effectiveness acceptability curve of nivolumab versus docetaxel and nintedanib in combination with docetaxel



Abbreviation: WTP = Willingness to Pay.

5.9.2 Deterministic sensitivity analysis

A one-way sensitivity analysis was undertaken by varying cost, utility and OS base-case parameter values by their CIs (where available) or ±20% (Table 103). As variability around OS and TTD for nivolumab and docetaxel are explored in the scenario analyses, they were not included in the deterministic sensitivity analysis. Table 104 and Figure 46 present the results of the analysis and a Tornado diagram, respectively for nivolumab vs docetaxel. Table 105 and Figure 46 present the results of the analysis and a Tornado diagram, respectively, for nivolumab versus nintedanib plus docetaxel.

The Tornado diagram shows that the ICER was most sensitive to the discount rate, average body weight of patients and HR for OS applied in the comparison with nintedanib in combination with docetaxel, where there is high uncertainty as a result of the indirect comparison. All other variables, including AE management, end-of-life care and monitoring costs, had minimal impact on the ICER.

Table 103: Deterministic sensitivity analysis parameters

Parameter	Mean deterministic	Lower value	Upper value
General			
Discount rate: costs	4%	0.00%	6.00%
Discount rate: outcomes	4%	0.00%	6.00%
Average body weight, kg	70	56	84
Body surface area, m^2	1.8	1.4	2.1
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	167.34	133.87	200.81
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	0.74	0.73	0.75
Utility weight, PD	0.69	0.67	0.71
Comparators			
HR on PFS: nintedanib plus docetaxel	[redacted]		
HR on OS: nintedanib plus docetaxel			

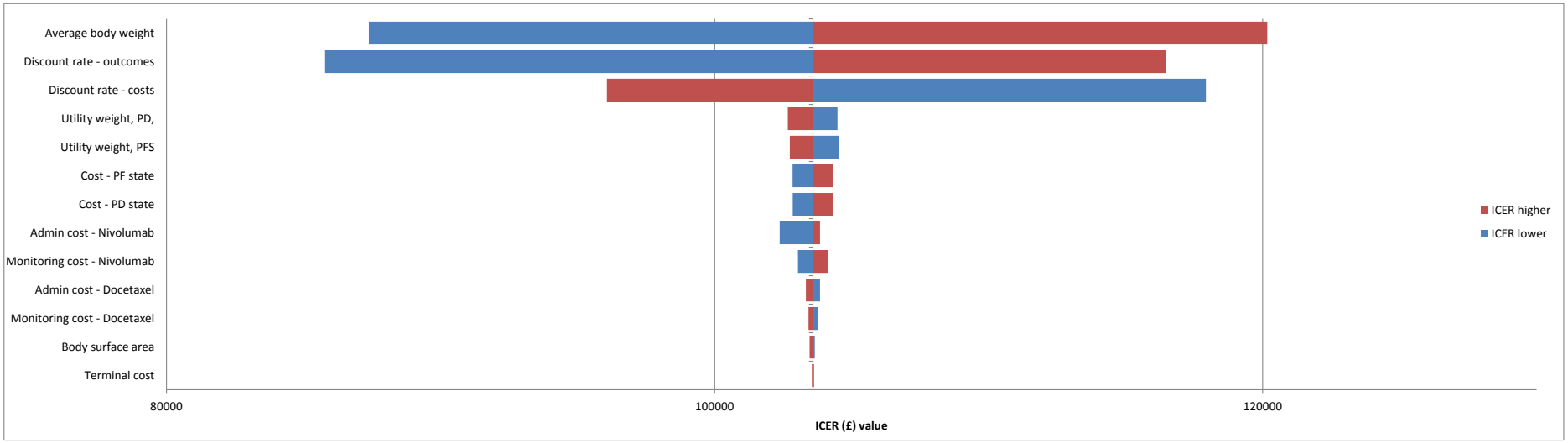
Abbreviations: HR = Hazard Ratio; OS = Overall Survival; PD = Progressed Disease; PF = Progression-Free; PFS = Progression-Free Survival

Table 104: Results of deterministic analysis versus docetaxel

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base-case analysis		75,452	0.73	103,589
Discount rate: costs	Lower	85,895	0.73	117,928
	Higher	69,973	0.73	96,068
Discount rate: outcomes	Lower	75,452	0.88	85,753
	Higher	75,452	0.65	116,472
Average body weight	Lower	63,650	0.73	87,386
	Higher	87,528	0.73	120,169
BSA	Lower	75,500	0.73	103,655
	Higher	75,360	0.73	103,463
Costs				
Cost: PF state	Lower	74,908	0.73	102,843
	Higher	75,995	0.73	104,335
Cost: PD state	Lower	74,911	0.73	102,848
	Higher	75,992	0.73	104,331
Terminal cost	Lower	75,481	0.73	103,630
	Higher	75,422	0.73	103,549
Administration cost: nivolumab	Lower	74,567	0.73	102,375
	Higher	76,336	0.73	104,804
Administration cost: docetaxel	Lower	75,639	0.73	103,847
	Higher	75,264	0.73	103,331
Monitoring cost: nivolumab	Lower	75,054	0.73	103,043
	Higher	75,849	0.73	104,135
Monitoring cost: docetaxel	Lower	75,572	0.73	103,755
	Higher	75,331	0.73	103,424
Outcomes				
Utility weight, PFS	Lower	75,452	0.72	104,546
	Higher	75,452	0.73	102,743
Utility weight, PD	Lower	75,452	0.72	104,484
	Higher	75,452	0.73	102,672

Abbreviations: BSA = Body Surface Area; PD = Progressed Disease; PF = Progression-Free; PFS = Progression-Free Survival; QALY = Quality-Adjusted Life-Year

Figure 46: Tornado diagram for nivolumab versus docetaxel



Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; PD = Progressed Disease; PF = Progression-Free; PFS = Progression-Free Survival

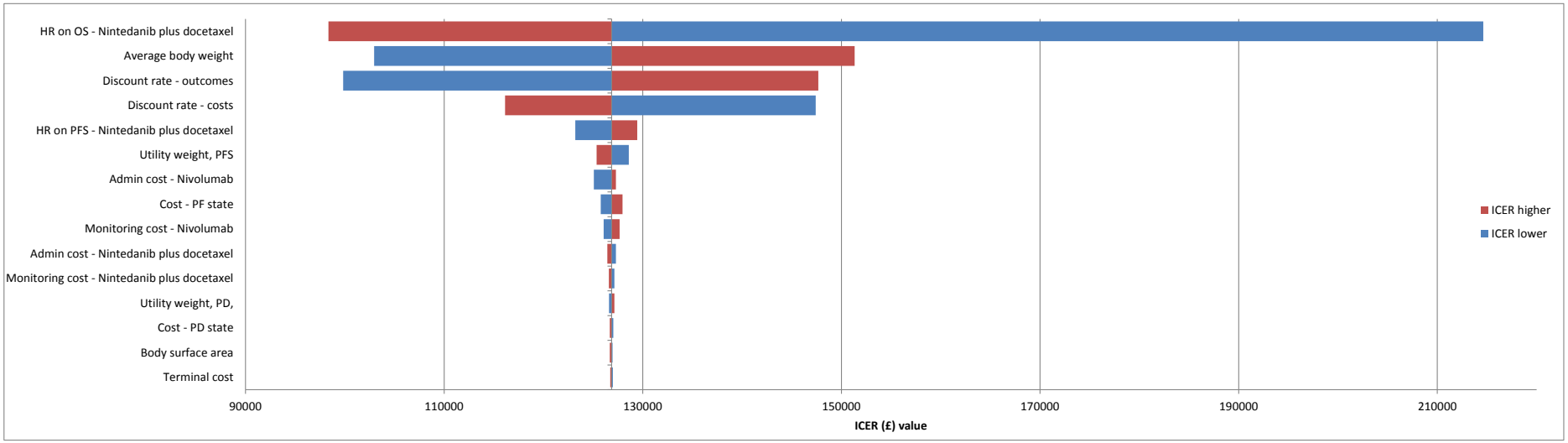
Table 105: Results of deterministic analysis versus nintedanib plus docetaxel

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base-case analysis		62,598	0.49	126,861
Discount rate: costs	Lower	72,736	0.49	147,407
	Higher	57,308	0.49	116,141
Discount rate: outcomes	Lower	62,598	0.63	99,830
	Higher	62,598	0.42	147,671
Average body weight	Lower	50,796	0.49	102,943
	Higher	74,674	0.49	151,335
BSA	Lower	62,646	0.49	126,959
	Higher	62,506	0.49	126,676
Costs				
Cost: PF state	Lower	62,058	0.49	125,767
	Higher	63,138	0.49	127,956
Cost: PD state	Lower	62,686	0.49	127,040
	Higher	62,510	0.49	126,683
Terminal cost	Lower	62,663	0.49	126,993
	Higher	62,533	0.49	126,730
Administration cost: nivolumab	Lower	61,713	0.49	125,069
	Higher	63,482	0.49	128,654
Administration cost: docetaxel	Lower	62,809	0.49	127,289
	Higher	62,387	0.49	126,433
Monitoring cost: nivolumab	Lower	62,200	0.49	126,055
	Higher	62,996	0.49	127,668
Monitoring cost: docetaxel	Lower	62,734	0.49	127,137
	Higher	62,462	0.49	126,585
Outcomes				
Utility weight, PFS	Lower	62,598	0.49	128,588
	Higher	62,598	0.50	125,347
Utility weight, PD	Lower	62,598	0.49	126,601
	Higher	62,598	0.49	127,134

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Survival outcomes				
HR on PFS: nintedanib plus docetaxel	Lower	60,246	0.49	123,209
	Higher	64,293	0.50	129,442
HR on OS: nintedanib plus docetaxel	Lower	59,328	0.28	214,630
	Higher	65,217	0.66	98,353

Abbreviations: BSA = Body Surface Area; PD = Progressed Disease; PF = Progression-Free; PFS = Progression-Free Survival; QALY = Quality-Adjusted Life-Year

Figure 47: Tornado diagram for nivolumab versus nintedanib plus docetaxel



Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; PD = Progressed Disease; PF = Progression-Free; PFS = Progression-Free Survival

5.9.3 Scenario analysis

Survival analysis

Scenario analyses were undertaken on the survival modelling approaches applied for OS and TTD. Details of these scenarios are explained in more detail in Section 5.1.

Results are presented in Table 108 for the scenario where OS was modelled using a gamma and 2-knot spline hazards model for docetaxel and nivolumab, respectively. The increased ICER of £144,594 per QALY versus docetaxel and £195,348 versus nintedanib plus docetaxel predicted from this approach is attributable to lower incremental QALYs accrued with nivolumab using the 2-spline hazard model in comparison to the base-case generalised gamma model for OS. However, as explained in Section 5.1, the spline-2 knots distribution was not considered clinically plausible based on validation against CheckMate 003, with only 7% OS at 4 years compared with 15% in CheckMate 003.

A scenario analysis was also considered where TTD was modelled using a gamma and 1-knot spline hazards model for docetaxel and nivolumab, respectively. The increased ICER of £120,773 per QALY versus docetaxel and £149,112 versus nintedanib plus docetaxel predicted from this approach is likely attributed to the higher treatment duration of nivolumab using the 1-knot spline hazard model in comparison to the base-case generalised gamma model. However, as explained in Section 5.1, the generalised gamma distribution was selected in order to maintain consistency in the functional form adopted for OS and PFS between nivolumab and comparators.

Scenario 1: Testing alternative parametric models for overall survival: gamma for docetaxel overall survival and 2-knot spline hazards model for nivolumab overall survival

Table 106: Scenario 1: summary of QALY gain by health state

	QALYs			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib plus docetaxel**	**Incremental**	**% Absolute incremental**	**Incremental**	**% Absolute incremental**
PF	[redacted]						
PD							
AE disutility							
Total							

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year

Note: No utility is assigned to the death state.

Table 107: Scenario 1: summary of costs

	Cost (£)			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib plus docetaxel**	**Incremental**	**% Absolute incremental**	**Incremental**	**% Absolute incremental**
PF	[redacted]						
PD*							
Drug acquisition cost							
Administration cost							
Monitoring cost							
Subsequent treatment							
AEs							
Total treatment cost							

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free

*PD 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 1: cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	89,553	1.16			
Docetaxel	17,375	0.66	72,178	0.50	144,594
Nintedanib plus docetaxel	29,612	0.85	59,941	0.31	195,348

Abbreviations: QALY = Quality-Adjusted Life-Year

Scenario 2: Testing alternative parametric models for TTD: Gamma for docetaxel TTD and 1-knot spline hazards model for nivolumab TTD

Table 109: Scenario 2: summary of QALY gain by health state

	QALYs			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel Q**	**Nintedanib plus docetaxel**	**Incremental**	**% Absolute incremental**	**Incremental**	**% Absolute incremental**
PF	[redacted]						
PD							
AE disutility							
Total							

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year; TTD = Time to Treatment Discontinuation

Note: No utility is assigned to the death state.

Table 110: Scenario 2: summary of costs

	Cost (£)			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib plus docetaxel**	**Incremental**	**% Absolute incremental**	**Incremental**	**% Absolute incremental**
PF	[redacted]						
PD*							
Drug acquisition cost							
Administration cost							
Monitoring cost							
Subsequent treatment							
AEs							
Total treatment cost							

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free

*PD includes the costs of managing patients who have progressed and end-of-life/terminal care. No costs are assigned to the death state.

Table 111: Scenario 2: cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	112,380	1.48			
Docetaxel	17,858	0.70	94,522	0.78	120,773
Nintedanib plus docetaxel	30,709	0.93	81,671	0.55	149,112

Abbreviations: QALY = Quality-Adjusted Life-Year

Treatment discontinuation

The duration of treatment in the base-case economic analysis assumed a treat-to-progression treatment regimen for nivolumab. This was consistent with CheckMate 057, 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 TTD Kaplan-Maier curves from CheckMate 057 are shown in Figure 28 and Figure 34, respectively. At 1 year, the OS rate was 51% and 20% of patients remained on treatment with nivolumab.

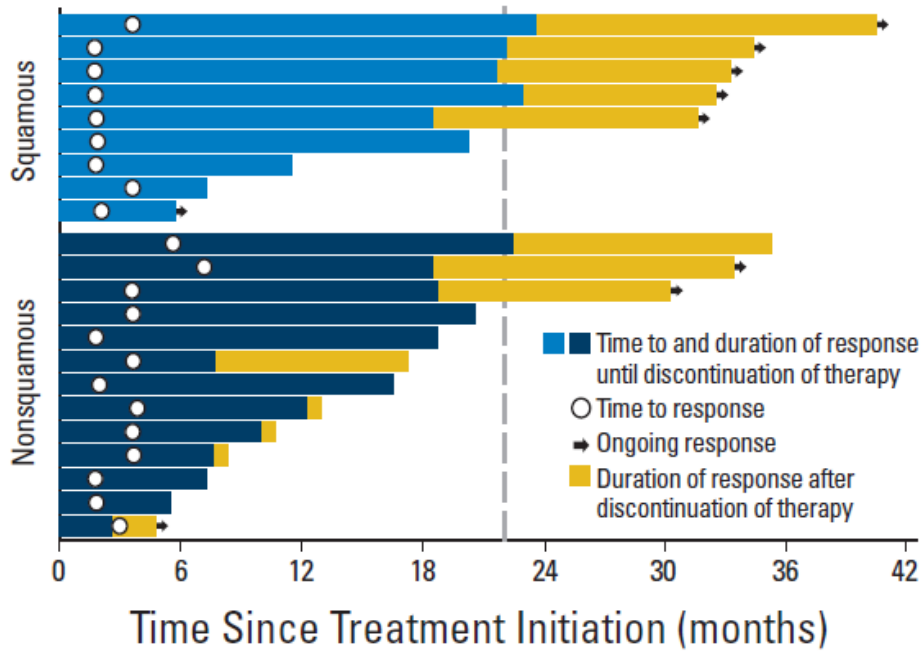
In patients who experienced a durable response, it may be feasible to stop nivolumab treatment before they progress and still maintain clinical benefit. Evidence to support this approach can be seen in study CheckMate 003, which had a 96-week stopping rule (Gettinger et al., 2015). This is the only study of nivolumab in lung cancer to use anything other than a treat-to-progression regimen. cFigure 48 presents the swimmers plot from CheckMate 003.

As can be seen from this plot (cFigure 48), 7 of 22 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, 6 of the 7 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 IIIb/IV CheckMate 153 safety study in which responders are randomised at 1 year to either stop nivolumab or to continue nivolumab treatment until progression. BMS plan to analyse the results of CheckMate 153 in Q2-Q3 of 2016, and it is estimated that approximately 100 patients who have been randomised into cohorts A or B will have a minimum of 6 months of post-randomisation follow-up available for this analysis.

Based on the projected availability of these data, and the evidence from 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. These scenario analyses are outlined in Table 112 through Table 117.

cFigure 48: Swimmers plot from CheckMate 003



Source: Gettinger et al. (2015)

Scenario 3: Testing a 1-year treatment-stopping rule to simulate the impact of an ongoing clinical benefit with nivolumab beyond treatment cessation

Table 112: Scenario 3: summary of QALY gain by health state

	QALYs			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel Q**	**Nintedanib plus docetaxel**	**Incremental**	**% Absolute incremental**	**Incremental**	**% Absolute incremental**
PF	[redacted]						
PD							
AE disutility							
Total							

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year

Note: No utility is assigned to the death state.

Table 113: Scenario 3: summary of costs

	Cost (£)			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib plus docetaxel**	**Incremental**	**% Absolute incremental**	**Incremental**	**% Absolute incremental**
PF							
PD*							
Drug acquisition cost							
Administration cost							
Monitoring cost							
Subsequent treatment							
AEs							
Total treatment cost							

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free

*PD includes the costs of managing patients who have progressed and end-of-life/terminal care. No costs are assigned to the death state.

Table 114: Scenario 3: cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	51,986	1.42			
Docetaxel	17,854	0.70	34,132	0.73	46,860
Nintedanib plus docetaxel	30,708	0.93	21,278	0.49	43,122

Abbreviation: QALY = Quality-Adjusted Life-Year

Scenario 4: Testing a 2-year treatment-stopping rule to simulate the impact of an ongoing clinical benefit with nivolumab beyond treatment cessation

Table 115: Scenario 4: summary of QALY gain by health state

	QALYs			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel Q**	**Nintedanib plus docetaxel**	**Incremental**	**% Absolute incremental**	**Incremental**	**% Absolute incremental**
PF	[redacted]						
PD							
AE disutility							
Total							

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year

Note: No utility is assigned to the death state.

Table 116: Scenario 4: summary of costs

	Cost (£)			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib plus docetaxel**	**Incremental**	**% Absolute incremental**	**Incremental**	**% Absolute incremental**
PF	[redacted]						
PD*							
Drug acquisition cost							
Administration cost							
Monitoring cost							
Subsequent treatment							
AEs							
Total treatment cost							

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free

*PD includes the costs of managing patients who have progressed and end-of-life/terminal care. No costs are assigned to the death state.

Table 117: Scenario 4: cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	62,252	1.42			
Docetaxel	17,854	0.70	44,398	0.73	60,955
Nintedanib plus docetaxel	30,708	0.93	31,544	0.49	63,928

Abbreviation: QALY = Quality-Adjusted Life-Year

5.10 Sub-group analysis

Appendix 16 presents the results of analyses for the EGFR mutation-negative/unknown and PD-L1 expresser sub-groups.

5.11 Validation

Several sources were used to validate the survival models used in the base-case analysis (Section 5.3). These include the following:

1. The Phase III CheckMate 057 KM data reported in the CSR for OS and TTD—specifically in terms of the median,12-month and 18-month rates for nivolumab and docetaxel where available
2. The Phase Ib safety study CheckMate 003 KM data, which provide 3 years of PFS and 4 years of OS follow-up for patients receiving nivolumab for advanced squamous and non-squamous NSCLC across all three doses (1 mg/kg, 3 mg/kg and 10 mg/kg)
3. The NLCA dataset (data for up to 5 years—relevant to UK clinical practice)

Table 118 shows the validation of the parametric survival models against CheckMate 057 and CheckMate 003 in terms of TTD and PFS. Table 119 shows the validation of the survival models for OS against CheckMate 057 and CheckMate 003. The data show that the survival patterns in the economic model were aligned well with the survival data available from all the nivolumab clinical studies.

In addition, external validation of these survival models for OS was explored using NLCA registry data, and details of these validations are presented in Section 5.3. Conditional survival estimates from NLCA closely matched those predicted by the long-term extrapolation techniques explored, which revealed that the economic model predicted OS estimates were clinically plausible (Table 120).

Table 118: In-study validation of parametric survival models for time to treatment discontinuation

Data source	Curve	Proportion alive (%)									Median treatment duration (months)	Mean treatment duration (months)
		1 year	18 months	2 years	3 years	4 years	5 years	10 years	15 years	20 years		
Base-case: TTD	Nivolumab	20%	14%	11%	8%	6%	5%	2%	2%	1%	3.4	13.5
	Docetaxel	3%	0%	0%	0%	0%	0%	0%	0%	0%	3.2	4.1
	Nintedanib plus docetaxel	3%	0%	0%	0%	0%	0%	0%	0%	0%	3.2	4.1
Sensitivity analysis: TTD	Nivolumab	20%	16%	13%	10%	8%	7%	5%	4%	3%	3.2	18.1
	Docetaxel	2%	0%	0%	0%	0%	0%	0%	0%	0%	3.2	4.1
	Nintedanib plus docetaxel	2%	0%	0%	0%	0%	0%	0%	0%	0%	3.2	4.1
CheckMate 057: TTD	Nivolumab	20%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Docetaxel	3%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CheckMate 057: PFS	Nivolumab	19%	NA	NA	NA	NA	NA	NA	NA	NA	2.3	NA
	Docetaxel	8%	NA	NA	NA	NA	NA	NA	NA	NA	4.2	NA
CheckMate 003: PFS	Nivolumab	33%	22%	9%	5%	NA	NA	NA	NA	NA	NA	NA

Abbreviations: NA = Not Applicable; PFS = Progression-Free Survival; TTD = Time to Treatment Discontinuation

Table 119: In-study validation of parametric survival models for overall survival

Data source	Curve	Proportion alive (%)									Median OS (months)	Mean OS (months)
		1 year	18 months	2 years	3 years	4 years	5 years	10 years	15 years	20 years		
Base-case: OS	Nivolumab	48%	37%	29%	20%	15%	12%	5%	2%	1%	11.0	26.8
	Docetaxel	40%	24%	14%	6%	2%	1%	0%	0%	0%	9.2	13.1
	Nintedanib plus docetaxel	50%	34%	23%	12%	6%	3%	0%	0%	0%	12.0	17.2
Sensitivity analysis: OS	Nivolumab	51%	37%	27%	14%	7%	5%	2%	2%	1%	12.0	21.2
	Docetaxel	41%	23%	13%	4%	1%	0%	0%	0%	0%	9.7	12.4
	Nintedanib plus docetaxel	51%	33%	21%	8%	3%	1%	0%	0%	0%	12.2	15.7
CheckMate 057: OS	Nivolumab	51%	39%	NA	NA	NA	NA	NA	NA	NA	2.3	NA
	Docetaxel	39%	23%	NA	NA	NA	NA	NA	NA	NA	4.2	NA
CheckMate 003: OS	Nivolumab	42%	31%	24%	18%	NA	NA	NA	NA	NA	NA	NA

Abbreviations: NA = Not Applicable; OS = Overall Survival

Table 120: Comparison of conditional survival estimates predicted from overall survival parametric distributions versus real-world data

OS parametric distributions	**Curve**	**Conditional survival**	
	Start year	**2**	**3**
	End year	**3**	**4**
Docetaxel	Gamma	29%	28%
	Generalised gamma	39%	41%
	1-knot spline	33%	31%
Nivolumab	2-knot spline	52%	52%
	Log-normal	69%	74%
	Generalised gamma	69%	74%
RWD (NLCA)*	**Start year**	**3**	**4**
	End year	**4**	**5**
NLCA stage IV	Treatment not specified	78.6%	90.9%

Abbreviations: NLCA = National Lung Cancer Audit; OS = Overall Survival; RWD = Real-World Data

* The NLCA dataset measures absolute survival rates of patients diagnosed with NSCLC; therefore, it inherently captures "all-cause" mortality. The dataset also includes squamous and non-squamous NSCLC.

Throughout the development of the economic model, external clinical and health economic experts were consulted, including the following:

1. Three EU advisory workshops attended by four health economists representing the 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.

5.12 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 non-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 non-squamous NSCLC in a second-line setting who have previously received platinum-based therapy. This population reflects patients enrolled in CheckMate 057 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 as follows:

- The patient population in CheckMate 057 and the economic analysis is reflective of patients with advanced NSCLC treated in the UK; 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 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 CheckMate 057, which collected data on efficacy (including OS), treatment patterns and quality of life. Survival extrapolation was essential to quantify the survival benefit beyond the study 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 study 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 1,413 patients will be eligible to receive nivolumab in the previously treated setting (Table 121). The analysis is based on a closed cohort and, therefore, the eligible population is 1,413 for each subsequent year.

Table 121: Eligible population for nivolumab

Population	Proportion of patients	Number of patients	Reference
Total NSCLC	N/A	27,300	Health and Social Care Information Centre (2014)
Stage IIIb/IV NSCLC	N/A	19,138	Health and Social Care Information Centre (2014)
Non-squamous NSCLC	64.35%	12,315	Powell et al. (2013)
Second-line setting	11.5%	1,413	NICE (2010d); Sculier and Moro-Sibilot (2009)

Abbreviations: N/A = not applicable; NICE = National Institute for Health and Care Excellence; 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 study data used in the economic model. Specifically, the mean number of doses received by patients undergoing treatment with nivolumab and docetaxel are sourced from CheckMate 057. For nintedanib, a treatment duration of 4.32 months (6.3 doses) is assumed, based on TTD in LUME-Lung 1 (Reck et al., 2014), whereas for docetaxel (given in combination with nintedanib) the treatment duration seen in the CheckMate 057 study is again assumed. BSC has no associated treatment costs. Details of these treatment durations for the intervention and comparators are presented in Table 122.

Table 122: Mean duration of treatment

Treatment	Mean duration of treatment (months)	Mean number of doses
Nivolumab	5.80	12.6
Docetaxel	3.79	5.5
Nintedanib plus docetaxel	4.32 (nintedanib) / 3.79 (docetaxel)	6.3/5.5
Best supportive care	N/A	N/A

Abbreviations: N/A = Not Applicable

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 123 and represents the scenario without nivolumab. Based on internal projections, it is estimated that the uptake of nivolumab will reach 42% by year 3 following introduction (Table 124). Due to limited forecasts, the market share projections for years 4 to 5 are assumed to be the same as for year 3. In the scenario with nivolumab, the distribution of treatments (for patients not on nivolumab) is assumed to be equivalent to the distribution in the scenario without nivolumab for years 1-5. The use of nintedanib is expected to increase from the date of NICE guidance in mid-2015, so its uptake is based on a further growth of 2% from October 2015 MAT (Bristol-Myers Squibb, 2015d). It is anticipated that nivolumab's share will largely come from docetaxel, but also from nintedanib in combination with docetaxel.

Table 123: Market share analysis: scenario without nivolumab

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Nivolumab	[redacted]				
Docetaxel					
Nintedanib plus docetaxel					
Best supportive care					
Total					

Table 124: Market share analysis: scenario with nivolumab

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Nivolumab	[redacted]				
Docetaxel					
Nintedanib plus docetaxel					
Best supportive care					
Total					

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 125 as costs per dose and based on the weight and body surface area calculator provided by the ERG during the review of the nivolumab in squamous NSCLC model. The mean duration of treatment for nivolumab, docetaxel and the additional interventions were sourced from CheckMate 057 and published literature.

Table 125: Drug acquisition costs

Comparator	Cost of each treatment	Mean duration of treatment (months)	Cost per Dose	Total drug acquisition cost*
Nivolumab	£439.00 (per 40 mg vial)	5.80	£2,538.25	£31,960
Docetaxel	Docetaxel: £35.35 (per 160 mg vial) Dexamethasone: £5.16 (per pack of 100 tablets)	3.79	£47.59	£262
Nintedanib (plus docetaxel)	£2,151 (per 60 tablets)	4.32	£1,553.29	£9,725
Best supportive care	N/A	N/A	N/A	N/A

Abbreviations: N/A = Not Applicable

* The differences between the total drug acquisition cost and the manual calculation based on the numbers in Table 38 and table 40 are due to rounding

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 121. For the purposes of the analysis, it is assumed that nivolumab is introduced to the market in April 2016.

The budget-impact analysis compares scenarios with and without nivolumab from years 1 to 5 after nivolumab introduction (Table 123 and Table 124). The results of this analysis show the net cumulative budget impact of introducing nivolumab from 2016 to 2020 is [redacted] (Table 126 and Table 127).

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. Also, the uncertainty of sales projections limits the accuracy of the budget-impact calculation.

Table 126: Scenario with nivolumab

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Patients on all comparators					
Total drug acquisition cost on all comparators					
Total drug administration cost on all comparators					
Total drug monitoring cost on all comparators					
Total drug AE cost on all comparators					
Patients on nivolumab					
Total drug acquisition cost on nivolumab					
Total drug administration cost on nivolumab					
Total drug monitoring cost on nivolumab					
Total drug AE cost on nivolumab					
Total					

Abbreviations: AE = Adverse Event

Table 127: Scenario without nivolumab

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Patients on all comparators					
Total drug acquisition cost on all comparators					
Total drug administration cost on all comparators					
Total drug monitoring cost on all comparators					
Total drug AE cost on all comparators					
Total					

Abbreviations: AE = Adverse Event

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Single technology appraisal

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900]

Dear Emir,

The Evidence Review Group, Liverpool Reviews and Implementation Group, and the technical team at NICE have looked at the submission received on 05/01/2016 from Bristol-Myers Squibb. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Friday 12 February 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Boglarka Mikudina, Technical Lead Boglarka.Mikudina@nice.org.uk. Any procedural questions should be addressed to Stephanie Yates, Project Manager Stephanie.Yates@nice.org.uk.

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

CheckMate 057:

A1. Considering Table 54 in the company's submission (CS), please clarify:
   a. Does this table show subsequent therapy received after the study was stopped at the time of the interim analysis?
   b. Were patients allowed to crossover to nivolumab from docetaxel when the study was stopped?
   c. Did the data for all patients who switched to other treatments after the study was stopped contribute to the updated 18-month analysis?

A2. In the protocol for CheckMate 057 (Table 8.1-1), it is stated that the interim analysis of overall survival (OS) would be performed after 262 deaths had occurred, and the final analysis of OS would be performed after 403 deaths. However, in the CS (p.65), it is stated that the interim analysis of OS was planned to take place after 380 deaths, and the final analysis of OS was planned to take place after 574 deaths. Please explain the discrepancies in these numbers.

A3. Please provide OS results for the EGFR mutation-positive population at the 18-month updated analysis; specifically:
   a. Number of events for each treatment arm
   b. Median OS for each treatment arm
   c. Hazard ratio (HR) and 95% confidence interval (CI) for nivolumab versus docetaxel.

A4. Please provide the p-values for the tests for interaction for the subgroup analyses presented in Figure 16 of the CS (p84).

A5. In Table 27 of the CS, the HRs and corresponding 95% CIs for OS and PFS for Checkmate 057 EGFR mutation-negative/unknown patients differ to the HRs and 95% CIs presented on pages 85 and 87 of the CS:

OS

Page 85: "At the 12-month interim analysis, the HR for OS with nivolumab versus docetaxel was 0.69 (95% CI: 0.56 to 0.85) in patients with EGFR mutation-negative/unknown (combined)."

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Table 27 (OS HR and 95% CI reported for CheckMate 057): Pooled EGFR mutation-negative/unknown NSCLC: 0.68 (0.54, 0.83)

PFS

Page 87: "At the interim analysis, the HR for PFS with nivolumab versus docetaxel was 0.83 (95% CI 0.68 to 1.02) in patients with EGFR mutation-negative/unknown (combined)."

Table 27 (PFS HR and 95% CI reported for CheckMate 057): Pooled EGFR mutation-negative/unknown NSCLC: 0.83 (0.59 to 0.997)

Please clarify the reasons for these discrepancies.

Indirect treatment comparisons:

A6. **Priority question.** When conducting the indirect treatment comparisons (ITCs) for the EGFR mutation-negative patient population, were results for this subpopulation used from the four studies included in this network? Only results for the overall patient population are provided in Table 27. Please provide the data inputs for the EGFR mutation-negative patient population ITC (and for the additional analysis requested in question A9 below).

A7. **Priority question;** In Appendix 7.4 it is stated that the proportional hazards assumption was tested by generating plots and performing statistical tests.

a. Was this testing carried out for all studies included in the ITC?
b. Please provide the graphs generated to investigate the proportional hazards assumption and the results of any statistical tests performed for all studies where proportional hazards were tested.

A8. **Priority question.** For the Restricted Mean Survival Time (RMST) analysis, in Appendix 7.4 it is stated that t* was chosen to be the longest minimum follow-up time for the two treatment arms.

a. Please confirm how t* was determined for both the all-comers and EGFR mutation-negative/unknown population networks, given that 4/5 studies were included in these networks, respectively, with each study having two treatment arms.
b. Please confirm how this method accounts for the fact that some studies have shorter follow-up times. Could the area under the curve (AUC) be overestimated for these studies, as survival probability remains constant after the last observed event for the study with the shortest follow-up time?
c. Please provide figures similar to Figure 2 in Appendix 7.4 showing the calculation of RMST for each treatment arm for each study.

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A9. The indirect comparison used data from the LUME-Lung 1 second-line patient population, and the CheckMate 057 second and third-line patient population. Please perform an indirect comparison of nivolumab versus nintedanib+docetaxel using data only for the second-line population from CheckMate 057, completing the following table:

Outcome	Nivolumab vs nintedanib+docetaxel
Patient population: 'All-comers' NSQ NSCLC	
OS (HR [95% CI]; p value)	
OS (RMST difference (95% CI]; p value)	
PFS (HR ([95% CI]; p value)	
PFS (RMST difference [95% CI]; p value)	
ORR (RR [95% CI]; p value)	
Any adverse event (RR [95% CI]; p value)	
Any grade 3/4 adverse event (RR [95% CI]; p value)	
Patient population: EGFR mutation-negative/unknown NSQ NSCLC	
OS (HR [95% CI]; p value)	
OS (RMST difference [95% CI]; p value)	
PFS (HR [95% CI]; p value)	
PFS (RMST difference [95% CI]; p value)	
ORR (RR [95% CI]; p value)	

A10. Concerning the search for studies to be included in the ITC:

a. Were studies excluded if they compared an included intervention/comparator to a non-included comparator?
b. If this is the case, please justify this approach. Non-included comparators may be common comparators between included relevant treatments, therefore providing additional indirect evidence to the network.

A11. In Appendix 7.17, some of the ITC results presented differ to those provided in Table 28 of the CS. Please clarify the reasons for these differences:

a. EGFR mutation-negative/unknown patient population, OS HR for nivolumab versus BSC: Table 16 in Appendix 7.17, HR=[redacted] (95% CI: [redacted]), p=[redacted]; Table 28, HR=[redacted] (95% CI: [redacted]), p=[redacted]
b. EGFR mutation-negative/unknown patient population, OS using RMST for nivolumab versus BSC: Table 18 in Appendix 7.17, RMST difference=[redacted] months (95% CI: [redacted]), p=[redacted]; In Table 28 in the CS, RMST difference is not reported. Please provide this data.
c. EGFR mutation-negative/unknown patient population, any adverse event RR for nivolumab versus nintedanib+docetaxel: Table 27 in Appendix 7.17, RR =

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[redacted](95% CI [redacted]), [redacted]; In Table 28 in the CS, any adverse event RR not reported. Please provide this data. For this analysis, please also provide the data inputs from CheckMate 057, the number of EGFR mutation negative/unknown patients experiencing any adverse event are not provided in Table 27 in the CS.

A12. How was a result for the outcome of any grade 3 or 4 adverse event data for the comparison of nivolumab versus nintedanib+docetaxel generated by the ITC for the entire population of the CheckMate 057 study (all-comers population)? Data for this outcome were not reported for the CheckMate 057 study, which links these two treatments.

A13. There is a result from the ITC for any grade 3 or 4 adverse event for nivolumab versus nintedanib+docetaxel for the EGFR mutation-negative/unknown population, this is provided in Table 10 in the Appendix 7.11. This result is not found anywhere else in the CS it is not in the results tables in Appendix 7.17 or in the results section of the CS. Please clarify how this result was calculated, given that data for this outcome were not reported for the CheckMate 057 study.

Section B: Clarification on cost-effectiveness data

B1. **Priority request: Kaplan-Meier data.** Please provide the following Kaplan-Meier analyses (listed in a to g below) to the following specification:
Population: Use the 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/PPS), and not at the date of last tumour assessment (PFS). Please use the format of the table provided below.
Format: Please present analysis outputs using the format of the sample table shown below.
Trial data set: CheckMate 057, latest data cut (02 July 2015 or later, if available). N.B if any patients crossed over or moved to an extension trial in the latest data cut, please censor them at the time they moved from the original trial or their randomised trial arm

a. Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (nivolumab vs docetaxel).
b. Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (nivolumab vs docetaxel).

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c. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis stratified by treatment arm (nivolumab vs docetaxel).
d. Time to treatment discontinuation Kaplan-Meier analysis stratified by treatment arm (nivolumab vs docetaxel).
e. Time to death from any cause (OS) Kaplan-Meier analysis for patients randomised to the nivolumab treatment arm, excluding all patients who continued to receive nivolumab beyond investigator assessed disease progression.
f. Time to disease progression or death (PFS) based on investigator assessment Kaplan-Meier analysis, for patients randomised to the nivolumab treatment arm, excluding all patients who continued to receive nivolumab beyond investigator assessed disease progression.
g. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis, for patients randomised to the nivolumab treatment arm, excluding all patients who continued to receive nivolumab beyond investigator assessed disease progression.

The rationale for this request is as follows:

All Kaplan-Meier analyses are specified to use the alternative censoring rule:
When trials are stopped early or subject to early analysis, the conventional censoring rule (censor when last contacted/reviewed) always understates the time patients are exposed to risk but is much less likely to understate events, especially deaths. The result is that the inter-event period hazard rates calculated by Kaplan-Meier algorithm are exaggerated when multiple patients are censored in any period. The resulting Kaplan-Meier estimated time-to-event trends may therefore be distorted by 'informative censoring' and poorly reflect the true profile of time-to-event hazards. In some of the specified analyses there are suggestive indications that such effects are present, but it is not possible to confirm or refute this possibility without having access to re-analysis using the alternative censoring rule.
a, b, c: Survival gain for nivolumab vs docetaxel is the most important parameter governing cost effectiveness. Careful analysis of OS and its components (PFS and Post-Progression Survival) is essential to validation of the survival gains estimated by the decision model.
d: Time to treatment discontinuation offers an alternative to PFS as a basis for estimating treatment costs in both trial arms. This analysis will allow the sensitivity of incremental costs to the method of estimation to be assessed.
e, f, g: These analyses facilitate exploration of the role of extended nivolumab treatment beyond conventionally defined disease progression and its impact on model results.

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Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

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: EQ-5D.** Please provide results for EQ-5D utility scores (using the UK value set) in the CheckMate 057 trial (02 July 2015 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:

a. treatment (nivolumab vs docetaxel)
b. disease response (stable disease, responding disease (CR & PR) and progressive disease).

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B3. **Priority request: EQ-5D.** Please repeat the B2 analyses (02 July 2015 data cut if available, otherwise the most recent data) for each of three subgroups defined by country of origin:

a. USA and Canada (32 sites with 215 patients)
b. Europe (44 sites with 268 patients, including Russia)
c. Other (30 sites with 99 patients from Asia, Central & South America and Australia)

The rationale for these requests is as follows:

The summary of EQ-5D results in the CS is very limited, and it is not clear how conclusions have been drawn which underlie the model assumptions (e.g. that utility in PFS and PD state do not vary by treatment arm, and that EQ-5D responses do not vary systematically by region of origin). The requested analyses should resolve these uncertainties.

B4. **Priority request: time from diagnosis to randomisation.** Please provide time from diagnosis to randomisation as a frequency table with bins of 6 months and include mean OS, mean PFS, mean age (each with standard deviation), and proportion male for each bin, stratified by treatment arm.

The rationale for this request is as follows:

The survival profile is likely to change depending on how far a patient is from diagnosis. Although median time from diagnosis in the CheckMate 057 trial is 0.8 years, some patients had been diagnosed for 8.5 years before randomisation. It is important to understand if and how patients who have already lived with the disease for varying amounts of time might have influenced survival data.

B5. **Priority request: Adverse events.** Please provide the number of grade ≥ 3 adverse events per quarter (3 months) in the CheckMate 057 trial as per table 53 of the CS. These should be split by whether the AEs are initial or repeat events and should aggregate figures for AEs occurring in quarter 5 or later (see example format below). Please provide separate tables for nivolumab and for docetaxel.

	Patients	Events									
		Time= Q1		Time= Q2		Time= Q3		Time= Q4		Time = Q5+	
AE type	No. affected	Initial events	Repeat events	Initial events	Repeat events	Initial events	Repeat events	Initial events	Repeat events	Initial events	Repeat events
AE1											
AE2											
AE3											
etc											

B6. **Priority request: Subsequent therapies.** Please clarify how the proportion of patients receiving various subsequent therapies given in table 54 of the CS (and the Excel model) corresponds with table S.5.9 in the CSR. Table 54 of the CS appears to

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underestimate the proportion of patients receiving subsequent therapies in comparison with those listed on page 3 in table S.5.9 of the CSR, particularly for nivolumab.

B7. **Priority question: Treatment with docetaxel.** Please provide details by cycle of the number of patients separately receiving full or reduced doses of docetaxel, or for whom treatment was missed/suspended for any reason, tabulated as follows:

	No. of patients still 'on treatment'	No. on full dose (75mg/m^2)	No. on reduced dose 1 (55mg/m^2)	No. on reduced dose 2 (37.5mg/m^2)	No. with treatment suspended
Cycle 1					
Cycle 2					
Cycle 3					
….etc					

N.B Number of patients still 'on treatment' should equal the sum of the other 4 columns, as well as corresponding to the number of patients 'at risk' per cycle in the time to treatment discontinuation data.

B8. Please confirm whether figure 32 is correct. One of the curves for the nivolumab OS extrapolation is labelled as 1-knot spline, when table 47 (and elsewhere in the CS), a 2-knot spline is referred to for nivolumab OS projection.

B9. Please provide a breakdown, using the latest database lock, of the treatment duration and survival of patients in the nivolumab arm of the CheckMate 057 trial who received treatment after progression. Please use the following table format:

Patient	Total duration of treatment (months)	Duration of treatment before progression (months)	# doses after initial progressive disease	Duration of treatment after initial progressive disease (months)	Overall survival (months)	Post treatment survival (months)	Meets non-conventional benefit criteria (Y/N)	Censore (Y/N)
1								
2								
…etc								

B10. Please provide details of the NHS Reference Cost code(s) and/or other values used to calculate the cost of fatigue in table 71 of the CS.

Section C: Textual clarifications and additional points

C1. The CSR for CheckMate 057 that we received was not complete. Please provide the following two items from the appendix of the report;

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a. The statistical analysis plan (SP)

b. Appendix 2.3: End of Treatment Period Subject Status Listing All Treated Subjects pg 29606

RE: BMS response to NICE/ERG questions for Single Technology Appraisal: Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900]

Section A: Clarification on effectiveness data

CheckMate 057:

A1. Considering Table 54 in the company's submission (CS), please clarify:

a. Does this table show subsequent therapy received after the study was stopped at the time of the interim analysis?

This table represents the subsequent therapy received after a patient experiences progression within the trial not the treatment received after the study was stopped

b. Were patients allowed to crossover to nivolumab from docetaxel when the study was stopped?

Yes, patients were allowed to crossover after the study stopped.

c. Did the data for all patients who switched to other treatments after the study was stopped contribute to the updated 18-month analysis?

Yes, the 18-month KM curve are based on the ITT population and include the patients that crossed over. Only 2 patients had crossed over by the 18 months.

A2. In the protocol for CheckMate 057 (Table 8.1-1), it is stated that the interim analysis of overall survival (OS) would be performed after 262 deaths had occurred, and the final analysis of OS would be performed after 403 deaths. However, in the CS (p.65), it is stated that the interim analysis of OS was planned to take place after 380 deaths, and the final analysis of OS was planned to take place after 574 deaths. Please explain the discrepancies in these numbers.

Page 65 of the CS states "The final analysis of OS was planned to take place after 442 deaths were observed among 574 randomised patients. One interim analysis of OS was planned after at least 380 deaths (86% of total deaths required for final analysis) had been observed" in line with the CSR which is cited. On further assessment we have discovered that the previously provided protocol was superseded by one dated April 2015 (attached: ERG Question A2 ca209057-revised protocol 04_1), in which the numbers match those in the CSR.

A3. Please provide OS results for the EGFR mutation-positive population at the 18-month updated analysis; specifically:

a. Number of events for each treatment arm
b. Median OS for each treatment arm
c. Hazard ratio (HR) and 95% confidence interval (CI) for nivolumab versus docetaxel.

Table 1. Subgroup Analysis for OS, EGFR mutation positive population at the 18-month cut-off

	N	Patients with event (%)	Kaplan-Meier estimate (95% CI)*	HR nivolumab vs docetaxel (95% CI), p value†‡	Test for interaction P value‖
Nivolumab	44	33 (75.0)	9.31 (5.19, 15.67)	1.12 (0.67, 1.86), 0.6679	0.4689
Docetaxel	38	27 (71.1)	11.53 (5.75, 16.99)	-	-

* Kaplan Meier estimate of median time

† Unstratified Cox proportional hazard model. HR is Nivolumab over Docetaxel (057)

‡ Unstratified Log-rank Test

‖ Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup

A4. Please provide the p-values for the tests for interaction for the subgroup analyses presented in Figure 16 of the CS (p84).

Please note that Table 2 provides the data presented in the Forest plot but updated for the 18-month data cut. There are some slight differences in subsets, as noted below the table.

Table 2. CheckMate 057: Treatment effect on OS in predefined subsets: 18-month data cut

Subset	N	HR, nivolumab vs docetaxel (95% CI)*†	Test for interaction P-value†
Overall	582	0.74 (0.61, 0.89)	N/A
Prior use of maintenance therapy			0.7577
Yes	233	0.78 (0.58, 1.06)	
No	349	0.71 (0.56, 0.91)	
Line of therapy			0.0431
Second line	514	0.68 (0.56, 0.83)	
Third line/other	68	1.29 (0.74, 2.25)	
Region			0.0006
US/Canada	215	0.54 (0.39, 0.74)	
Europe	269	0.74 (0.57, 0.98)	
Rest of World	98	1.54 (0.96, 2.48)	
Age categorisation (years)			0.9960
< 65	339	0.77 (0.60, 0.99)	
≥ 65 and < 75	200	0.68 (0.49, 0.93)	
≥ 75	43	0.76 (0.37, 1.56)	
Sex			0.3484
Male	319	0.69 (0.53, 0.89)	
Female	263	0.82 (0.62, 1.08)	
Race			
White	533	0.72 (0.59, 0.88)	
Baseline ECOG PS			0.5236
0	179	0.63 (0.44, 0.90)	
≥1	402	0.78 (0.62, 0.97)	
Smoking status			0.0446
Yes	458	0.66 (0.54, 0.82)	
Other	124	1.08 (0.70, 1.65)	

EGFR mutation status			0.4689
Positive	82	1.12 (0.67, 1.86)	
Not detected	342	0.64 (0.50, 0.82)	
Not reported	158	0.76 (0.53, 1.09)	
ALK translocation status			0.2970
Positive	13	0.50 (0.12, 2.04)	
Not detected	254	0.71 (0.53, 0.94)	
Not reported	315	0.79 (0.61, 1.02)	
KRAS mutation status			0.9695
Positive	28	0.57 (0.32, 1.02)	
Not detected	60	0.96 (0.65, 1.43)	
Not reported	204	0.71 (0.56, 0.89)	
MET receptor status			
Not reported	566	0.72 (0.59, 0.87)	
Cell type			0.2536
Adenocarcinoma	541	0.76 (0.63, 0.93)	
Other	41	0.51 (0.25, 1.02)	
Time from diagnosis to randomisation			0.6366
< 1 year	350	0.78 (0.62, 0.99)	
Other	232	0.68 (0.50, 0.92)	
Time from completion of most recent regimen to randomisation			0.2018
< 3 months	364	0.82 (0.65, 1.04)	
3-6 months	114	0.76 (0.49, 1.16)	
> 6 months	103	0.46 (0.28, 0.76)	
Prior neo-adjuvant			0.8844
Yes	19	0.76 (0.26, 2.21)	
No	563	0.74 (0.61, 0.89)	
Prior adjuvant			0.5121
Yes	42	0.92 (0.45, 1.87)	
No	540	0.73 (0.60, 0.89)	
CNS metastases			0.3246
Yes	69	0.98 (0.59, 1.65)	
No	513	0.71 (0.58, 0.87)	

* Unstratified Cox proportional hazard model. HR is Nivolumab over Docetaxel (057)

† Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup

Note: the populations for ALK-mutation status and smoking history and the analysis of prior neo-adjuvant or adjuvant therapy vary slightly in this analysis to those presented in Borghai 2015.

A5. In Table 27 of the CS, the HRs and corresponding 95% CIs for OS and PFS for Checkmate 057 EGFR mutation-negative/unknown patients differ to the HRs and 95% CIs presented on pages 85 and 87 of the CS:

OS

Page 85: "At the 12-month interim analysis, the HR for OS with nivolumab versus docetaxel was 0.69 (95% CI: 0.56 to 0.85) in patients with EGFR mutation-negative/unknown (combined)."

Table 27 (OS HR and 95% CI reported for CheckMate 057): Pooled EGFR mutation-negative/unknown NSCLC: 0.68 (0.54, 0.83)

PFS

Page 87: “At the interim analysis, the HR for PFS with nivolumab versus docetaxel was 0.83 (95% CI 0.68 to 1.02) in patients with EGFR mutation-negative/unknown (combined).”

Table 27 (PFS HR and 95% CI reported for CheckMate 057): Pooled EGFR mutation-negative/unknown NSCLC: 0.83 (0.59 to 0.997)

Please clarify the reasons for these discrepancies.

The data reported on page 85 of the CS was taken from additional analysis conducted by BMS, while Table 27 uses data from an analysis of published HRs and CIs for the EGFR wild-type and EGFR unknown populations using the metan function in Stata. This resulted in a slight variation in HRs obtained from the meta-analysis to those reported on page 85.

A comparison of results of ITC obtained by using data from either of the sources is presented in Table 3. Only minor variations were observed between the two analyses. However, the revised results below are based on the observed data and therefore more appropriate for use.

Table 3. Results of the indirect treatment comparison Patient population: EGFR mutation-negative/unknown NSQ NSCLC

Outcome	Nivolumab vs. nintedanib plus docetaxel	Nivolumab vs. BSC
Data in current dossier (EGFR –ve and unknown pooled)		
OS (HR [95% CI]; p value)	[redacted]	
PFS (HR [95% CI]; p value)		NA
Data using revised HR and CI from BMS analysis		
OS (HR [95% CI]; p value)	[redacted]	
PFS (HR [95% CI]; p value)		NA

Indirect treatment comparisons:

A6. **Priority question.** When conducting the indirect treatment comparisons (ITCs) for the EGFR mutation-negative patient population, were results for this subpopulation used from the four studies included in this network? Only results for the overall patient population are provided in Table 27. Please provide the data inputs for the EGFR mutation-negative patient population ITC (and for the additional analysis requested in question A9 below).

In all the trials included in the analysis (except CheckMate 057), either the whole population was EGFR negative or the proportion of EGFR negative patients was ≥80% of the whole population. Therefore only the data for nivolumab differed between the all-comer and EGFR mutation negative/unknown analyses.

A7. **Priority question;** In Appendix 7.4 it is stated that the proportional hazards assumption was tested by generating plots and performing statistical tests.

a. Was this testing carried out for all studies included in the ITC?
b. Please provide the graphs generated to investigate the proportional hazards assumption and the results of any statistical tests performed for all studies where proportional hazards were tested.

Yes, the proportional hazards assumption was tested for all the trials included in the analysis. The plots generated while testing the PH assumption for trials included in the analysis have been attached in a separate word file 'ERG Question A7 SR Test of PH assumptions'.

A8. **Priority question.** For the Restricted Mean Survival Time (RMST) analysis, in Appendix 7.4 it is stated that t* was chosen to be the longest minimum follow-up time for the two treatment arms.

a. Please confirm how t* was determined for both the all-comers and EGFR mutation-negative/unknown population networks, given that 4/5 studies were included in these networks, respectively, with each study having two treatment arms.

The KM curves for all the trials included in the networks (respectively for all comers and wild-type NSQ NSCLC) were digitized and later analysed using the RMST technique at the minimum follow-up time of all the trials included in the analysis. Restricting the survival to minimum follow up time avoid overestimation of the survival from trials with longer follow up time.

b. Please confirm how this method accounts for the fact that some studies have shorter follow-up times. Could the area under the curve (AUC) be overestimated for these studies, as survival probability remains constant after the last observed event for the study with the shortest follow-up time?

For the comparison with BSC, the minimum duration of follow-up for both OS and PFS was reported in the ISEL trial, and hence the analyses were restricted to 13 months. While, for the comparison nivolumab versus. nintedanib+docetaxel, the minimum follow-up was observed in the nivolumab arm of CheckMate 057. A table for duration of follow up for each outcome is reported in the attached file, "ERG Question A8 RMST estimates", worksheet "Truncation time determination".

c. Please provide figures similar to Figure 2 in Appendix 7.4 showing the calculation of RMST for each treatment arm for each study.

These figures are provided were reported in the attached file, "ERG Question A8 RMST estimates", worksheet "RMST plots and results", which is redacted as Commercial in Confidence.

A9. The indirect comparison used data from the LUME-Lung 1 second-line patient population, and the CheckMate 057 second and third-line patient population. Please perform an indirect comparison of nivolumab versus nintedanib+docetaxel using data

only for the second-line population from CheckMate 057, completing the following table:

Conducting these analyses has required both the 2nd line analysis of the study data and incorporation of the results into the NMA. This analysis request is currently ongoing 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 February 19 2015).

Outcome	Nivolumab vs nintedanib+docetaxel
Patient population: 'All-comers' NSQ NSCLC	
OS (HR [95% CI]; p value)	
OS (RMST difference (95% CI]; p value)	
PFS (HR ([95% CI]; p value)	
PFS (RMST difference [95% CI]; p value)	
ORR (RR [95% CI]; p value)	
Any adverse event (RR [95% CI]; p value)	
Any grade 3/4 adverse event (RR [95% CI]; p value)	
Patient population: EGFR mutation-negative/unknown NSQ NSCLC	
OS (HR [95% CI]; p value)	
OS (RMST difference [95% CI]; p value)	
PFS (HR [95% CI]; p value)	
PFS (RMST difference [95% CI]; p value)	
ORR (RR [95% CI]; p value)	

A10. Concerning the search for studies to be included in the ITC:

a. Were studies excluded if they compared an included intervention/comparator to a non-included comparator?

Yes. Studies assessing non-included comparators, either alone or in combination with included interventions were excluded from the SLR

b. If this is the case, please justify this approach. Non-included comparators may be common comparators between included relevant treatments, therefore providing additional indirect evidence to the network.

An assessment of studies with docetaxel or nintedanib+docetaxel in one arm revealed that no trials that could possibly link into the networks for the NMA had been excluded from the SLR.

A11. In Appendix 7.17, some of the ITC results presented differ to those provided in Table 28 of the CS. Please clarify the reasons for these differences:

a. EGFR mutation-negative/unknown patient population, OS HR for nivolumab versus BSC: Table 16 in Appendix 7.17, HR=[redacted] (95% CI: [redacted]), p=[redacted]; Table 28, HR=[redacted] (95% CI: [redacted]), p=[redacted]

This was a transcription error, and the correct result is that shown in Table 28: HR=[redacted] (95% CI[redacted]), p=[redacted].

b. EGFR mutation-negative/unknown patient population, OS using RMST for nivolumab versus BSC: Table 18 in Appendix 7.17, RMST difference=[redacted] months (95% CI: [redacted]), p=[redacted]; In Table 28 in the CS, RMST difference is not reported. Please provide this data.

Table 28 in the CS and Table 10 should include the data for the EGFR negative/unknown subgroup - RMST difference in OS for nivolumab vs BSC: [redacted]

c. EGFR mutation-negative/unknown patient population, any adverse event RR for nivolumab versus nintedanib+docetaxel: Table 27 in Appendix 7.17, RR = [redacted] (95% CI [redacted]), [redacted]; In Table 28 in the CS, any adverse event RR not reported. Please provide this data. For this analysis, please also provide the data inputs from CheckMate 057, the number of EGFR mutation negative/unknown patients experiencing any adverse event are not provided in Table 27 in the CS.

The RR for adverse events was included in the appendix in error as data were not available for this subgroup. Therefore Tables 27 and 28 of the CS are correct.

A12. How was a result for the outcome of any grade 3 or 4 adverse event data for the comparison of nivolumab versus nintedanib+docetaxel generated by the ITC for the entire population of the CheckMate 057 study (all-comers population)? Data for this outcome were not reported for the CheckMate 057 study, which links these two treatments.

In table 27 of the CS, and in the appendices, data on the % of patients in CheckMate 057 experiencing any grade 3 or 4 adverse event should be included as follows: 132 (46%) in the nivolumab arm, 180 (67%) in the docetaxel arm, as reported in the supplementary appendix of Borghaei et al. (2015).

A13. There is a result from the ITC for any grade 3 or 4 adverse event for nivolumab versus nintedanib+docetaxel for the EGFR mutation-negative/unknown population, this is provided in Table 10 in the Appendix 7.11. This result is not found anywhere else in the CS it is not in the results tables in Appendix 7.17 or in the results section of the CS. Please clarify how this result was calculated, given that data for this outcome were not reported for the CheckMate 057 study.

The RR for adverse events was included in the appendix in error as data were not available for this subgroup. Therefore Tables 27 and 28 of the CS are correct.

Section B: Clarification on cost-effectiveness data

B1. **Priority request: Kaplan-Meier data.** Please provide the following Kaplan-Meier analyses (listed in a to g below) to the following specification:

Population: Use the 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/PPS), and not at the date of last tumour assessment (PFS). Please use the format of the table provided below.
Format: Please present analysis outputs using the format of the sample table shown below.
Trial data set: CheckMate 057, latest data cut (02 July 2015 or later, if available). N.B if any patients crossed over or moved to an extension trial in the latest data cut, please censor them at the time they moved from the original trial or their randomised trial arm

Analyses have been repeated for the population specified. However, please note as discussed in email correspondence, only 2 patients had crossed over at the time of the data cut, one only days prior, and one within a month. These patients have not been censored and no follow-up was available for them after the switch.

All information presented in these figures and the associated data file is considered commercial in confidence

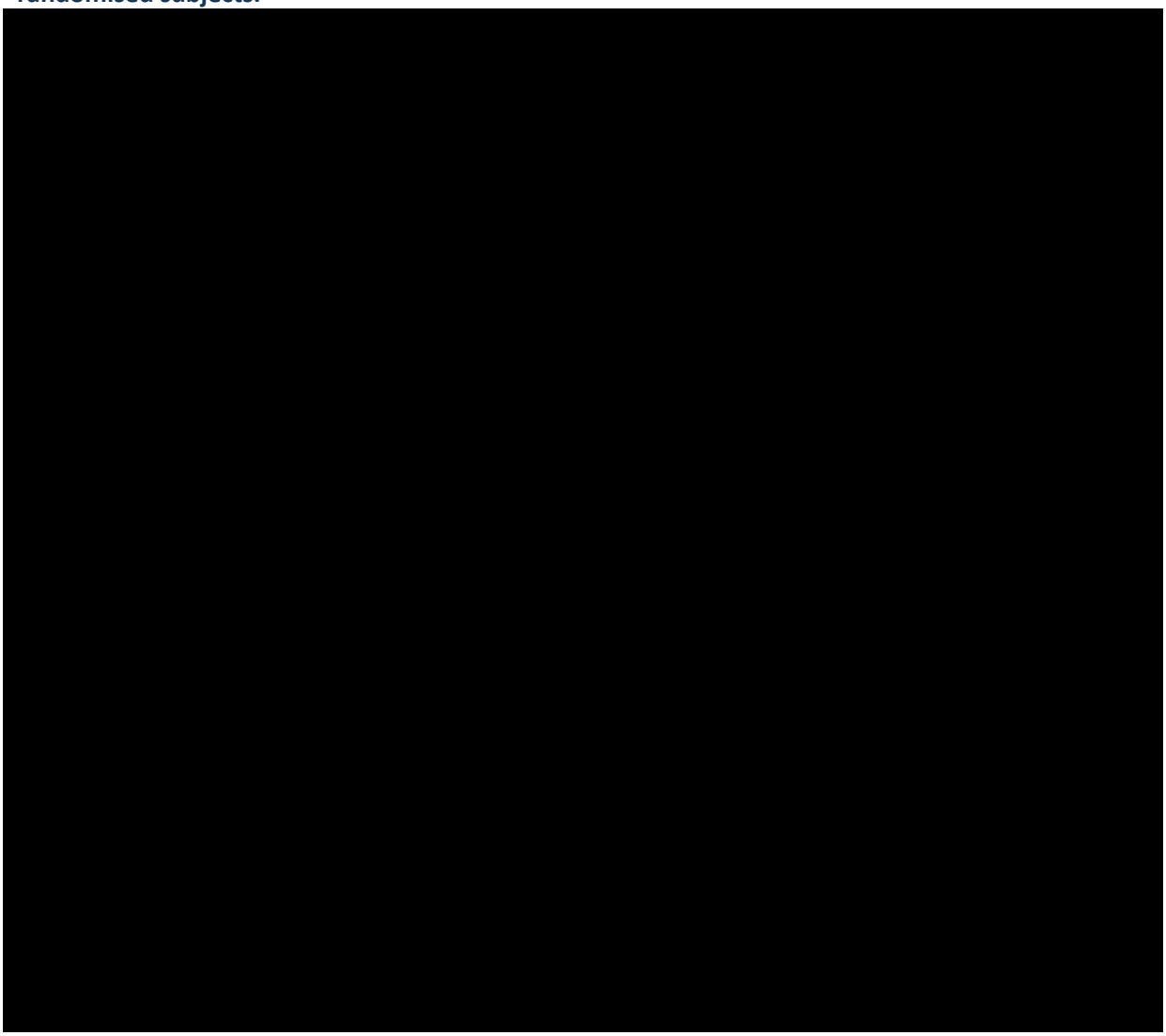
a. Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (nivolumab vs docetaxel).

Figure 1. Kaplan-Meier plot of OS with censoring at database lock date for 18-month data lock. All randomised subjects.

Please see separate redacted Excel file “ERG Question B1_ BMS response data tables” for all Kaplan-Meier data in the specified format (one worksheet for each part of question B1).

b. Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (nivolumab vs docetaxel).

Figure 2. Kaplan-Meier plot of PFS with censoring at database lock date for 18-month data lock. All randomised subjects.



Please see separate redacted Excel file “ERG Question B1_ BMS response data tables” for all Kaplan-Meier data in the specified format (one worksheet for each part of question B1).

c. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis stratified by treatment arm (nivolumab vs docetaxel).

Figure 3. Kaplan-Meier plot of PPS with censoring at database lock date for 18-month data lock. All randomised subjects who progressed.

Please see separate redacted Excel file “ERG Question B1_ BMS response data tables” for all Kaplan-Meier data in the specified format (one worksheet for each part of question B1).

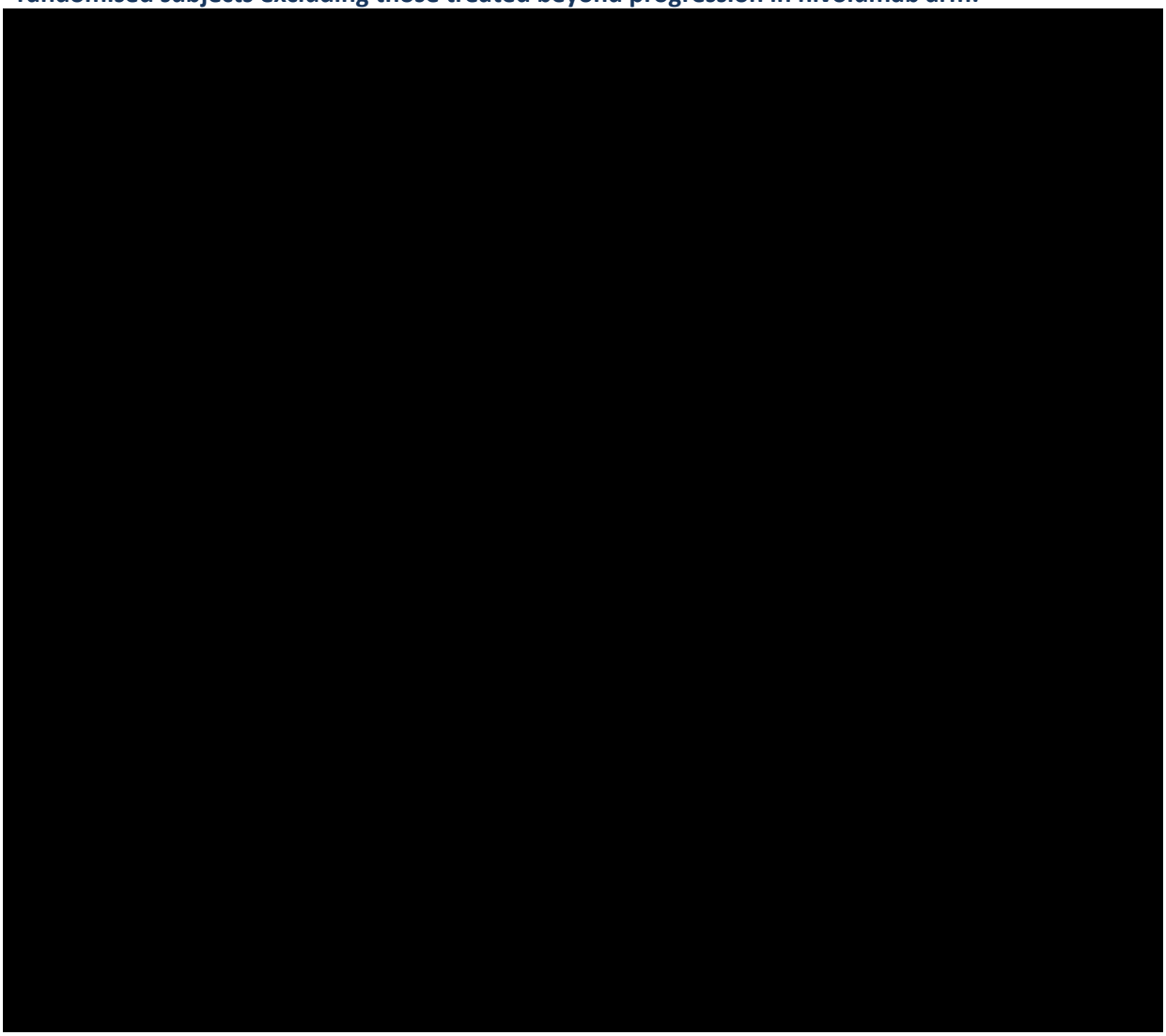
d. Time to treatment discontinuation Kaplan-Meier analysis stratified by treatment arm (nivolumab vs docetaxel).

Figure 4. Kaplan-Meier plot of time to treatment discontinuation with censoring at database lock date for 18-month data lock. All treated subjects.

Please see separate redacted Excel file “ERG Question B1_ BMS response data tables” for all Kaplan-Meier data in the specified format (one worksheet for each part of question B1).

e. Time to death from any cause (OS) Kaplan-Meier analysis for patients randomised to the nivolumab treatment arm, excluding all patients who continued to receive nivolumab beyond investigator assessed disease progression.

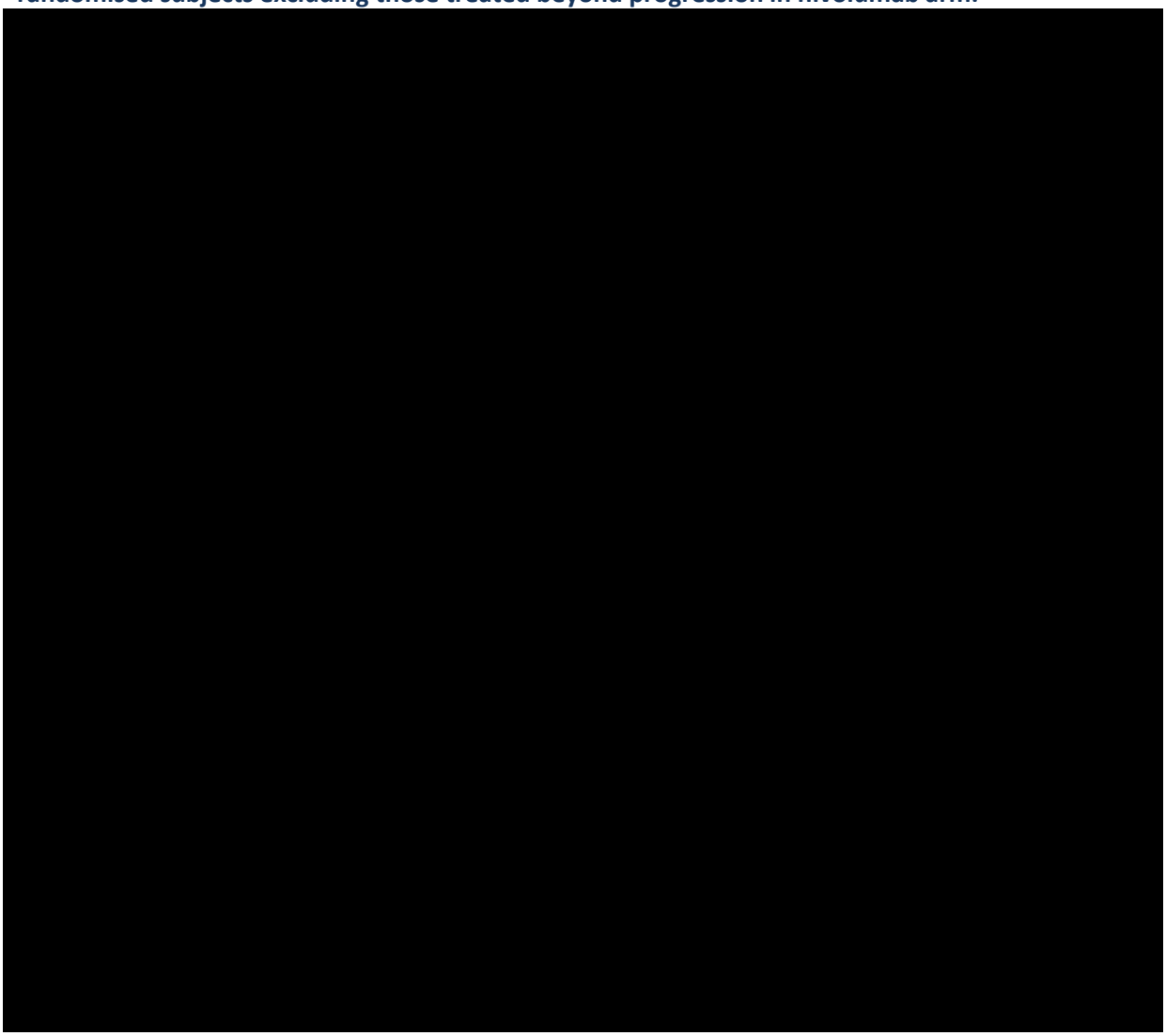
Figure 5. Kaplan-Meier plot of OS with censoring at database lock date for 18-month data lock. All randomised subjects excluding those treated beyond progression in nivolumab arm.



Please see separate redacted Excel file “ERG Question B1_ BMS response data tables” for all Kaplan-Meier data in the specified format (one worksheet for each part of question B1).

f. Time to disease progression or death (PFS) based on investigator assessment Kaplan-Meier analysis, for patients randomised to the nivolumab treatment arm, excluding all patients who continued to receive nivolumab beyond investigator assessed disease progression.

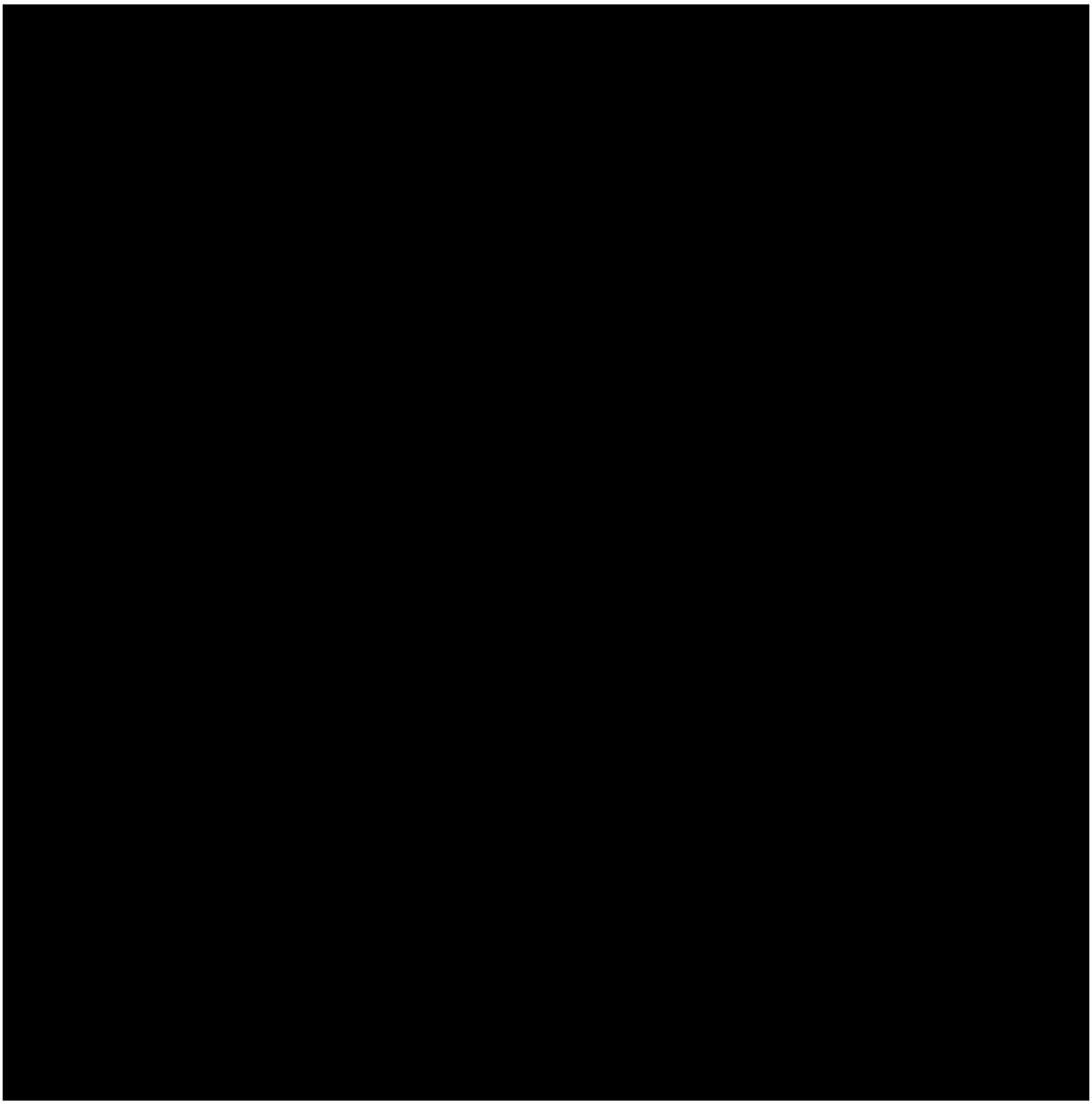
Figure 6. Kaplan-Meier plot of PFS with censoring at database lock date for 18-month data lock. All randomised subjects excluding those treated beyond progression in nivolumab arm.



Please see separate redacted Excel file “ERG Question B1_ BMS response data tables” for all Kaplan-Meier data in the specified format (one worksheet for each part of question B1).

g. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis, for patients randomised to the nivolumab treatment arm, excluding all patients who continued to receive nivolumab beyond investigator assessed disease progression.

Figure 7. Kaplan-Meier plot of PPS with censoring at database lock date for 18-month data lock. All randomised subjects who progressed, excluding those treated beyond progression in nivolumab arm.



Please see separate redacted Excel file “ERG Question B1_ BMS response data tables” for all Kaplan-Meier data in the specified format (one worksheet for each part of question B1).

B2. **Priority request: EQ-5D.** Please provide results for EQ-5D utility scores (using the UK value set) in the CheckMate 057 trial (02 July 2015 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:

a. treatment (nivolumab vs docetaxel)
b. disease response (stable disease, responding disease (CR & PR) and progressive disease).

These results are presented below in Table 4. Please note that EQ-5D data are not currently available for the 18-month data cut, and therefore these are for the 12 month cut.

Table 4: Descriptives for EQ-5D scores by tumor response by visit using UK weights for the all randomized population, 12 month data cut.

Week	[redacted]
Baseline	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 3	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
Week 4	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 6	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 8	
Overall	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 9	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 12	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 15	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 16	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	

Week	[redacted]
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 18	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 20	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

Week	[redacted]
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 21	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 24	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
Week 30	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 36	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 42	
Overall	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 48	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 54	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 60	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 66	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	

Week	[redacted]
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 72	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 78	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

Week	[redacted]
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 84	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 90	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
Week 96	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 102	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 108	
Overall	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Follow-up 1	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Follow-up 2	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 1	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 2	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	

Week	[redacted]
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 3	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 4	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

Week	[redacted]
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

The Header N refers to the number of subjects with any non-missing EQ-5D data and tumor response data. Sample consists of the number of subjects with any non-missing EQ-5D data and tumor response data at each visit.
SD: Stable Diease, PR: Partial Response, CR: Complete Response; PD: Progressive Disease.

B3. **Priority request: EQ-5D.** Please repeat the B2 analyses (02 July 2015 data cut if available, otherwise the most recent data) for each of three subgroups defined by country of origin:

a. USA and Canada (32 sites with 215 patients)

These results are presented below in Table 5. Please note that EQ-5D data are not currently available for the 18-month data cut, and therefore these are for the 12 month cut.

Table 5: Descriptives for EQ-5D scores by tumor response by visit using UK weights for the USA and Canada population, 12 month data cut.

Week	[redacted]
Baseline	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 3	
Overall	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 4	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 6	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 8	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 9	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	

Week	[redacted]
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 12	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 15	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

Week	[redacted]
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 16	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 18	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
Week 20	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 21	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 24	
Overall	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 30	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 36	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 42	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 48	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	

Week	[redacted]
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 54	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 60	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

Week	[redacted]
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 66	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 72	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
Week 78	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 84	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 90	
Overall	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 96	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 102	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 108	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Follow-up 1	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	

Week	[redacted]
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Follow-up 2	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 1	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

Week	[redacted]
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 2	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 3	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
Survival Follow-up 4	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

The Header N refers to the number of subjects with any non-missing EQ-5D data and tumor response data.
Sample consists of the number of subjects with any non-missing EQ-5D data and tumor response data at each visit.
SD: Stable Diease, PR: Partial Response, CR: Complete Response; PD: Progressive Disease.

b. Europe (44 sites with 268 patients, including Russia)

These results are presented below in Table 6. Please note that EQ-5D data are not currently available for the 18-month data cut, and therefore these are for the 12 month cut.

Table 6: Descriptives for EQ-5D scores by tumor response by visit using UK weights for the Europe population, 12 month data cut.

Week	[redacted]
Baseline	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 3	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 4	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	

Week	[redacted]
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 6	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 8	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

Week	[redacted]
Week 9	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 12	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 15	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	

Week	[redacted]
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 16	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 18	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 20	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 21	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 24	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 30	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	

Week	[redacted]
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 36	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 42	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

Week	[redacted]
Week 48	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 54	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 60	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	

Week	[redacted]
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 66	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 72	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 78	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 90	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 96	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 102	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 108	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Follow-up 1	

Week	[redacted]
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Follow-up 2	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 1	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 2	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 3	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	

Week	[redacted]
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 4	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

The Header N refers to the number of subjects with any non-missing EQ-5D data and tumor response data. Sample consists of the number of subjects with any non-missing EQ-5D data and tumor response data at each visit.
SD: Stable Diease, PR: Partial Response, CR: Complete Response; PD: Progressive Disease.

c. Other (30 sites with 99 patients from Asia, Central & South America and Australia)

These results are presented below in Table 7. Please note that EQ-5D data are not currently available for the 18-month data cut, and therefore these are for the 12 month cut.

Table 7: Descriptives for EQ-5D scores by tumor response by visit using UK weights for the rest of the world sample, 12 month data cut.

Week	[redacted]
Baseline	

Week	[redacted]
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 3	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 4	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 6	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 8	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	

Week	[redacted]
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 9	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 12	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 15	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 16	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 18	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 20	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 21	

Week	[redacted]
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 24	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 30	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 36	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 42	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	

Week	[redacted]
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 48	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 54	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 60	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 66	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 72	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 78	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 84	

Week	[redacted]
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 90	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 96	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	

Week	[redacted]
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 102	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Week 108	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	

Week	[redacted]
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Follow-up 1	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Follow-up 2	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	

Week	[redacted]
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 1	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 2	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	

Week	[redacted]
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 3	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
Survival Follow-up 4	
Overall	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
SD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PR/CR	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	
PD	
N	
Mean (SD)	
Median (Q1, Q3)	
Min - Max	
95% CI	

The Header N refers to the number of subjects with any non-missing EQ-5D data and tumor response data.

Sample consists of the number of subjects with any non-missing EQ-5D data and tumor response data at each visit.
SD: Stable Disease, PR: Partial Response, CR: Complete Response; PD: Progressive Disease.

The rationale for these requests is as follows:
The summary of EQ-5D results in the CS is very limited, and it is not clear how conclusions have been drawn which underlie the model assumptions (e.g. that utility in PFS and PD state do not vary by treatment arm, and that EQ-5D responses do not vary systematically by region of origin). The requested analyses should resolve these uncertainties.

B4. **Priority request: time from diagnosis to randomisation.** Please provide time from diagnosis to randomisation as a frequency table with bins of 6 months and include mean OS, mean PFS, mean age (each with standard deviation), and proportion male for each bin, stratified by treatment arm.

Table 8. Time from diagnosis to randomisation, all randomised patients, 18-month data lock

	Time from diagnosis to randomisation (months)				
	<6	6-12	12-18	18-24	>24
Nivolumab arm (n = 292)					
N	[redacted]				
Age, mean (SD)					
Male, n (%)					
OS mean (SE)					
PFS mean (SE)					
Docetaxel arm (n = 290)					
N	[redacted]				
Age, mean (SD)					
Male, n (%)					
OS mean (SE)					
PFS mean (SE)					

B5. **Priority request: Adverse events.** Please provide the number of grade ≥ 3 adverse events per quarter (3 months) in the CheckMate 057 trial as per table 53 of the CS. These should be split by whether the AEs are initial or repeat events and should aggregate figures for AEs occurring in quarter 5 or later (see example format below). Please provide separate tables for nivolumab and for docetaxel.

Table 9. Nivolumab Adverse events grade ≥3 included in the economic model, per quarter in CheckMate 057

	Patients (N=287)	Events									
		Time= Q1		Time= Q2		Time= Q3		Time= Q4		Time = Q5+	
AE type	No. affected	Initial events	Repeat events	Initial events	Repeat events	Initial events	Repeat events	Initial events	Repeat events	Initial events	Repeat events
Fatigue	[redacted]										
Asthenia											
Pain											
Dyspnoea											
Pleural effusion											
Hyperglycemia											
Pneumonia											
Neutrophil count decreased											
White blood cell count decreased											
Anaemia											
Neutropenia											
Febrile neutropenia											
Leukopenia											
Diarrhoea											
Increased ALT											
Increased AST											
Hyponatraemia											

Each quarter is 3 months, starting from the first dose of study therapy.
Repeated events are differentiated by onset date.
Includes events reported between first dose and 30 days after last dose of study therapy.
Based on 18 months data cut.

Table 10. Docetaxel Adverse events grade ≥3 included in the economic model, per quarter in CheckMate 057

	Patients (N = 268)	Events									
		Time= Q1		Time= Q2		Time= Q3		Time= Q4		Time = Q5+	
AE type	No. affected	Initial events	Repeat events	Initial events	Repeat events	Initial events	Repeat events	Initial events	Repeat events	Initial events	Repeat events
Fatigue	[redacted]										
Asthenia											
Pain											
Dyspnoea											
Pleural effusion											
Hyperglycemia											
Pneumonia											
Neutrophil count decreased											
White blood cell count decreased											
Anaemia											
Neutropenia											
Febrile neutropenia											
Leukopenia											
Diarrhoea											
Increased ALT											
Increased AST											
Hyponatraemia											

Each quarter is 3 months, starting from the first dose of study therapy.
Repeated events are differentiated by onset date.
Includes events reported between first dose and 30 days after last dose of study therapy.
Based on 18 months data cut.

B6. **Priority request: Subsequent therapies.** Please clarify how the proportion of patients receiving various subsequent therapies given in table 54 of the CS (and the Excel model) corresponds with table S.5.9 in the CSR. Table 54 of the CS appears to underestimate the proportion of patients receiving subsequent therapies in comparison with those listed on page 3 in table S.5.9 of the CSR, particularly for nivolumab.

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.

B7. **Priority question: Treatment with docetaxel.** Please provide details by cycle of the number of patients separately receiving full or reduced doses of docetaxel, or for whom treatment was missed/suspended for any reason, tabulated as follows:
N.B Number of patients still 'on treatment' should equal the sum of the other 4 columns, as well as corresponding to the number of patients 'at risk' per cycle in the time to treatment discontinuation data.

Table 11. Treatment with docetaxel, all randomised patients, 18-month data lock.

Cycle	No. of patients still 'on treatment'	No. on full dose (75mg/m^2)	No. on reduced dose 1 (55mg/m^2)	No. on reduced dose 2 (37.5mg/m^2)	No. with treatment suspended
[redacted]					

Subjects only appear in one category per cycle.
A subject will fall into the treatment suspension category if dose was either interrupted or delayed.
If a subject experiences treatment suspension and dose reduction, they will be placed in corresponding dose reduction category.

B8. Please confirm whether figure 32 is correct. One of the curves for the nivolumab OS extrapolation is labelled as 1-knot spline, when table 47 (and elsewhere in the CS), a 2-knot spline is referred to for nivolumab OS projection.

The figure is labelled wrongly – the blue line represents a 2-knot spline model.

B9. Please provide a breakdown, using the latest database lock, of the treatment duration and survival of patients in the nivolumab arm of the CheckMate 057 trial who received treatment after progression. Please use the following table format:

Table 12 presents the data for the 12 month data cut. The analysis request for the 18-month data is currently ongoing 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 February 19, 2015).

Table 12. Treatment duration and survival of patients who received nivolumab treatment after progression

Patient	Total duration of treatment (months)	Duration of treatment before progression (months)	# doses after initial progressive disease	Duration of treatment after initial progressive disease (months)	Overall survival (months)	Post treatment survival (months)	Meets non-conventional benefit criteria (Y/N)	Censored (Y/N)
1	6.1	4.9	3	1.2	12.9	6.8	N	N
2	1.9	1.7	1	0.2	19.4	17.5	N	N
3	20.3	15.9	9	4.4	24.4	4.1	N	DOT N; OS Y
4	23.3	22.5	1	0.8	23.4	0.1	N	DOT Y; OS Y
5	5.6	3.5	5	2.1	11.1	5.5	N	N
6	18.0	10.4	16	7.6	18.5	0.5	N	DOT Y; OS Y
7	19.9	1.7	36	18.2	20.0	0.1	Y	DOT Y; OS Y
8	1.9	0.4	1	1.5	2.8	0.9	N	N
9	4.2	1.9	5	2.3	22.2	18	Y	N
10	6.0	4.7	3	1.3	19.4	13.4	Y	N
11	3.3	2.1	3	1.2	5.0	1.7	N	N
12	2.3	2.1	1	0.2	21.9	19.6	N	N
13	5.6	2.1	8	3.5	12.1	6.5	Y	N
14	22.7	2.2	32	20.5	16.9	-5.8	Y	DOT Y; OS Y
15	2.8	1.7	3	1.1	23.1	20.3	N	N
16	19.1	15.9	7	3.2	20.3	1.2	Y	DOT N; OS Y
17	7.5	6.3	3	1.2	8.7	1.2	N	N
18	3.0	1.8	1	1.2	7.6	4.6	N	N
19	8.4	6.3	5	2.1	16.8	8.4	N	N
20	10.6	5.9	9	4.7	24.4	13.8	N	N
21	9.7	7.6	3	2.1	13.0	3.3	N	N
22	8.0	7.5	1	0.5	21.0	13	N	DOT N; OS Y
23	5.8	4.8	3	1.0	20.6	14.8	N	N
24	8.8	7.7	3	1.1	15.7	6.9	Y	DOT N; OS Y

25	3.3	2.1	3	1.2	8.8	5.5	N	N
26	1.3	0.7	2	0.6	2.1	0.8	N	N
27	5.2	4.7	1	0.5	18.4	13.2	N	DOT N; OS Y
28	14.5	6.1	18	8.4	15.0	0.5	N	DOT Y; OS Y
29	12.5	4.9	15	7.6	12.6	0.1	N	DOT N; OS Y
30	2.6	2.1	1	0.5	9.1	6.5	N	N
31	5.6	4.4	3	1.2	15.0	9.4	N	N
32	15.7	11.8	9	3.9	20.0	4.3	N	DOT N; OS Y
33	8.5	3	10	5.5	9.0	0.5	Y	DOT N; OS Y
34	1.4	0.2	1	1.2	21.1	19.7	N	N
35	4.6	2.8	4	1.8	6.3	1.7	N	N
36	4.4	2.2	4	2.2	15.9	11.5	Y	DOT N; OS Y
37	4.4	2.1	6	2.3	5.9	1.5	N	N
38	2.6	2	2	0.6	11.7	9.1	N	N
39	3.4	1.9	4	1.5	12.3	8.9	N	N
40	5.2	5	1	0.2	21.3	16.1	N	DOT N; OS Y
41	15.6	11.7	9	3.9	15.7	0.1	N	DOT Y; OS Y
42	8.8	7.7	3	1.1	17.6	8.8	N	DOT N; OS Y
43	4.4	2.1	4	2.3	15.5	11.1	N	N
44	2.8	1.7	3	1.1	13.0	10.2	N	N
45	8.7	6	6	2.7	15.7	7	N	N
46	1.9	1.8	1	0.1	9.3	7.4	Y	N
47	2.7	1.6	2	1.1	3.6	0.9	N	N
48	16.7	1	19	15.7	17.1	0.4	N	DOT Y; OS Y
49	22.7	19.7	7	3.0	24.2	1.5	N	DOT Y; OS Y
50	3.4	2.2	3	1.2	20.3	16.9	N	DOT N; OS Y
51	14.3	14.2	1	0.1	19.6	5.3	N	DOT N; OS Y
52	3.3	2.1	3	1.2	6.5	3.2	Y	N
53	20.7	20	2	0.7	21.6	0.9	N	DOT Y; OS Y
54	9.0	2.2	14	6.8	17.9	8.9	Y	N
55	15.4	11.5	9	3.9	17.5	2.1	Y	DOT N; OS Y
56	2.8	1.6	3	1.2	17.7	14.9	N	DOT N; OS Y
57	2.6	1.6	2	1.0	4.1	1.5	N	N
58	3.4	3.3	1	0.1	3.4	0	N	N
59	2.3	2.2	1	0.1	10.0	7.7	N	N
60	8.4	2.2	13	6.2	20.3	11.9	Y	N
61	12.7	3.3	19	9.4	16.9	4.2	Y	DOT N; OS Y
62	9.3	7.8	3	1.5	13.4	4.1	N	N
63	20.7	14.7	13	6.0	20.7	0	N	DOT Y; OS Y
64	3.0	2	3	1.0	4.6	1.6	N	N
65	2.3	2	1	0.3	5.6	3.3	N	N
66	2.8	1.8	3	1.0	18.2	15.4	N	N
67	6.9	5.8	3	1.1	17.3	10.4	N	DOT N; OS Y

68	2.8	2.1	2	0.7	8.2	5.4	N	N
69	6.0	4.8	3	1.2	18.5	12.5	N	DOT N; OS Y
70	7.4	3.5	8	3.9	13.1	5.7	Y	N
71	4.8	4.8	1	0.0	20.1	15.3	N	DOT N; OS Y

B10. Please provide details of the NHS Reference Cost code(s) and/or other values used to calculate the cost of fatigue in table 71 of the CS.

The cost of fatigue was based on the HTA by Brown et al (2013) publication[1]. In this publication the cost of fatigue is quoted as follows: *"It is assumed that a typical patient will have one hospital admission during chemotherapy, corresponding to HRG code WA17X (other admissions related to neoplasms with intermediate complicating conditions) as a non-elective long-stay episode of 8–9 days costing £2,536.95."* (pg 115). Based on this description the 2013-14 NHS reference cost schedule was used and the weighted average of "neoplasm related admission with CC score 2" (Non-elective inpatients - long stay; Currency code: WA17B) and "neoplasm related admission with CC score 1" (Non-elective inpatients - long stay; Currency code: WA17C) was used which resulted in a cost of £3,015.

Section C: Textual clarifications and additional points

C1. The CSR for CheckMate 057 that we received was not complete. Please provide the following two items from the appendix of the report;

a. The statistical analysis plan (SP)

Please see separate attachment "ERG Question C1_ ca209057-csr-app-16-1-9-statplan-v3".

b. Appendix 2.3: End of Treatment Period Subject Status Listing All Treated Subjects pg 29606

Please see separate attachment " "ERG Question C1_Appendix 2.3_CA209057".

[1] Brown T, Pilkington G, Bagust A, Boland A, Oyee J, Tudur-Smith C, et al. Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. Health Technol Assess. 2013 Jul;17(31):1-278.

RE: BMS response to NICE/ERG questions for Single Technology Appraisal: Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900]

Section A: Clarification on effectiveness data

A9. The indirect comparison used data from the LUME-Lung 1 second-line patient population, and the CheckMate 057 second and third-line patient population. Please perform an indirect comparison of nivolumab versus nintedanib+docetaxel using data only for the second-line population from CheckMate 057, completing the following table:

Outcome	Nivolumab vs nintedanib+docetaxel
Patient population: 'All-comers' NSQ NSCLC	
OS (HR [95% CI]; p value)	[redacted]
OS (RMST difference (95% CI]; p value)	[redacted]
PFS (HR ([95% CI]; p value)	[redacted]
PFS (RMST difference [95% CI]; p value)	[redacted]
ORR (RR [95% CI]; p value)	[redacted]
Any adverse event (RR [95% CI]; p value)	[redacted]
Any grade 3/4 adverse event (RR [95% CI]; p value)	[redacted]
Patient population: EGFR mutation-negative/unknown NSQ NSCLC	
OS (HR [95% CI]; p value)	[redacted]
OS (RMST difference [95% CI]; p value)	[redacted]
PFS (HR [95% CI]; p value)	[redacted]
PFS (RMST difference [95% CI]; p value)	[redacted]
ORR (RR [95% CI]; p value)	[redacted]

Section B: Clarification on cost-effectiveness data

B9. Please provide a breakdown, using the latest database lock, of the treatment duration and survival of patients in the nivolumab arm of the CheckMate 057 trial who received treatment after progression. Please use the following table format:

Table 1 presents the data for the 18 month data cut.

Table 1. Treatment duration and survival of patients who received nivolumab treatment after progression

Patient	Total duration of treatment (months)	Duration of treatment before progression (months)	# doses after initial progressive disease	Duration of treatment after initial progressive disease (months)	Overall survival (months)	Post treatment survival (months)	Meets non-conventional benefit criteria (Y/N)	Censored (Y/N)
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Symbol + indicates a censored value (subject still on treatment). Sum of the intervals may not add up due to rounding.

Post-treatment survival does not account for censored patients (i.e. those marked as 'still on treatment').

Subjects treated beyond progression are defined as subjects with last available dose after RECIST 1.1 progression date.

Non conventional benefiters are subjects without PR/CR as BOR who met at least one of the following:

1. Appearance of a new lesion followed by decrease from baseline of at least 10% in sum of target lesions.
2. Initial increase from nadir >=20% in sum of target lesions followed by reduction from baseline of at least 30%.
3. Initial increase from nadir >=20% in sum of target lesions or appearance of new lesion followed by at least 2 tumour assessments showing no further progression defined as 10% additional increase in sum of target lesions and new lesions.

DOT: duration of treatment; OS: overall survival

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 non-squamous cell Non Small Cell Lung Cancer [900].

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 around 10%, 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 non-squamous cell Non Small Cell Lung Cancer (NSCLC).

General Points

1. The current outlook for patients with relapsed non-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 non-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 the Phase III Study, published in the New England Journal of Medicine, comparing Nivolumab with Docetaxel, in previously treated advanced non-squamous cell NSCLC patients. The median overall survival was 12.2months among 292 patients in the Nivolumab group and 9.4 months among 290 patients in the Docetaxel group. At 1 year, the overall survival rate was 51% with Nivolumab, compared with 39% with Docetaxel.
   Patients with relapsed advanced/metastatic non-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.

J Fox, Medical Director, RCLCF.

December 2015.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

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.

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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] submitting on behalf of:

Name of your organisation: BTOG-NCRI-RCP-ACP-RCR

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No

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What is the expected place of the technology in current practice?

Metastatic non-squamous NSCLC has a number of NICE approved systemic treatment options for patients requiring second line treatment having progressed after primary chemotherapy. In general 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.

Treatment is delivered by Oncologists in Teaching and District General Hospitals is increasing based on the molecular genotype using drugs that target specific mutational abnormalities (EGFR, ALK). When these mutations are present 'targeted' systemic drugs form the backbone of treatment strategies, however, most patients are "negative" for these mutations and are considered for docetaxel mono-chemotherapy, erlotinib or best supportive care. The choice of treatment will primarily be dictated by patient fitness (performance status PS).

Recent NICE assessment of docetaxel-nintedanib (TA347) has concluded the combination is superior to single agent docetaxel and is cost effective. Therefore, this combination is likely to establish itself as standard of care in the UK for patients fit enough to receive docetaxel.

Docetaxel has modest activity and significant toxicity limiting it is use to a minority of patients who are PS 0/1. Nintedanib is added as oral therapy that is usually prescribed in clinic and taken at home daily by the patient. The combination of docetaxel-nintedanib does not appear to have worse toxicities over docetaxel alone. EGFR mutation positive patients (5 – 10% of the Non squam NSCLC population) usually have an EGFR kinase inhibitor as initial treatment with platinum based chemotherapy on relapse. This group has a better prognosis and are often considered for second line chemotherapy with docetaxel and potentially suitable for this technology. ALK positive (2- 4% of the non-squam NSCLC population) patients in England would be treated with cisplatin-pemetrexed in the first line setting and assessed for crizotinib (via the CDF) on relapse. When further relapse occurs these patients would also be consider for docetaxel base treatment or clinical trials, or potentially would be suitable for this technology.

Clinical trial data indicates that Nivolumab is an innovative and effective systemic treatment option for patients with non-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.

Nivolumab is administered every two weeks intravenously and could be delivered though the specialist lung cancer oncology clinics / chemotherapy units that are operating across the UK. It is likely that nivolumab would be used in place of docetaxel monotherapy, or erlotinib in relapsed non-squamous NSCLC and offered as an alternative to docetaxel-nintedanib in eligible patients.

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Nivolumab has very recently received an EMA license which means there no current guidelines in place within the EU recommending the place of nivolumab used within those licensed indication. However, in the US, where nivolumab received its licence earlier, the NCCN has produced guidelines which recommend nivolumab use within licensed indication

The advantages and disadvantages of the technology

The clinical trials of nivolumab in the non-squam NSCLC population are consistent with our current standard NHS practice and the complexity of treatment delivery will be similar to the current standard chemotherapy treatments.

Those trail report improvements in response and survival for nivolumab when compared to standard docetaxel treatment with associated improvements in quality of life.

The side effect profile is different to standard chemotherapy treatment and generally better. However, some (relatively minor) modifications will be required 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.

Nivolumab is likely to place some further pressure on the chemotherapy units that would be delivering treatment. Nivolumab is administered i.v. every 2 weeks c.f. every 3 weeks for docetaxel and oral home administration of nintedanib or erlotinib. Nivolumab will therefore require additional capacity in oncology day-units. In addition Nivolumab (and nintedanib) is given until time of progression, significant toxicity, or clinician/patient decision (cf docetaxel median of 3 – 4 treatment given 3 weekly).

There is no current data on the activity of nivolumab in routine clinical practice compared to that reported in the trials.

Any additional sources of evidence

None at present though we would expect new data to be presented at the major oncology scientific meetings in 2016

Implementation issues

As above

Equality

We are not aware of any equality-related issues

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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]

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)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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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 British Thoracic Society strongly supports the appraisal of Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer

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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.

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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)?

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.

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Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: ROYAL COLLEGE OF PATHOLOGISTS
Are you (tick all that apply):

- 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)?

- **SPECIALIST ADVISOR TO RCPATH FOR LUNG PATHOLOGY, I REPRESENT PATHOLOGISTS WHO WOULD DEAL WITH THE BIOPSIES FOR DIAGNOSING LUNG CANCER AND HELP WRITE NATIONAL GUIDELINES FOR DATASETS AND HANDLING OF TISSUE**

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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.

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The main issue for pathologists in relation to treatment with this kind of drug is the possible/probable need for an associated diagnostic test that may decide whether the patient is eligible for treatment.

From what I understand of reported evidence to date, data suggest that those with greater immunostaining of the tumour for PD-L1 have a better response to this type of drug, though it is currently being called a complementary diagnostic (28-8pharmX) and not a companion diagnostic, as it is not deemed essential in terms of eligibility.

If it is not deemed a requirement, then there is little issue for pathologists. If it is deemed a requirement, then pathologists will have to be trained in interpretation and systems for validaton will need to be put in place, as well as the cost of the test (and possible rebiopsy) taken into account

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;
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Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small cell lung cancer [ID900]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/12

07 March 2016

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 non-squamous non-small cell lung cancer [ID900]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

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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:

Dickson R	Project lead, drafted clinical results section and supervised the final report
Hounsome J	Critical appraisal of the clinical evidence, production of initial report and incorporation of peer reviewer comments
Stainthorpe A	Critique of the company economic model and proposal of alternative interpretations of the economic evidence
Abdulla A	Summary and critical appraisal of economic evidence
Bagust A	Checking and validation of the economic model and critique
Richardson M	Critical appraisal of the statistical evidence
Boland A	Critical appraisal of the clinical and economic evidence
Kotas E	Critical appraisal of the database searching
Greystoke A	Clinical advice and critical appraisal of the clinical sections of the company submission

All authors read and commented on draft versions of the ERG report.

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LIST OF ABBREVIATIONS

AE	adverse event
ALK	anaplastic lymphoma kinase
ASBI	Average Symptom Burden Index
BMS	Bristol-Myers Squibb
BSC	best supportive care
CI	confidence interval
CR	Complete response
CS	company's submission
CSR	clinical study report
DMC	Data Monitoring Committee
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
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
NLCA	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
PFS	progression-free survival
PPS	post-progression survival
PR	partial response
PS	performance status
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
Q2W	every 2 weeks
Q3W	every 3 weeks
RCT	randomised controlled trial
RECIST	Response Evaluation in Solid Tumours
RMST	restricted mean survival time
STA	single technology appraisal
RWD	real world data
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 Bristol-Myers Squibb Pharmaceuticals Ltd in support of the use of nivolumab (Opdivo®) for patients who have received prior chemotherapy for locally advanced or metastatic non-squamous, non-small cell lung cancer (NSCLC). A European licence for nivolumab in this specific patient population has not been received but the company expects a decision to be made in the first quarter of 2016.

1.1 Critique of the decision problem in the company's submission

The company submission (CS) indicates a slight change in wording in the included population – changed from people with previously treated disease to those who have received prior chemotherapy (thus excluding epidermal growth factor receptor (EGFR) positive patients who have previously had a TKI). Although the company submission (CS) acknowledges the validity of all of the comparators in the scope they limit their analysis to available data which therefore provides comparison of nivolumab with docetaxel, nintedanib+docetaxel and best supportive care (BSC).

1.2 Summary of submitted clinical effectiveness evidence

Clinical evidence includes direct evidence of nivolumab compared with docetaxel from CheckMate 057. The trial was stopped early due to the pre-specified stopping rules related the superiority of nivolumab in relation to overall survival (OS). An indirect treatment comparison (ITC) comparing nivolumab with nintedanib+docetaxel as well as best supportive care (BSC) is provided. The company admits that the analysis of the original trial data and the ITC are limited by the fact that the proportional hazards assumption has been violated and therefore **none** of the hazard ratios (HRs) can be considered a reliable estimate of treatment effect.

CheckMate 057 provides evidence of median overall survival (OS) benefit of nivolumab over docetaxel at both 12 and 18 months (12.2 versus 9.4 and 39 versus 23 months respectively). Due to issues of pseudo progression (tumours that initially increase as a result of the treatment action before shrinking/stabilising) with nivolumab, the results for progression free survival (PFS) are less clear. Patients receiving nivolumab show less benefit at 12 month (4.2 versus 2.3 months). However, 12 month data show a reversal with PFS rates for

nivolumab versus docetaxel at 18.5 versus 8.1%. Subgroup analysis by EGFR status ('all comer'[1] population versus EGFR mutation-negative/unknown) show similar results.

The adverse event (AE) data presented indicate that nivolumab, although having a slightly different AE profile to standard cytotoxic chemotherapy, has fewer Grade 3-4 AEs than docetaxel. Data from additional non-randomised studies and studies of the use of nivolumab in patients with a variety of other cancers are provided to support this assertion. The CS makes the case that the uniqueness of the AE profile can be managed by established guidelines and that overall treatment with nivolumab is better tolerated than treatment with docetaxel alone and by association is also superior to nintedanib+docetaxel.

The ITC provides evidence using restricted mean survival time (RMST) analysis demonstrating no benefit of nivolumab versus nintedanib+docetaxel in relation to OS, PFS, overall response rate (ORR) or AEs in either the 'all comer' or EGFR mutation negative/unknown population. The comparison with BSC provides somewhat mixed results demonstrating the possible lack of homogeneity of the studies used in the comparison. No data are available for the EGFR positive population of patients.

1.3 Summary of the ERG's critique of clinical effectiveness evidence

The primary data provided in the CS comes from CheckMate 057 and an ITC that is limited by a lack of data to allow for comparison with all of relative comparators listed in the scope. The comparison of nivolumab is therefore limited to data related to docetaxel, nintedanib+docetaxel and BSC.

CheckMate 057 is a well conducted trial however the use of HRs in the analysis of the data cannot be considered a reliable estimate of treatment effectiveness as the CS points out that the proportional hazards assumption is violated for both OS and PFS. This limitation is also true of the ITC where only RMST analysis should be considered. The ITC is also limited by the fact differences in the patient populations included in the analysis (e.g. inclusion of patients with squamous disease, Asian population, length of follow-up etc.) The comparison with BSC provides mixed results demonstrating the effectiveness of nivolumab versus BSC in the all-comers group but not the EGFR mutation-negative/unknown patients supporting concerns that there were differences in the patient populations in the trials used in the ITC.

The CS infers that the AE experienced by patients receiving nivolumab will be fewer than those experienced by patients receiving nintedanib+docetaxel. The ERG is of the opinion that although the comparative data are limited that patients receiving docetaxel do have

[1] all comers- the term used in the CS to denote the entire population of CheckMate 057

higher rates of Grade3-4 AEs and it would be expected this would be at least the same when docetaxel was given in combination with nintedanib.

The CS makes a claim that OS in the patients receiving docetaxel in CheckMate 057 is longer then would be expected. Examination of data from other similar trials does not substantiate this claim. The CS also makes a claim that the pseudo progression seen in patients receiving nivolumab would have an effect on OS. The ERG is not convinced that the data presented support this claim.

Subgroup analyses suggest that nivolumab is statistically significantly more effective in patients with higher PD-L1 expression levels than those with lower PD-L1 expression levels. The report is however somewhat inconsistent with regards to whether all patients should therefore be tested for PD-L1.

1.4 Summary of submitted cost effectiveness evidence

The company developed a de novo cohort-based partitioned survival model in Microsoft Excel to compare the cost effectiveness of nivolumab 3mg/kg given every 2 weeks with docetaxel 75mg/m^2 given every 3 weeks as the base case comparator. 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 treatment for patients with cancer in a number of previous NICE STAs. The model time horizon was set to 20 years with a 1-week cycle length. As recommended by NICE, a discount rate of 3.5% has been used for both costs and outcomes; outcomes are measured in quality adjusted life years (QALYs). The model perspective was that of the UK NHS. Survival estimates were based on data collected from CheckMate 057 and published sources. Utility values were calculated from data collected during CheckMate 057. Resource use and costs were estimated based on information from CheckMate 057, published sources and advice from clinical and economic experts. The company also compared nivolumab versus nintedanib+docetaxel via an ITC. The company did not estimate the cost effectiveness of nivolumab versus BSC.

In the CS, the base case comparison describing nivolumab vs. docetaxel resulted in an incremental cost effectiveness ratio (ICER) per QALY gained of £103,589, with nivolumab being more expensive (+£75,452) and more effective (+1.15 life years and +0.73 QALYs) than docetaxel. The company carried out a range of deterministic sensitivity analyses. The most influential parameters were discount rate and average body weight. Other influential parameters include body surface area, utility weights, administration cost of nivolumab and progression-free state costs. The probabilistic sensitivity analysis (PSA) results show that

the probabilistic ICER of £99,291 per QALY gained has a 0% chance of being cost effective at a threshold of £30,000 per QALY gained and a 0.1% probability of being cost effective at a threshold of £50,000 per QALY gained.

The ICER per QALY gained for nivolumab versus nintedanib+docetaxel was £126,861; nivolumab had higher lifetime costs (+£62,598) and was more effective (+0.80 life years and +0.49 QALYs) than the combination therapy. The probabilistic ICER per QALY gained for nivolumab versus nintedanib+docetaxel was £111,934. Scenario analyses were undertaken by the company using different survival modelling approaches for OS and time to treatment discontinuation (TTD) and alternative treatment durations.

1.5 Summary of the ERG's critique of cost effectiveness evidence

The company's decision model is structured conventionally. The economic model relies on patient level data from CheckMate 057. Projection of survival data was required to enable a lifetime equivalent evaluation. Limited data from CheckMate 057 and published sources were used to identify suitable parametric models for survival extrapolation. The ERG has identified the following main areas of concern: (i) manner in which OS, PFS and post-progression survival (PPS) have been projected, (ii) use of time to treatment discontinuation (TTD) data instead of PFS in all parts of the company model, (iii) indirect treatment comparison of nivolumab with nintedanib+docetaxel, (iv) choice of utility values used in the model, (v) nivolumab dosing calculations and (vi) treatment administration costs.

The ERG considers the company's methods to project OS and PFS to be flawed for both the intervention and the comparators. Concerns relating to the modelling of each health state are compounded by the ERG's identification of subgroups of patients within the patients treated with nivolumab. The interdependence of OS, PFS and all cause population mortality in the model also results in questionable projections for nivolumab OS and PFS. The ERG also identified problems with the company's use of TTD data as a proxy for PFS. The projection of PFS/TTD is implausibly long with an unlikely proportion of patients remaining alive at 20 years, progression-free and continuing to receive treatment. Additionally, the ERG considers the use of TTD instead of PFS data to estimate QALYs to be inappropriate. In relation to the ITC of nivolumab versus nintedanib+docetaxel, the ERG considers that piecewise PH assumptions do not hold for OS and PFS in the LUME-Lung 1 trial, thus invalidating any potential inferences made by the company. The ERG is concerned with the possible over-estimation of utility values collected as part of CheckMate 057. Throughout the duration of the trial, the number of respondents steadily declined and it is likely that participants that continued to respond to the EQ-5D questionnaires were exhibiting self-selecting behaviour and are unlikely to match the characteristics of the initial trial population.

In addition, the ERG has identified two key issues with the company model related to costs. In the model there is an over-estimation of the average cost per dose of nivolumab due to a body weight calculation error and treatment administration costs are calculated according to the number of patients in treatment mid-cycle rather than at the start of the cycle.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG implemented various modifications to the company's model which yielded a mixture of effects. The individual execution of model amendments resulted in both increases and decreases in the size of the estimated ICER per QALY gained for nivolumab versus the comparator treatments. The combined impact of ERG recommended model revisions resulted in an estimated ICER per QALY gained of £165,234 for nivolumab versus docetaxel and £293,232 per QALY gained for nivolumab versus nintedanib+docetaxel.

The ERG considers that the company base case results substantially underestimate the size of the ICER per QALY gained for nivolumab versus docetaxel and nivolumab versus nintedanib+docetaxel for a previously treated non-squamous NSCLC patient population.

1.7 Summary of company's case for end of life criteria being met

The company makes the following case for nivolumab versus docetaxel 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 057 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=3570).

The company does not make the case for nivolumab versus nintedanib+docetaxel to be considered under NICE's end of life criteria.

1.8 ERG commentary on end of life criteria

The ERG agrees that patients with advanced NSCLC have a short life expectancy of less than 24 months and that the total number of patients who would be eligible for the treatment is small. It also considers that nivolumab offers an extension to life of more than 3 months in comparison with docetaxel; the ERG estimates a mean gain of 5.8 months for nivolumab versus docetaxel. The ERG estimates a mean extension to life of 3.1 months in comparison with nintedanib+docetaxel.

1.9 ERG commentary on the robustness of submitted evidence

1.9.1 Strengths

Clinical evidence

- Checkmate 057 is a good quality trial providing direct evidence of effectiveness of nivolumab versus docetaxel in relation to OS and demonstrating an acceptable AE profile.

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 similar treatments in a number of previous NICE STAs
- The decision model submitted by the company is generally implemented to a good standard.

1.9.2 Weaknesses and areas of uncertainty

Clinical evidence

- The validity of all assessed outcomes is limited by the fact that the proportional hazards assumption has been violated
- The comparison with all comparators in the original scope is limited by the available direct and indirect evidence.

Cost effectiveness evidence

Issues common to the modelling of nivolumab, docetaxel and nintedanib+docetaxel

- QALY calculations in the company model are linked to the time patients spend on treatment and not to their health state, which is incorrect
- The utility data used by the company lack credibility
- The model calculates treatment administration costs mid-treatment cycle when they should be applied at the start of the cycle, when treatment is received.

Issues specific to the modelling of nivolumab

- The method employed by the company to project nivolumab OS results in the model does not adequately represent the existing trial evidence from CheckMate 057
- The company's PFS model projects a small minority of patients treated with nivolumab to remain progression free throughout the lifetime of the model and to constitute 85% of those patients still alive after 20 years. It also predicts that any patient treated with nivolumab who is still in PFS by 18.4 years is cured of the disease and will never progress. The ERG considers both these outcomes to be implausible
- The company model creates an interdependence between OS and PFS projections that results in some values from the parametric OS model for nivolumab being replaced by PFS values to ensure that PFS is never greater than OS. This indicates

that at least one of the parametric models (PFS or OS) used for nivolumab is inappropriate

- In the company model, one-third of the survival gain (nivolumab versus docetaxel) occurs post-progression, but this does not take into account the subgroup of nivolumab patients treated beyond progression who continue to accrue extra survival benefit, whether due to extra treatment or other factors. ERG analysis suggests that post-progression survival constitutes 52% of survival gain when 25% of patients are treated beyond progression
- The nivolumab dosing calculations undertaken by the company are inaccurate

Issues specific to the modelling of nintedanib+docetaxel

- The proportional hazards assumptions required to validate the company's indirect method of comparing nivolumab with nintedanib+docetaxel do not hold

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

Key points from the description of the underlying health problem (lung cancer, and in particular non-squamous non-small cell lung cancer [NSCLC]) presented in the company's submission (CS) are summarised 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)
- In 2011, lung cancer was the underlying cause of 30,148 deaths in England and Wales
- The median survival for all lung cancer patients in England and Wales was 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

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 9.6 months
- Median survival for stage IV patients with NSCLC was only 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)

Non-squamous NSCLC

- NSCLC can be further divided into squamous or non-squamous NSCLC, based on the cell type responsible for the tumour
- Approximately 64% of patients within England and Wales had non-squamous NSCLC in 2013
- EGFR or ALK mutations are predominantly present in non-squamous NSCLC and if present lead to the following of a slightly different care pathway.

ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer
Source: CS, Sections 3.1 and 3.3

The Evidence Review Group (ERG) considers that, in general, these key points appropriately summarise the key points related to this health problem. The ERG notes that the prevalence of epidermal growth factor receptor (EGFR) mutation is 15% in patients in Spain,[1] 10% in patients in the USA and up to 35% of patients in Asia,[2] while the prevalence of anaplastic lymphoma kinase (ALK) mutations is 3-7% in patients with NSCLC.[3] Up-to-date data for patients in the UK are currently not available.

2.2 Overview of current service provision

The ERG has summarised (as bulleted items) the key points from the company's description of current treatment options for patients with non-squamous NSCLC in Box 2. The ERG considers that these points provide an accurate overview of current service provision.

Box 2 Current treatment options for patients with stage IIIB and IV non-squamous NSCLC

Current treatment options

- The aims of therapy are to prolong survival and improve HRQoL
- Treatment of patients with non-squamous NSCLC depends on a patient's ECOG PS, comorbidities, histology, presence of mutations and personal choice
- Patients are typically treated with platinum-based doublet chemotherapy at first-line
- At second-line patients can be treated with docetaxel chemotherapy or nintedanib in combination with docetaxel
- Third-line treatment can include erlotinib (if not received previously in patients with EGFR-unknown status) and docetaxel.

EGFR-positive tumours

- At first-line NICE recommends the use of the EGFR inhibitors erlotinib, afatinib and gefitinib
- At second-line patients may receive platinum-based chemotherapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane). If no previous EGFR-TKI therapy has been used afatinib or erlotinib may be given. In patients for whom platinum-based chemotherapy is inappropriate, patients may receive single-agent gemcitabine or vinorelbine
- Third-line treatment can include nintedanib in combination with docetaxel. Following the use of an EGFR-TKI and one other therapy, docetaxel monotherapy and BSC may be used, although these are not recommended by NICE in the third-line setting.

ALK-positive tumours

- As with ALK-negative patients, those with ALK-positive tumours may receive platinum-based chemotherapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane) at first-line
- Crizotinib is currently available as a second-line treatment in ALK-positive patients through the Cancer Drugs Fund
- Ceritinib (current NICE appraisal suspended) received FDA and conditional EMA approval for NSCLC treated with or intolerant to crizotinib.

Issues relating to current clinical practice

- Due to their age and/or co-morbidities, many patients in the UK are unlikely to receive systemic treatment
- 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
- Only 23% of patients with non-squamous NSCLC are treated with first-line therapy
- The mortality rate in these patients is high and the OS rate is low following first-line therapy
- Long-term survival, with a concomitant good HRQoL, is not currently deemed achievable with current treatments in this patient population
- BSC, such as analgesics, antiemetics, and palliative interventions, are a part of the care package offered to all patients with non-squamous NSCLC, regardless of eligibility for systemic anti-cancer therapies and line of treatment
- NICE[4] recommends five different tests for detecting EGFR status in NSCLC, test accuracy is dependent on the quality of the tissue samples available
- Turnaround times for EGFR mutation testing are from 3 to 7 days
- While sequential testing of EFGR and ALK is more cost-effective, parallel testing allows for more rapid turnaround of results

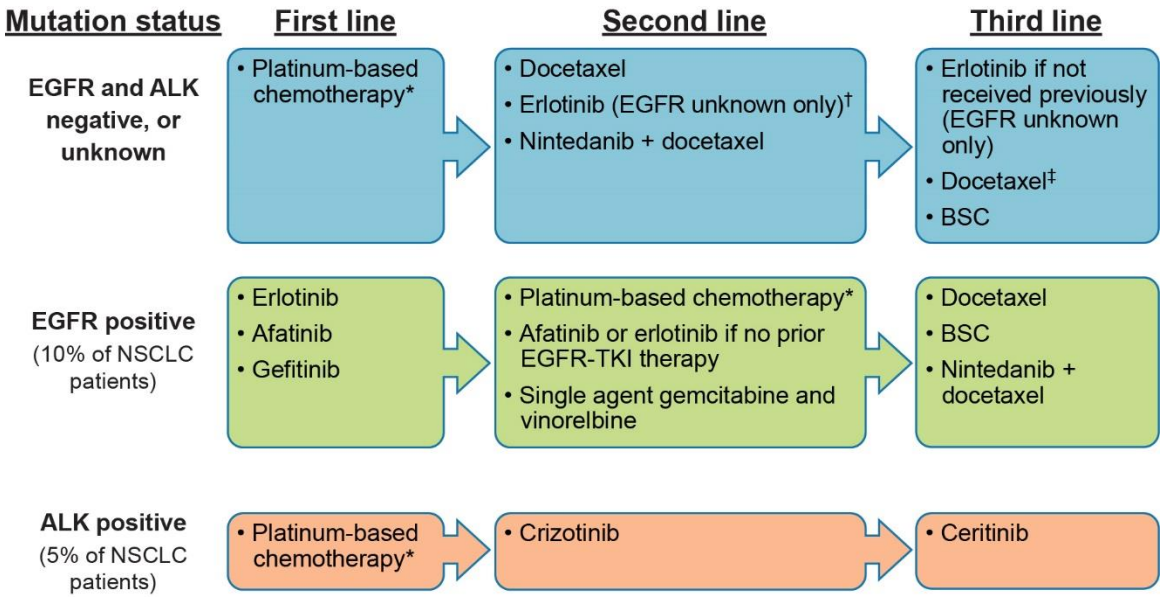
HRQoL=health related quality of life; NSCLC=non-small cell lung cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitors; NICE= National Institute for Health and Care Excellence; ALK=anaplastic lymphoma kinase; BSC=best supportive care; FDA=Food and Drug Administration; EMA=European Medicines Agency; OS=overall survival

Source: CS, Sections 3.2 and 3.5

Nivolumab has received marketing authorisation for use in the NSCLC squamous population but has not received marketing authorisation for use in the non-squamous NSCLC patient population. The company expects a decision to be made in the first quarter of 2016.

Nivolumab is a human, monoclonal immunoglobulin G4 antibody 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).[5,6] A 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.[7-9] 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 cytotoxic anti-cancer therapies which generally destroy all rapidly dividing and fast growing cell types. The cytotoxic 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.

The CS provides an overview of the current treatment pathway for patients with non-squamous NSCLC and is summarised in Figure 1).



Abbreviations: ALK=anaplastic lymphoma kinase; BSC=best supportive care; EGFR=Epidermal Growth Factor Receptor; NSCLC=non-small cell lung cancer; TKI= tyrosine kinase inhibitor; UK=United Kingdom

* Platinum-based chemotherapy + gemcitabine, vinorelbine, pemetrexed or a taxane

† Until recently, erlotinib was recommended second-line in patients with EGFR mutation-negative/unknown status; however, recent NICE guidance recommends erlotinib only in patients with EGFR unknown mutation status, which is a very small subgroup of patients

‡ As erlotinib is no longer recommended in second-line for patients with EGFR mutation-negative status, docetaxel (as monotherapy or in combination with nintedanib) is the only second-line option and, as a result, will no longer be used in third-line

Source: CS, Figure 1

Figure 1 Overview of treatments in the UK for this appraisal

In the CS (Figure 8), the company proposes nivolumab as a second- or even third-line treatment option for patients with non-squamous NSCLC. The CS estimates the potential number of patients eligible for nivolumab as a second-line treatment to be 1413 (Table 1). Clinical advice given to the ERG indicates that this may be an underestimate since clinicians would consider using nivolumab to treat patients whose condition means that they would be unlikely to be able to tolerate the side effects of docetaxel or nintedanib+docetaxel.

Table 1 Estimate of those eligible for nivolumab for non-squamous NSCLC in England

Population	Proportion of patients	Number of patients	Reference
Total NSCLC	N/A	27,300	Health and Social Care Information Centre 2014b[10]
Patients with stage IIIb/IV NSCLC	N/A	19,138	Health and Social Care Information Centre 2014b[10]
Non-squamous NSCLC	64.35%	12,315	Powell 2013[11]
Second-line setting	11.5%	1413	NICE,[12] Sculier and Moro-Sibilot (2009)[13]

NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer
Source: CS, Table 121

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2 summarises the decision problem described by the company in the CS in relation to the final scope issued by NICE with reasons for any differences.

3.1 Population

The CS limits the population to those patients who had previously received chemotherapy rather than those who had received any prior treatment. This therefore excludes those patients with EGFR positive non-squamous NSCLC who have *only* received an EGFR-TKI. However, the ERG concurs that this is a very small group and that the population included is appropriate.

3.2 Intervention

The intervention (nivolumab) described in the CS matches the intervention described in the final scope issued by NICE. Nivolumab (brand name Opdivo®) is administered via intravenous infusion at 3mg/kg over 60 minutes every 2 weeks.

At the time of writing, nivolumab is still awaiting marketing authorisation from the European Medicines Agency (EMA) for use in patients with non-squamous NSCLC.

3.3 Comparators

For the clinical effectiveness systematic review all comparators outlined in the NICE scope are included. However the CS notes that for the non-squamous population "The comparators listed in the final scope are representative of the standard treatments used in the NHS. However, not all are relevant comparators to nivolumab." The CS considers that the relevant comparators are docetaxel, nintedanib+docetaxel and best supportive care (BSC). Their rationale for this decision are outlined in sections 1.4 (Figure 2) and 3.2 of the CS. The basis for this decision is that there are no or limited data available to compare nivolumab to the other current standard treatments.

The ERG agrees that the available data allow only for a comparison of nivolumab with docetaxel, nintedanib+docetaxel and BSC. Currently docetaxel is the standard of care. However, with the recent approval of nintedanib+docetaxel it is expected that this will replace docetaxel monotherapy and become the standard care for patients fit enough to tolerate the treatment.

3.4 Outcomes

The outcomes in the CS match the outcomes described in the final scope. The measurements of outcomes are appropriate.

3.5 Economic analysis

As specified in the final NICE scope, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained through modelling that extended over a 20-year time horizon (equivalent to a lifetime horizon) and costs were 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. The company carried out a range of subgroup analyses (including analyses by PD-L1 status) to assess clinical effectiveness.

Subgroup analyses for EGFR mutation-negative/unknown and PD-L1 to assess cost-effectiveness were also conducted and reported in CS appendices.

3.7 Other considerations

The CS does not identify any equality issues.

Table 2 NICE scope and company's decision problem

	Final scope issued by NICE	Decision problem in the company's submission	Rationale for difference
Population	People with previously treated locally advanced or metastatic non-squamous non-small cell lung cancer	Adults with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	In line with expected marketing authorisation
Intervention	Nivolumab	As per scope	
Comparator(s)	**Non-squamous EGFR-TK mutation negative or unknown tumours:** • After one prior therapy: - Docetaxel monotherapy - Erlotinib (subject to ongoing NICE appraisal) - Nintedanib in combination with docetaxel - Crizotinib (only for patients with ALK positive mutation status) - Ceritinib (only for patients with ALK positive mutation status; subject to ongoing NICE appraisal) - Best supportive care • After two prior therapies: - Docetaxel monotherapy - Erlotinib (if not received previously; subject to ongoing NICE appraisal) - Best supportive care **Non-squamous EGFR-TK mutation positive tumours:** • After one prior therapy: - Platinum therapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane) - Single agent gemcitabine and vinorelbine (for people for whom platinum therapy is not appropriate) - Afatinib, erlotinib or gefitinib (if no previous EGFR-TKI therapy received due to delayed confirmation of mutation status; erlotinib and gefitinib subject to ongoing NICE appraisal) • After two prior therapies (an EGFR-TKI and one other therapy): - Docetaxel monotherapy - Erlotinib - Nintedanib in combination with docetaxel - Best supportive care	Base case economic analysis in a previously treated setting is nivolumab versus: • Docetaxel monotherapy • Nintedanib in combination with docetaxel	**EGFR negative/unknown** *Erlotinib* - no data from trial available *ALK mutation positive* - too few patients in trial to allow for subgroup analysis *Ceritinib* - at the time of CS not recommended by NICE – currently the appraisal has been suspended[14] *BSC* - lack of data available for comparison[15] **EGFR positive** *Platinum based therapy* - patients in trial had already received this therapy so this is not a valid comparator *Gemcitabine or vinorelbine* - no available data *Erlotinib, afatinib* - limited data *Gefitinib* - not recommended for second-line

	Final scope issued by NICE	Decision problem in the company's submission	Rationale for difference
Outcomes	The outcome measures to be considered include: • PFS • OS • ORR • AEs • HRQoL	As per scope	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY 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	
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	As per scope	

ALK=anaplastic lymphoma kinase; BSC=best supportive care; EGFR=epidermal growth factor receptor; OS=overall survival; PFS=progression-free survival; ORR=objective response rate; AE=adverse event; HRQoL=health related quality of life; QALY=quality adjusted life year
Source: CS, adapted from Table 1

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The CS adequately describes the search strategies used to identify relevant studies relating to the use of nivolumab for the treatment of patients with previously treated locally advanced or metastatic non-squamous NSCLC. The search strategies were updated versions of the searches run in a 2013 NICE multiple technology appraisal by the Liverpool Reviews and Implementation Group.[16] The company conducted a systematic search for randomised controlled trial (RCT) evidence, the same search strategy was employed for the indirect treatment comparisons (ITC). Separate searches were conducted for the retrieval of cost effectiveness studies. The date of the searches and the full date span are included in the CS.

Clinical effectiveness

Full details of the strategies used to locate clinical evidence were reported in Section 4.1.1 and Appendix 2 of the CS. The search terms were relevant and included MeSH and free text as well as an RCT filter. No animal or language filters were used. The company searched the following databases: Medline, Medline in Process, Embase and The Cochrane Library (CENTRAL only). The company reported results from hand searches of three conference sites: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and World conference on Lung Cancer. Four clinical trial registries were searched: clinicaltrials.gov, International Clinical Trials Registry Platform (ICTRP) and Australian and New Zealand Clinical Trials Registry. The CS did not include details of the search terms used to search these additional resources; therefore the ERG was unable to comment on the search terms used.

Summary of searching

In summary, the ERG concludes that the company's searches were carried out to an adequate standard and accurately reflected the population and indication described in the final scope issued by NICE. The ERG is confident that no relevant references were missed.

4.1.2 Eligibility criteria

All citations were assessed for potential inclusion through two stages. Detailed eligibility criteria are presented in the CS (Table 7). The ERG considers these criteria to be essentially consistent with the NICE scope in relation to population and outcomes. The ERG notes that the comparators of two single chemotherapy agents (i.e. gemcitabine and vinorelbine) are

not included in the company's eligibility criteria, in line with the company decision problem but differing from the NICE decision problem.

The review included RCTs and studies published as full texts in English. 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 non-squamous NSCLC or if the study included a relevant subgroup analysis describing patients with non-squamous NSCLC. The ERG concurs that these criteria were appropriate.

4.1.3 Risk of bias

A descriptive critical appraisal of all of the trials included in the systematic review was conducted by the company using multiple criteria (e.g. Centre for Reviews and Dissemination's guidance,[17] Jadad score,[18] and the Cochrane Collaboration risk of bias tool[19]). The results of the quality assessment for all of the included studies are presented in Table 10 and Appendix 3 of the CS. The ERG notes that whilst there are some minor errors in referencing, the quality assessment for the five studies used in subsequent analyses is presented and are accurate. The company also assessed the methodological quality of the company sponsored non-randomised studies that were provided as supportive evidence using the Down and Black's checklist for non-randomised studies.[20]

4.2 Critique of trials of the technology of interest

4.2.1 Identified studies in the systematic review

Thirty three RCTs were included in the company's review but only one trial (CheckMate 057)[21] assessed the clinical effectiveness of nivolumab (versus docetaxel). The trial characteristics and findings of CheckMate 057 were appropriately presented narratively in the CS. Characteristics of the other 32 RCTs included in the systematic review were reported in tables in the CS (CS, Appendices 7.14 to 7.16). The supporting evidence from the two non-randomised studies (CheckMate 153[22] and CheckMate 003[23]) were presented narratively in Section 4.11 and in Appendices 17 and 18 of the CS.

To compare nivolumab with the comparators of nintedanib+docetaxel and BSC the company conducted ITCs using evidence derived from CheckMate 057, LUME-Lung 1;[24] ISEL;[25] ISTANA;[26] and V-15-32.[27] trials. The ERG's critique of the company's ITCs is presented in Section 4.3. The ERG is not aware of any additional studies that should have been included.

4.2.2 Methodological approach for the synthesis and analysis of trials included in the systematic review

Since CheckMate 057 was the only study to provide direct evidence for nivolumab the company conducted ITCs to compare nivolumab to the other comparators (nintedanib+docetaxel, BSC). This is described in Section 4.3 of the ERG report.

4.2.3 Characteristics of the studies included in the systematic review

CheckMate 057 is a phase III open-label RCT of nivolumab versus docetaxel in patients with locally advanced or metastatic non-squamous NSCLC after failure of at least one prior platinum doublet-based chemotherapy. The key characteristics of CheckMate 057 are summarised in Table 3.

Table 3 Summary of methodology of CheckMate 057

	CheckMate 057
Location	106 sites in 22 countries worldwide Argentina, Australia, Austria, Brazil, Canada, Chile, Czech Republic, France, Germany, Hong Kong, Hungary, Italy, Mexico, Norway, Peru, Poland, Romania, Russian Federation, Singapore, Spain, Switzerland and the United States
Study design (including method of randomisation)	Global, phase III, randomised, open-label study Patients were randomised via interactive voice response system in a ratio of 1:1 Randomisation was stratified according to prior treatment with maintenance therapy vs. no maintenance and second-line therapy vs. third-line therapy
Study drugs	Nivolumab at 3 mg/kg by intravenous infusion every 2 weeks (n=292) Docetaxel at 75 mg/m^2 by intravenous infusion every 3 weeks (n=290)
Overview of patient population	Adult (≥ 18 years) patients with metastatic or recurrent non-squamous NSCLC after failure of prior platinum doublet-based chemotherapy
Primary outcomes	OS
Secondary outcomes	• Investigator-assessed ORR • Duration of response • Time to response • Investigator-assessed PFS • HRQoL • Safety and tolerability • Immunogenicity of nivolumab (exploratory outcome)
Duration of follow-up	The enrolment period was from November 2012 until December 2013. The last patient was randomised on 31 December 2013, and the last patient last visit occurred on 5 February 2015, providing a minimum follow-up of 13.2 months

HRQoL=health-related quality of life; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival
Source: CS, adapted from Table 10

Due to differences in adverse events (AE), dosing and drug action CheckMate 057 was an open-label study.

Eligibility criteria for entry into CheckMate 057 are provided in the Appendices to the ERG report, Section 10.1. Clinical advice to the ERG is that the eligibility criteria for the trial are reasonable, although the prohibition of oral steroids may become problematic when

implementing the treatment in clinical practice. Patients may be on chronic low dose steroids for cancer related symptoms and/or short courses of steroids for exacerbations of chronic obstructive pulmonary disease (a frequent co-morbidity). Therefore, treatment of these patients may subsequently be delayed. This is the case for all immune-oncology drugs as the use of steroids is directly antagonistic to the mechanism of action. The company provided detailed information on permitted concomitant medications for CheckMate 057 (CS, Table 10).

Baseline characteristics of the CheckMate 057 patient population are provided in Table 4. The median age of patients in CheckMate 057 was 61 years in the nivolumab arm and 64 years in the docetaxel arm. There was a greater percentage of males in the docetaxel arm than in the nivolumab arm (58% versus 52%); this slight imbalance may favour nivolumab as the clinical advice received by the ERG suggests that male patients have poorer outcomes. However, there was also a 4% difference in the proportion of patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) score 0 in the docetaxel arm in comparison to patients in the nivolumab arm (33% versus 29%). As ECOG PS 0 patients would be expected to do better than ECOG PS 1 patients, this slight imbalance may favour docetaxel. Overall, the ERG does not consider that these differences are likely to lead to major bias and/or favour one treatment over another.

Table 4 Baseline characteristics of patients in CheckMate 057

Baseline characteristic		**CheckMate 057**	
		Nivolumab (n=292)	**Docetaxel (n=290)**
Age (years)	Median (range) <65, n (%) 65-74, n (%) ≥75, n (%)	61 (37-84) 184 (63) 88 (30) 20 (7)	64 (21-85) 155 (53) 112 (39) 23 (8)
Sex, n (%)	Male	151 (52)	168 (58)
Race, n (%)	White	267 (91)	266 (92)
Patients with quantifiable PD-L1 status at baseline, n (%)		231 (79.1%)	224 (77.2%)
PD-L1 expression level* n (%)	<1% ≥1% <5% ≥5% <10% ≥10 Not quantifiable at baseline	108 (46.8) 123 (53.2) 136 (58.9) 95 (41.1) 145 (62.8) 86 (37.2) 61 (20.9)	101 (45.1) 123 (54.9) 138 (61.6) 86 (38.4) 145 (64.7) 79 (35.3) 66 (22.8)
Smoking status, n (%)	Current/former Never smoked Unknown	231 (79) 58 (20) 3 (1)	227 (78) 60 (21) 3 (1)

Baseline characteristic		CheckMate 057	
		Nivolumab (n=292)	Docetaxel (n=290)
ECOG PS, n (%)	0	84 (29)	95 (33)
	1	208 (71)	193 (67)
	Not reported	0	1 (<1)
Disease stage, n (%)	IIIb	20 (7)	24 (8)
	IV	272 (93)	266 (92)
CNS metastases, n (%)	Yes	34 (12)	34 (12)
Median time from initial diagnosis,	Years (range)	0.8 (0.2-8.4)	0.8 (0.0-8.5)
No. of prior systemic cancer therapies received, n (%)	1	256 (88)	259 (89)
	2	35 (12)	31 (11)
	Other	1 (<1)	0
Prior radiotherapy, n (%)	Yes	139 (48)	138 (48)
Type of prior systemic cancer therapy n (%)	Prior platinum-based therapy	292 (100)	290 (100)
	Prior ALK inhibitor	1 (0.3)	2 (0.7)
	Prior EGFR-TKI	29 (9.9)	24 (8.3)
	Other – chemotherapy	292 (100)	290 (100)
	Other – experimental drugs	23 (7.9)	18 (6.2)
Time from completion of most recent prior systemic therapy regimen to randomisation, n (%)	<3 months	181 (62)	183 (63.1)
	3-6 months	59 (20.2)	56 (19.3)
	>6 months	52 (17.8)	51 (17.6)
Best response to most recent prior regimen, n (%)	CR or PR	73 (25)	68 (23.4)
	SD	103 (35.3)	96 (33.1)
	PD	111 (38.0)	116 (40.0)
	Unknown/Not reported	5 (1.7)	10 (3.4)

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; TKI=tyrosine kinase inhibitor
*Percent membranous staining in ≥100 tumour cells.
Source: CS, adapted from Table 14

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 characteristics of the patient population in CheckMate 057 are likely to be similar to the characteristics of patients treated in routine clinical practice in England.

4.2.4 Statistical approach adopted for the conduct and analysis of studies included in the systematic review

Information relevant to the statistical approach taken by the company has been taken from the clinical study report (CSR),[28] the trial statistical analysis plan (TSAP),[29] the trial protocol,[30] and from the CS.

Trial population

For the analysis of all efficacy outcomes, the intention-to-treat (ITT) population was used. Safety outcomes were analysed using the safety population, consisting of all patients who received study medication.

Outline of analyses

The company states that an interim OS analysis was scheduled to take place when at least 380 deaths had been reported. As a consequence of this interim review (18 March 2015 data-cut), the independent data monitoring committee (DMC) declared that the trial had reached its primary endpoint, and recommended that the trial be stopped (April 2015). The trial protocol[30] was consequently modified to provide a mechanism for eligible subjects who were originally randomised to the docetaxel treatment group to receive subsequent nivolumab therapy as part of a nivolumab extension phase. However the ERG notes that this affected a very small number of patients. The results from this interim analysis are based on a minimum follow-up of 13.2 months; in the ERG report this analysis is referred to as the "12-month interim analysis" for consistency with how the term is used in the CS.

The company also provides updated results with additional follow-up, on the basis of data from a 2 July 2015 data-cut. The results from this analysis are based on a minimum follow-up of 17.1 months; in the ERG report this analysis is referred to as the "18-month updated analysis" for consistency with how the term is used in the CS. The ERG notes that although the company states that updated results are available for OS only, PFS results at the 18-month updated analysis are presented in the CS.

The ERG was initially concerned that CheckMate 057 had been stopped early for benefit as previous technology appraisals have highlighted that early closure of cancer trials can lead to exaggerated treatment effects that are not borne out in the longer term.[31-34] However, considering the 18-month updated analysis results, the ERG is of the view that stopping the trial early does not appear to have biased the efficacy results in any way since the OS data are now mature and consistent with the findings from the 12-month interim analysis.

Efficacy outcomes

The definitions, and methods of analysis, for the primary and key secondary efficacy outcomes from CheckMate 057 are listed in Table 5. The ERG is satisfied that all of the outcomes were pre-specified in the TSAP[29] and that all outcomes were fully reported in the CSR.[28]

Table 5 Analysis strategy for key efficacy endpoints

Endpoint	Definition	Statistical method
Primary outcome		
OS	Time between the date of randomisation and the date of death	OS was analysed with the use of a two-sided log-rank test stratified according to prior maintenance treatment and line of therapy. HR and CI were estimated with the use of a stratified Cox PH model. Survival curves and rates were estimated with the use of the K-M method
Secondary outcomes		
Investigator-assessed ORR*	The number of patients whose BOR was either a confirmed complete or partial response, as determined by the investigator, divided by the number of randomised patients	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 Cochran-Mantel-Haenszel methodology and adjusted by the same stratification factors as in primary analysis of OS
Investigator-assessed PFS*	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	PFS was analysed with the use of a two-sided log-rank test stratified according to prior maintenance treatment and line of therapy. HR and CI were estimated with the use of a stratified Cox PH model. Survival curves and rates were estimated with the use of the K-M method

BOR=best confirmed objective response; CI=confidence interval; CR=complete response; HR=hazard ratio; KM=Kaplan-Meier; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PR=partial response; RECIST= Response Evaluation Criteria in Solid Tumors; CI=confidence interval
*Non-conventional benefit (i.e. a reduction in the size or number [or both] of target lesions with simultaneous appearance of new lesions or initial progression followed by either tumour reduction or no further progression for at least two tumour assessments) in patients treated beyond initial progression was not included in response-based analyses (ORR or PFS)
Source: CS, adapted from Table 10 and Table 11

Censoring methods

For OS, subjects without documentation of death were censored on the last date that 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 that 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.

Proportional hazard ratios

The analyses carried out by the company to generate PFS and OS hazard ratios (HRs) were conducted using Cox proportional hazards (PH) modelling. The validity of this method relies on the hazards of the two comparative drugs being proportional. To investigate the assumption of PH, the company inspected log-log plots (log cumulative hazard versus log time); if the curves for each treatment arm were approximately parallel, it was assumed that PH was valid. The company also performed statistical tests, namely the Global Test for PH assumption,[35] and a supremum test for PH assumption.

The results of the testing carried out by the company (see Appendix 10.2) indicate that the assumption of PH is violated for both OS and PFS data for CheckMate 057. Consequently, it

is inappropriate to summarise these data by using HRs and 95% confidence intervals (CI) estimated by a Cox PH model. For this reason, the ERG considers that HRs ought to be interpreted with caution. The ERG would have preferred for the company to provide a rationale for using this approach and an explanation as to why alternative approaches were not considered.

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 CheckMate 057 is provided in Table 6.

Table 6 ERG assessment of statistical approach used to analyse CheckMate 057 data

Component	Statistical approach	ERG comments
Sample size calculation	Provided in the CS (pg 65-66)	The ERG considers that the methods used to calculate the sample size are correct
Protocol amendments	Provided in the CSR[28] (Section 4.5)	The ERG notes that all protocol amendments were carried out prior to the interim analysis, with the exception of the modification to the protocol after stopping the trial, when patients in the docetaxel arm were allowed to switch to receive nivolumab. All other amendments were not driven by the results of the trial, and are therefore not of concern
Missing data approach	Provided in the CS (pg 65-66)	The ERG is satisfied that the company took a suitable approach to handling missing data
Pre-specified subgroup analyses	Efficacy (OS, PFS, ORR) based on pre-study PD-L1 expression level Pre-specified expression level cut-off values of 1%, 5% and 10% were used Efficacy (OS, ORR and PFS) based on: • Age • Sex • Race • Region • Baseline ECOG PS • Smoking status • Presence of CNS metastases • Prior neoadjuvant vs. adjuvant treatment • Prior use of maintenance therapy • Line of therapy • EGFR mutation status • ALK translocation status • KRAS mutation status • MET receptor status • Cell type • Time from diagnosis to randomisation • Time from completion of most recent regimen to randomisation	The ERG is satisfied that the results of all subgroup analyses are provided in the CSR[28]
Adverse events	Safety was assessed through summaries of deaths, AEs, serious AEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, Select AEs and specific clinical laboratory assessments	The ERG is satisfied that the results of all the AE data analyses are provided in the CSR[28]
Health related quality of life	Disease-related symptom improvement rate by week 12 as measured by the LCSS Overall health status using the EQ-5D Index and Visual Analogue Scale (exploratory outcome)	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; MET=mesenchymal epithelial transition; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death 1 ligand; PFS=progression-free survival; PS=performance status
Source: CS, CSR[28] and ERG comment

4.2.5 Assessment of risk of bias of included studies

The ERG is generally satisfied with the assessments of risk of bias that are presented in the CS (see Table 7). CheckMate 057 was not a double-blind trial but the ERG concurs that blinding patients and health professionals would have been difficult for a number of reasons i.e. different dosing regimes, different side effect profiles.

Table 7 Quality assessment of CheckMate 057

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 057 are thought to reflect patients seen in UK clinical practice • Comparator in the study is docetaxel, which represents standard of care in previously treated patients in the UK. • First-line treatment in the UK is a platinum-based chemotherapy; patients who had received a platinum-based chemotherapy were included in the study. • Doses for both nivolumab and docetaxel used in the study are reflective of UK clinical practice. • Baseline characteristics are similar to patients seen in UK clinical practice (e.g. ex-smokers).

RCT=randomised controlled trial
Source: CS, adapted from Table 15

4.2.6 Results from the studies included in the systematic review

Overall survival

The results for OS are provided in Table 8. Nivolumab was found to significantly improve survival in comparison to docetaxel (HR=0.73, 95% CI: 0.59 to 0.89; p=0.002) at the 12-month interim analysis. Median OS was 2.8 months longer for patients in the nivolumab arm than for patients in the docetaxel arm. OS rates were also higher for nivolumab patients than docetaxel patients (50.5% versus 30.9%). This treatment benefit with nivolumab was shown

to be consistent over time, as results from the updated analysis suggest that OS rates at 18 months are still higher in the nivolumab arm than in the docetaxel arm (39% versus 23%).

Table 8 CheckMate 057 OS results

	CheckMate 057	
	Nivolumab (n=292)	**Docetaxel (n=290)**
12-month interim analysis		
Events, n (%)	190 (65.1)	223 (76.9)
Stratified log-rank test p value		0.002
HR for death (95% CI) at 12 months		0.73 (0.59 to 0.89)
Median OS, months (95% CI)	12.2 (9.7 to 15.0)	9.4 (8.1 to 10.7)
OS rate at 12 months (95% CI)	50.5 (44.6 to 56.1)	39.0 (33.3 to 44.6)
18-month updated analysis		
OS rate at 18 months (95% CI)	39 (34 to 45)	23 (19 to 28)

CI=confidence interval; HR=hazard ratio; OS=overall survival
Source: CS, Table 16

The company also provides Kaplan-Meier (K-M) curves to demonstrate OS, as shown in Figure 2. For the first 7 months, patients in the docetaxel arm are less likely to have an OS event than patients in the nivolumab arm. At 7 months, the K-M curves begin to separate, and nivolumab appears to improve OS in comparison to docetaxel for the remainder of the follow-up period. The company states that pseudo-progression (tumours that initially increase as a result of the treatment action before shrinking/stabilising) may be responsible for the 7-month delay in OS benefit for patients treated with nivolumab.

As the assumption of PH for the two treatments is violated, HRs should be interpreted with caution.

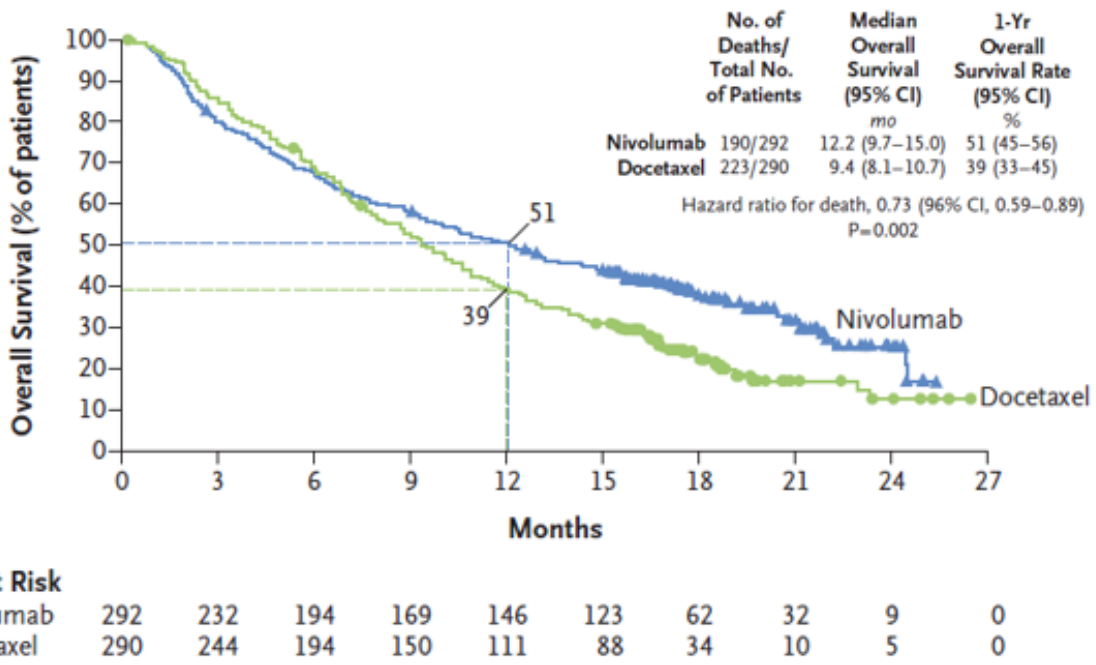


Figure 2 CheckMate 057 K-M overall survival plot – all randomised patients

Abbreviations: CI=confidence interval
Note: The analysis included all the patients who underwent randomisation. Symbols indicate censored observations, and horizontal lines the rates of OS at 1 year.
Source: CS, Figure 11

K-M curves with the additional follow-up from the 18-month updated analysis are also provided in the CS (Figure 12). The HR at the time of the updated analysis was consistent with the HR reported at the time of the interim analysis, suggesting that nivolumab statistically significantly improves OS in comparison to docetaxel (HR=0.72, 95% CI: 0.60 to 0.88; p=0.0009). Once again, the ERG is of the opinion that this HR should be interpreted with caution. 18-month OS rates were also higher for nivolumab patients than for docetaxel patients (39% versus 23%).

Progression-free survival

The results for PFS are provided in Table 9. There was no statistically significant difference between nivolumab and docetaxel in terms of PFS at the time of the 12-month interim analysis (HR=0.92, 95% CI: 0.77 to 1.11; p=0.3932). Median PFS was 1.9 months longer for patients in the docetaxel arm than for patients in the nivolumab arm (4.2 months versus 2.3 months). However, 12-month PFS rates were higher for nivolumab patients than for patients receiving docetaxel (18.5% versus 8.1%).

Table 9 CheckMate 057 PFS results

PFS at 12-month interim analysis	CheckMate 057	
	Nivolumab (n=292)	Docetaxel (n=290)
Events, n (%)	234 (80.1)	245 (84.5)
Stratified log-rank test p value		0.3932
HR for progression or death (95% CI) at 12 months		0.92 (0.77 to 1.11)
Median, months (95% CI)	2.3 (2.2 to 3.3)	4.2 (3.5 to 4.9)
PFS rate at 12 months (95% CI)	18.5 (14.1 to 23.4)	8.1 (5.1 to 12.0)

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival
Source: CS, Table 17

The nivolumab and docetaxel K-M curves provided by the company, as shown in Figure 3, explain why different measures of effect for PFS favour different treatments. It is clear that the K-M curves for the two treatments show markedly different profiles. For the first 7 months, patients in the docetaxel arm are less likely to have a PFS event than those in the nivolumab arm, resulting in median PFS values which favour docetaxel. At 7 months, the K-M curves begin to separate, and nivolumab appears to improve PFS in comparison to docetaxel for the remainder of the follow-up period. Hence, the PFS rate at 12 months favours nivolumab over docetaxel. The company states that pseudo-progression may be responsible for the 7-month delay in PFS benefit for patients treated with nivolumab, although a number of theories exist for this delay, and the exact underlying mechanism is unclear.

As the assumption of PH for the two treatments is violated the HR should be interpreted with caution.

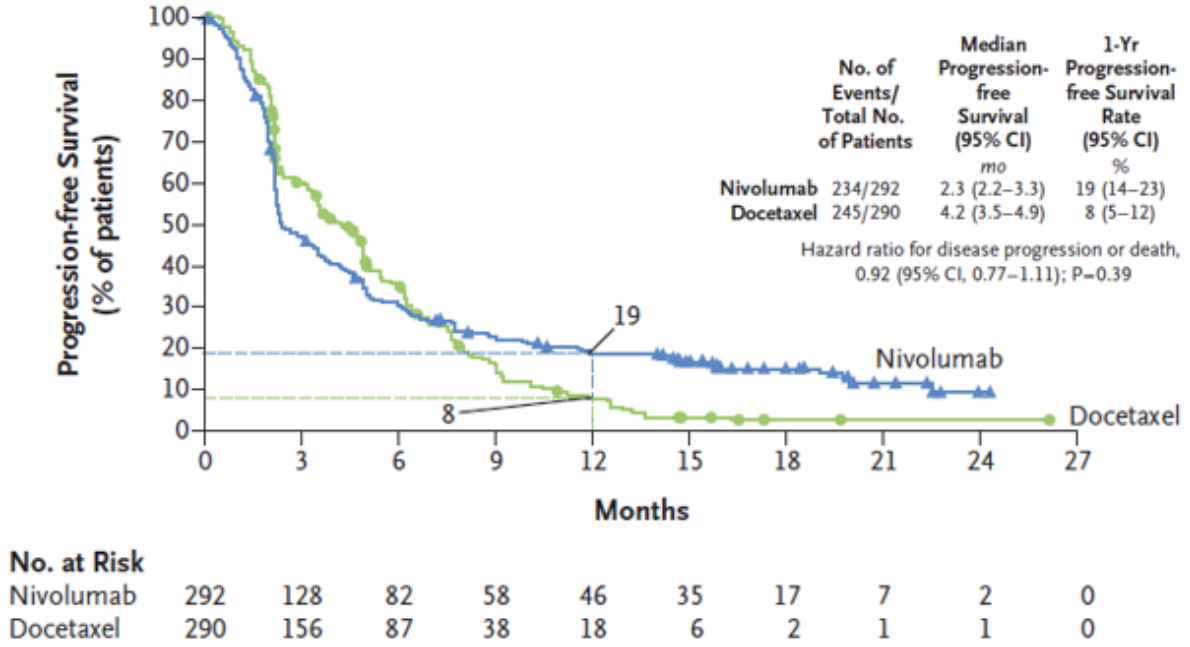


Figure 3 CheckMate 057 K-M PFS plot – all randomised patients in the study

CI=confidence interval
Source: CS, Figure 13

At the 18-month updated analysis, the HR for PFS with nivolumab versus docetaxel was 0.91 (95% CI: 0.76 to 1.09). Once again, the ERG does not believe that the use of HR is an appropriate way to summarise the PFS data. The ERG also notes that the company states that only OS results from the 18-month updated analysis are available, but then proceeds to present PFS results from this same time point.

Response

The ORR results are provided in Table 10. Nivolumab was found to statistically significantly improve ORR in comparison to docetaxel (OR 1.7, 95% CI: 1.1 to 1.6; p=0.02). Four patients in the nivolumab group (1.4%) achieved a complete response (CR) compared with one patient (0.3%) in the docetaxel group. Median time to treatment response (TTR) was slightly shorter in the nivolumab arm than in the docetaxel arm (2.1 versus 2.6 months), and median duration of response (DoR) was found to be much longer in the nivolumab arm than in the docetaxel arm (17.2 versus 5.6 months). These findings are also demonstrated by the characteristics of responses provided by the company in Figure 14 of the CS. Patients achieving a response in either arm usually responded early on in the follow-up period, and often by the time of the first scan.

Table 10 CheckMate 057 summary of response analyses

	CheckMate 057	
	Nivolumab (n=292)	**Docetaxel (n=290)**
ORR		
n, responders	56	36
% of patients (95% CI)	19 (15 to 24)	12 (9 to 17)
Odds ratio estimate (95% CI)	1.7 (1.1 to 2.6)	
P value	0.02	
TTR		
Median, months	2.1	2.6
Min-Max (months)	1.2-8.6	1.4-6.3
DOR		
N, responders	56	36
Median, months (95% CI)	17.2	5.6
Min-Max (months)	1.8-22.6+	1.2+-15.2+

CI=confidence interval; DOR=duration of response; ORR=objective response rate; TTR=time to treatment response
The + symbol indicates a censored value. The value of 1.2 was censored because the patient discontinued treatment without disease progression, and the other values were censored because the response was ongoing at the time of the analysis.
Source: CS, Table 18

Treatment beyond progression

The CheckMate 057 protocol outlines how subjects treated with nivolumab were permitted to continue treatment beyond initial Response Evaluation Criteria in Solid Tumours (RECIST 1.1) defined progressive disease (PD), as long as they met specific criteria (trial protocol,[30] Section 4.3.4). For the nivolumab treatment group, 71 patients received treatment beyond progression, 16 of whom demonstrated a non-conventional pattern of benefit. Non-conventional benefit was experienced by patients who had not experienced a best objective response of partial response (PR) or CR prior to initial progression and met at least one of the following criteria:

- Criterion 1: Appearance of a new lesion followed by decrease from baseline of ≥ 10% in the sum of the target lesions (12 patients).
- Criterion 2: Initial increase from nadir ≥ 20% in the sum of the target lesions followed by reduction from baseline of ≥ 30% (no patients).
- Criterion 3: Initial increase from nadir ≥ 20% in the sum of the target lesions or appearance of new lesion followed by at least two tumour assessments showing no further progression defined as a 10% additional increase in sum of target lesions and new lesions (7 patients).

Furthermore, 14 patients had extended nivolumab treatment (defined as >3 doses received after initial progression) and extended OS (defined as more than the median OS of 12.2 months in the nivolumab group) after initial progression but did not meet the criteria for non-conventional benefit as defined above.

Subgroup analyses

The company conducted subgroup analyses for OS using a range of pre-specified characteristics. The company presents results for subgroup analyses performed at the time of the 12-month interim analysis (CS, Figure 16). The results of the subgroup analyses using data from the 18-month updated analysis are provided in Appendix 10.3.

OS benefit for nivolumab was observed across most pre-specified subgroups, except for the following: third-line therapy, 'Rest of the World' region, never smokers and EGFR mutation-positive status. The company observes that CIs in these subgroups were wide due to small subgroup sizes, that the study was not powered to identify significant differences in these subgroups, and that the "Rest of the World" subgroup may also have been confounded by smoking status.

The ERG agrees with the company's interpretation of the results of the subgroup analyses, although to inform further investigation, the ERG requested the corresponding p values for the tests for interaction for the performed subgroup analyses. Statistically significant

subgroup differences were observed for line of therapy (p=0.0431), region (p=0.0006), and smoking status (p=0.0446), suggesting that treatment effect is statistically significantly greater for second-line patients than third-line patients, US/Canada and Europe patients than "Rest of the World" patients, and smokers than never-smokers.

In terms of PFS, HRs favoured nivolumab in comparison to docetaxel for all pre-specified subgroups, except for third-line therapy, Europe and 'Rest of the World' region, females, never smokers, kirsten rat sarcoma 2 viral oncogene homolog (KRAS) mutation not detected, EGFR mutation-positive status, ALK translocation status not reported, and prior adjuvant treatment (CSR,[28] Section 7.4.1).

Efficacy results by EGFR mutation status

The efficacy of nivolumab was analysed according to EGFR mutation status. Many patients had unknown EGFR mutation status as the test was not mandatory as per the study protocol;[30] EGFR mutation status was either reported by the investigator or collected from case-report forms if the patients had been tested for EGFR mutation status as part of routine care prior to study entry.

The results for OS (Table 11) suggest that the nivolumab benefit observed for the overall trial population in comparison to docetaxel is also seen within the EGFR mutation-negative/unknown population (HR=0.7, 95% CI: 0.6 to 0.8). However, results for the EGFR mutation-positive patients suggest that there is no statistically significant difference between nivolumab and docetaxel within this population, with the HR actually favouring docetaxel (HR=1.18, 95% CI: 0.69 to 2.00).

As the ERG has previously mentioned, the presented HRs are not an appropriate way to summarise treatment effect. In the EGFR mutation-negative unknown population, median OS was 3.5 months longer for patients in the nivolumab arm than for patients in the docetaxel arm (12.8 months versus 9.3 months). However, in the EGFR mutation-positive patients, median OS was 2.3 months longer for docetaxel patients than for nivolumab patients (11.5 months versus 9.2 months).

The ERG notes that the p value for interaction provided for the EGFR mutation status subgroup analysis at the 18-month data-cut was not statistically significant (p=0.4689).

Table 11 CheckMate 057 treatment effect on OS by EGFR mutation status

EGFR mutation status	Nivolumab		Docetaxel		HR for nivolumab vs. docetaxel (95% CI)
	Event no. (pt no.)	Median OS (95% CI)	Event no. (pt no.)	Median OS (95% CI)	
12-month interim analysis					
Positive (n=82)	31 (44)	9.2 (5.2 to 13.1)	25 (38)	11.5 (5.8 to 17.8)	1.2 (0.7 to 2.0)
Negative (n=340)	104 (168)	13.6 (10.4 to 18.4)	133 (172)	9.3 (7.7 to 10.7)	NR
Unknown (n=160)	55 (80)	11.3 (7.7 to 15.7)	65 (80)	9.3 (7.2 to 12.0)	NR
Negative/unknown combined (n=500)	159 (248)	12.8 (10.0 to 15.7)	198 (252)	9.30 (8.0 to 10.6)	0.7 (0.6 to 0.9)
18-month updated analysis					
Positive (n=82)	33 (44)	9.31 (5.2 to 15.7)	27 (38)	11.53 (5.8 to 17.0)	1.1 (0.7 to 1.9)
Negative/unknown combined (n=500)	173 (248)	12.8 (10.0 to 15.7)	209 (252)	9.3 (8.0 to 10.6)	0.7 (0.6 to 0.8)

CI=confidence interval; HR=hazard ratio; OS=overall survival; no=number; pt=patient
Source: CS, Table 20 and text in Section 4.8.2 and clarification response-question A3

The company also provided a K-M plot (CS, Figure 17) to demonstrate OS in the EGFR mutation-negative/unknown patients; the K-M curves for nivolumab and docetaxel suggest a similar pattern of survival to the overall patient population. For the first 7 months, patients in the docetaxel arm are less likely to have an OS event than those in the nivolumab arm. At 7 months, the K-M curves begin to separate, and nivolumab appears to improve OS in comparison to docetaxel for the remainder of the follow-up period.

In the CS the company reports that the 1-year OS rate for docetaxel is higher than expected in CheckMate 057 and suggests that this underestimates the true survival benefit of nivolumab (CS, Section 4.71). For comparison, the company cites OS results from the docetaxel arm of CheckMate 017. However, the ERG is unclear why this study was chosen for comparison as this trial only included squamous patients. A more appropriate study for comparison may be the TAILOR[36] study or one of the other three studies[24,26,27] with a docetaxel arm that were included in the ITC. The median OS and 1-year survival results in these studies are reported in Table 12 and demonstrate similar rates to those found in CheckMate 057.

Table 12 Comparison of OS in docetaxel arms of comparator studies

Study	Median OS (95% CI) mths	1 year OS (95% CI)
CheckMate 057	9.4 (8.1 to 10.7)	39.0% (33 to 45)
CheckMate 017[37]	6.0 (5.1 to 7.3)	24% (17 to 31)
Tailor[36]	8.2 (5.8 to 10.9)	39.6% (36.1 to 43.4)
Lume-Lung 1 adenocarcinoma[24]	10.3	44.7% (38.9 to 49.8)
ISTANA[26]	12.2 (NR)	NR
V-15-32[27]	14 (11.7 to 16.5)	53.7% (NR)

OS=overall survival; NR=not reported

The HRs for PFS (Table 13) suggest that there were no statistically significant differences between nivolumab and docetaxel for either the EGFR mutation-positive or EGFR mutation-negative/unknown patients. Once again, these HRs need to be interpreted with caution. For EGFR mutation-positive patients, median PFS was 2.7 months longer for patients in the docetaxel arm than for patients in the nivolumab arm (4.8 months versus 2.1 months). In the EGFR mutation-negative/unknown patients, median PFS was 1.6 months longer for docetaxel patients than for nivolumab patients (4.2 months versus 2.6 months). The company also provided PFS results for the EGFR mutation negative/unknown patients from the 18-month updated analysis; the reported HRs concurred with the HRs reported at the 12-month interim analysis.

Table 13 CheckMate 057 treatment effect on PFS by EGFR mutation status

		Nivolumab (n=292)		Docetaxel (n=290)		HR for nivolumab vs. docetaxel (95% CI)
EGFR mutation status	**N**	**Events (patients)**	**Median PFS (95% CI)**	**Events (patients)**	**Median PFS (95% CI)**	
12-month interim analysis						
Positive	82	39 (44)	2.1 (1.6 to 3.3)	29 (38)	4.8 (2.1 to 6.9)	1.5 (0.9 to 2.47
Negative	340	131 (168)	3.1 (2.2 to 4.2)	144 (172)	3.9 (3.5 to 4.9)	-
Unknown	160	64 (80)	2.3 (2.1 to 5.0)	72 (80)	4.7 (2.2 to 5.5)	-
Negative/unknown combined	500	195 (248)	2.6 (2.2 to 3.7)	216 (252)	4.2 (3.5 to 4.9)	0.8 (0.7 to 1.0)
18-month updated analysis						
Negative/unknown combined	500	198 (248)	2.6 (2.2 to 3.7)	218 (252)	4.2 (3.5 to 4.9)	0.82 (0.7 to 1.0)

CI=confidence interval; PFS=progression-free survival; no=number; pt=patient
Source: CS, Table 21 and text in section 4.8.2

The company also provided a K-M plot (CS, Figure 18) to demonstrate PFS in the EGFR mutation-negative/unknown patients; the K-M curves for nivolumab and docetaxel suggest a similar pattern of PFS to the overall patient population.

4.2.7 Efficacy results by PD-L1 expression level

The efficacy of nivolumab was also analysed according to PD-L1 status in terms of both OS and PFS; 78% (455/582) of randomised patients had an evaluable PD-L1 status (231/292 in the nivolumab arm and 224/290 in the docetaxel arm). The company used three different categorisations to investigate the impact of PD-L1 status on treatment efficacy (<1% versus ≥1%, <5% versus ≥ 5%, and <10% versus ≥ 10%).

Firstly, the company used HRs to summarise treatment effect for each of the subgroups (CS, Figure 19). HRs are not an appropriate way to measure treatment effectiveness for nivolumab in comparison to docetaxel, and therefore the ERG does not believe that the results presented in Figure 19 of the CS are valid.

Instead, the ERG considered the median OS results in order to evaluate how PD-L1 status might influence the efficacy of nivolumab. The company provided K-M graphs and median OS for each subgroup for each categorisation of PD-L1 status, with additional follow-up from the 18-month updated analysis (CS, Figure 20 and Figure 21). Median OS was 10.5, 9.8, and 9.9 months for nivolumab patients compared to 10.1, 10.1, and 10.3 for docetaxel subjects in PD-L1 negative subgroups defined by the <1%, <5%, and <10% expression levels, respectively.

ORR results by PD-L1 expression status are shown in Table 14. Higher ORRs were observed in nivolumab patients versus docetaxel patients for high expressors at each of the pre-specified PD-L1 expression levels (31% versus 12% by the ≥1% expression level, 36% versus 13% by the ≥5% expression level and 37% versus 13% by the ≥10% expression level). In low expressors, ORRs were lower in nivolumab patients in comparison to docetaxel patients, (9% versus 15% by the <1% expression level, 10% versus 14% by the <5% expression level and 11% versus 14% by the <10% expression level).

Table 14 Outcomes nivolumab vs. docetaxel by baseline PD-L1 expression level

	Baseline PD-L1 expression level						**Not quantifiable†**
	1%*		**5%***		**10%***		
	<1%	**≥1%**	**<5%**	**≥5%**	**<10%**	**≥10%**	
Nivolumab							
n (%)	108 (47)	123 (53)	136 (59)	95 (41)	145 (63)	86 (37)	61 (21)
ORR‡ n (%) [95% CI]	10 (9) [5 to 16]	38 (31) [23 to 40]	14 (10) [6 to 17]	34 (36) [26 to 46]	16 (11) [6 to 17]	32 (37) [27 to 48]	8 (13) [6 to 24]
Median DOR, months (95% CI) N	18.3 (4.2 to NE) 10	16.0 (8.4 to NE) 38	18.3 (5.5 to NE) 14	16.0 (8.4 to NE) 34	18.3 (7.5 to NE) 16	16.0 (6.9 to NE) 32	7.3 (2.2 to NE) 8
Docetaxel							
n* (%)	101 (45)	123 (55)	138 (62)	86 (38)	145 (65)	79 (35)	66 (23)
ORR‡ n (%) [95% CI]	15 (15) [9 to 23]	15 (12) [7 to 19]	19 (14) [9 to 21]	11 (13) [7 to 22]	20 (14) [9 to 21]	10 (13) [6 to 22]	6 (9) [3 to 19]
Median DOR, months (95% CI) n	5.6 (4.2 to 9.9) 15	5.6 (3.0 to 5.7) 15	5.6 (4.2 to 7.1) 19	5.6 (3.0 to 7.0) 11	5.6 (4.2 to 7.1) 20	5.6 (1.6 to 6.2) 10	6.6 (2.8 to 14.2) 6
OR‖ (95% CI)	0.6 (0.2 to 1.5)	3.2 (1.6 to 6.7)	0.7 (0.3 to 1.6)	3.8 (1.7 to 9.0)	0.8 (0.4 to 1.7)	4.1 (1.8 to10.1)	1.5 (0.4 to 5.6)

CI=confidence interval; DOR=duration of response; NE=not evaluable; OR=odds ratio; ORR=objective response rate; PD-L1=programmed death-ligand 1
* Number and percent of evaluable patients with membranous staining at the respective expression level in ≥ 100 tumour cells.
† Number and percent of randomised patients with PD-L1 expression not quantifiable.
‡ Confirmed complete and partial responses per RECIST v1.1 criteria, as assessed by the investigator. CI based on the Clopper-Pearson method.
‖ Ratio of nivolumab over docetaxel
Source: C
S, Table 22

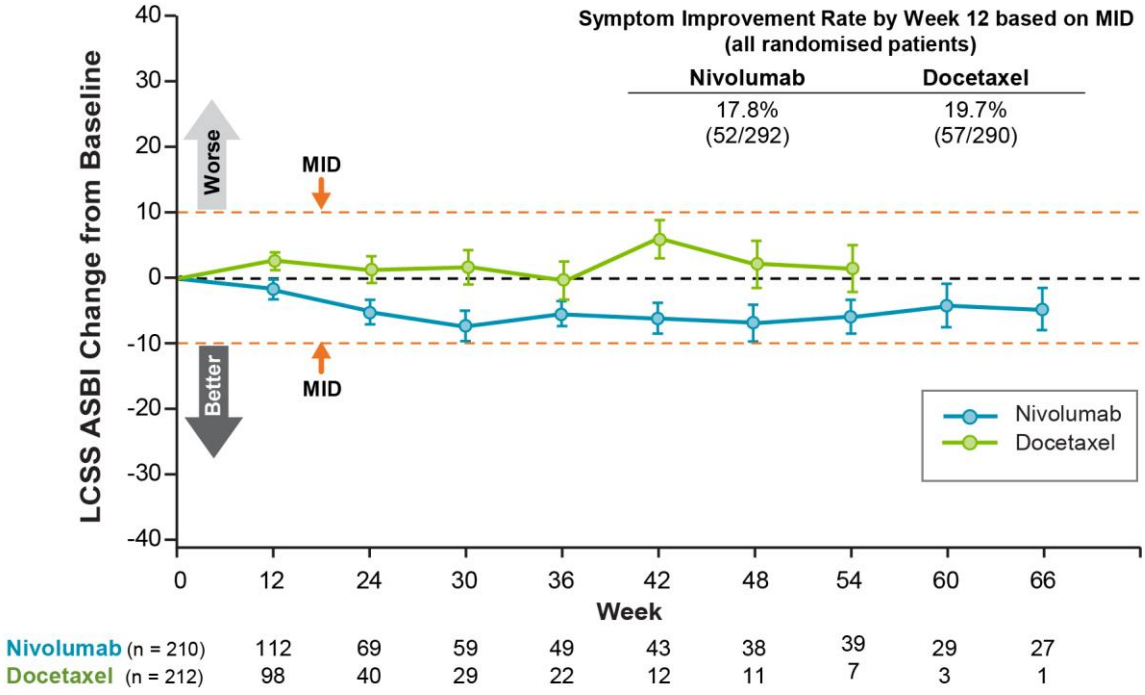
Both high expressors and low expressors experienced a benefit in terms of DOR, which was greater in nivolumab patients than in docetaxel patients for all pre-specified PD-L1 expression levels.

4.2.8 Health related quality of life

In CheckMate 057 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), the EuroQol 5-Dimensions utility index (EQ-5D) and the EuroQol Visual Analogue Scale (EQ-VAS) at each assessment point. As described in Table 55 of the CS and on pg 258 of the CSR,[28] assessments for both EQ-5D/EQ-VAS and LCSS 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 differences in time of initial measurement reflect the fact that nivolumab is administered every 2 weeks while docetaxel is administered every 3 weeks. The scores were also assessed at 100 days following the last dose administered to patients and every 3 months for the first 12 months, and every 6 months after. Disease-related symptom improvement rate is defined as a decrease of 10 points or more from baseline in average symptom burden by week 12.

LCSS questionnaire completion rates were ≥75% at baseline and ≥65% through to week 66. From week 66 compliance rates were lower but remained at ≥45%, though by week 42 for the docetaxel group the number of available patients had fallen to below 20.

Results of the LCSS ASBI are shown in Figure 15 of the CS. Mean (standard deviation) baseline scores for LCSS ASBI were 26.2 (16.2) for nivolumab patients and 24.4 (15.5) for docetaxel patients. By week 12, the rate of disease-related symptom improvement was comparable between the groups i.e. 17.8% for nivolumab patients and 19.7% for docetaxel patients. The ERG concurs that this is correct as any difference would not be clinically significant as neither curve crosses the minimally important difference i.e. a change of ≥10 points (See Figure 4).



Source Horn, Brahmer, Reck, Borghaei, Spigel, Steins, *et al.* [38]

Abbreviations: ASBI = Average Symptom Burden Index; LCSS = Lung Cancer Symptom Scale; MID = Minimally Important Difference

Higher scores indicate greater symptom burden. Mean (standard deviation) scores at baseline were 24.8 (15.9) for nivolumab and 24.4 (15.8) for docetaxel. Only time points that had patient-reported outcome data available for ≥ 5 patients in either treatment arm are plotted on the graph. MID consists of a change of ≥ 10 points.

Figure 4 CheckMate 057: change in LCSS ASBI (on treatment)

The company also states (CS, p80) that, at the two follow-up visits after treatment discontinuation, the average symptom burden for both groups indicated a worsening of symptoms relative to baseline (range 3.6-6.3). However, no further details are reported in the CS, so the ERG cannot provide further comment.

Completion rates for the EQ-VAS were high and were greater than 50% for most of the on-treatment assessments and were similar across the two arms of the tria. 'The average EQ-VAS increased over time for both treatment groups (although the increase began later for docetaxel patients), indicating better overall health status for patients remaining on treatment. The average EQ-VAS score exceeded the average baseline score by more than the 7-point MID from week 16 through week 72 in the nivolumab group and from week 36 through week 48 for the docetaxel group. For both treatment groups, the EQ-VAS assessments in the follow-up visits following discontinuation returned to values in the region of the baseline scores (range: 60.6-66.4)'.

4.2.9 Adverse events

Comparative safety data from CheckMate 057 demonstrated that nivolumab had a more favourable safety profile than docetaxel (Table 15). There was one drug related death in

each arm of the trial. Any Grade treatment related AEs were lower in the nivolumab arm (69% versus 88%) as were Grade 3-4 AE (10% versus 54%). The overall number of AEs is similar in each group.

Table 15 Summary of safety profiles in CheckMate 057

Type of AE	Patients with each type of AE (%)	
	Nivolumab (n=287)	Docetaxel (n=268)
All cause and any Grade AE	280 (98)	265 (99)
All cause Grade 3 to 4 AE	132 (46)	180 (67)
Treatment related AE- all	199 (69)	236 (88)
All cause AE leading to discontinuation	48 (17)	58 (22)
All cause Grade 3 to 4 AE leading to discontinuation†	38 (13)	34 (13)
All cause Select AEs Grade 3 to 4		
Endocrine	0 (0)	0 (0)
Gastrointestinal	2 (1)	3 (1.1)
Hepatic	3 (1.0)	2 (0.7)
Pulmonary	4 (1.4)	1 (0.4)
Renal	0 (0)	0 (0)
Skin	2 (0.7)	0 (0)

AE=adverse event; SAE=serious adverse event
Source: CS, Table 32

The AE profile of nivolumab is different to that of standard chemotherapy because of the action of the drug and therefore the company describes a set of 'Select AEs'. The company claims that these Select AEs are manageable and patients may be successfully treated using the recommended treatment algorithm guidelines provided in the Summary of Product Characteristics.[39] The Select AEs are defined as immune-related adverse events (irAEs) that may require more frequent monitoring and treatment with immune modulating medications. A more detailed list of AEs that occurred in ≥5% of patients is presented in Table 16. As can be seen the most important differences are the increased rates of AE related to neutropenia and febrile neutropenia in the docetaxel patients.

The company provides additional clinical data from two non-randomised studies[22,23] of nivolumab (in patients with a variety of different types of cancer including NSCLC, melanoma and renal cancer); the safety profile of nivolumab in these two studies is similar to the safety profile of nivolumab that was seen in CheckMate 057.

Table 16 Summary of treatment related AE in ≥5% of treated patients in CheckMate 057

	Nivolumab n=287		Docetaxel n=268	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Event	Number of patients with an event (%)			
Any event	199 (69)	30 (10)	236 (88)	144 (54)
Fatigue	46 (16)	3 (1)	78 (29)	13 (5)
Nausea	34 (12)	2 (1)	70 (26)	2 (1)
Decreased appetite	30 (10)	0	42 (16)	3 (1)
Asthenia	29 (10)	1 (<1)	47 (18)	6 (2)
Rash	27 (9)	1 (<1)	8 (3)	0
Pruritus	24 (8)	0	4 (1)	0
Diarrhoea	22 (8)	2 (1)	62 (23)	3 (1)
Hypothyroidism	19 (7)	0	0	0
Arthralgia	16 (6)	0	16 (6)	0
Vomiting	15 (5)	0	20 (8)	0
Constipation	13 (5)	0	21 (8)	2 (1)
Peripheral oedema	8 (3)	0	28 (10)	1 (<1)
Pyrexia	8 (3)	0	17 (6)	0
Myalgia	7 (2)	1 (<1)	30 (11)	0
Anaemia	6 (2)	1 (<1)	53 (20)	7 (3)
Dysgeusia	5 (2)	0	25 (9)	0
Paraesthesia	5 (2)	0	20 (7)	0
Pain	4 (1)	0	14 (5)	0
Peripheral neuropathy	3 (1)	0	25 (9)	3 (1)
Stomatitis	3 (1)	0	23 (9)	2 (1)
Mucosal inflammation	2 (1)	0	20 (7)	5 (2)
Lacrimation increased	1 (<1)	0	14 (5)	0
Alopecia	1 (<1)	0	67 (25)	0
Neutrophil count decreased	1 (<1)	1 (<1)	19 (7)	16 (6)
Neutropenia	1 (<1)	0	83 (31)	73 (27)
Febrile neutropenia	0	0	27 (10)	26 (10)
Leukopenia	0	0	27 (10)	22 (8)
White blood cell count decreased	0	0	22 (8)	12 (4)

Note: A patient may be recorded as having more than one adverse event within a category
Source: adapted from CS, Table 34

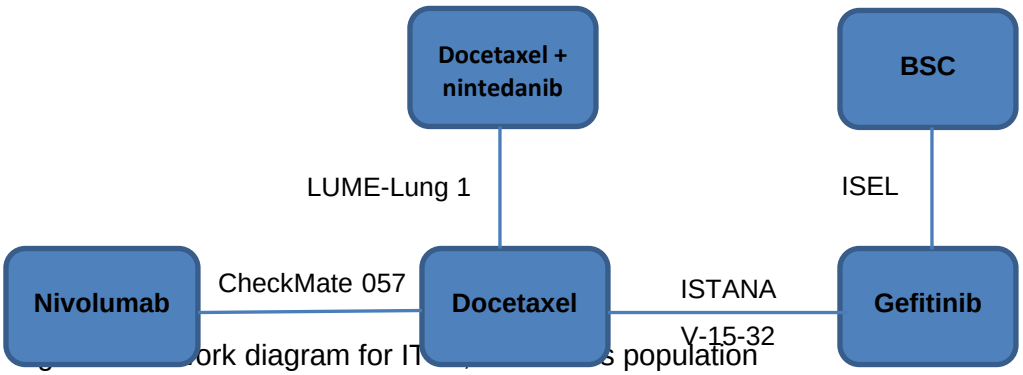
4.3 Critique of trials identified and included in the indirect comparisons

4.3.1 Studies identified for inclusion in the indirect comparisons

Using broad criteria, 33 trials were eligible for inclusion in the company's original systematic review of clinical effectiveness data; these trials included patients as described in the company's decision problem, i.e. previously treated patients with locally advanced or metastatic non-squamous NSCLC. This population is henceforth referred to as the all-comers population. However, as indicated in the NICE scope, the company also considered the subpopulations of EGFR mutation-negative/unknown and EGFR mutation-positive

patients. Thirty studies reported data for the EGFR mutation-negative/unknown population, and ten studies reported data for the EGFR mutation-positive population (see Appendix 7.1.4 Table 11).

For the all-comers population, i.e. any EGFR status, only five studies (Figure 5) contained data and formed a network which enabled ITCs between nivolumab and the relevant comparators to be carried out: CheckMate 057,[21] ISEL,[25] ISTANA;[26] LUME-Lung 1;[24] V-15-32.[27]



ork diagram for IT s population

BSC=best supportive care
References: ISEL,[25] ISTANA,[26] LUME-Lung 1,[24] V-15-32[27]
Source: CS, adapted from Appendix 7.17 Figure 6

For the EGFR mutation-negative/unknown population, only four studies (Figure 6) contained data and formed a network which enabled ITCs between nivolumab and the relevant comparators to be carried out: CheckMate 057;[21] LUME-Lung 1;[24] ISEL;[25] and ISTANA.[26]

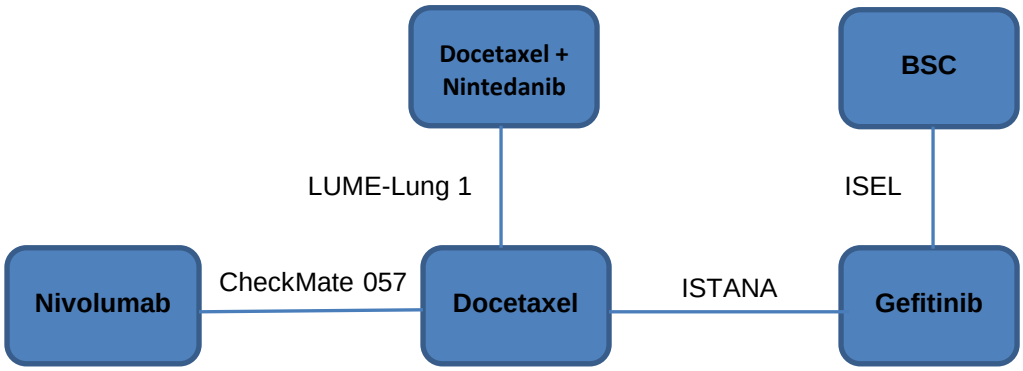


Figure 6 Network diagram for ITCs, EGFR mutation-negative/unknown population

BSC=best supportive care
References: ISEL,[25] ISTANA,[26] LUME-Lung 1,[24]
Source: CS, adapted from Appendix 7.17 Figure 4

For the EGFR mutation-positive population, no studies formed a network enabling ITCs between nivolumab and the relevant comparators to be carried out. No ITCs were conducted for this patient population.

The ERG did not identify any additional studies that met the company's eligibility criteria for inclusion in either the all-comers or EGFR mutation-negative/unknown networks. The key characteristics of the RCTs used to inform the ITCs are summarised in Table 17.

Table 17 Summary of RCTs reporting data for previously treated non-squamous NSCLC population and included in analyses

Study	Design	Location	Intervention/ comparators (n)	Duration	Patient population
Studies connected in BOTH networks (EGFR mutation-negative/unknown AND all-comers NSQ NSCLC)					
LUME-Lung 1[24]	Randomised, multicentre international, double-blind, placebo controlled, phase III	27 countries (211 centres)	Docetaxel (659) Docetaxel+nintedanib (655)	31·7 months	ECOG PS 0-1 At least one measurable target lesion One previous first-line chemotherapy regimen
ISTANA[26]	Randomised, multicentre, open-label, active-controlled, phase III	Korea (6 centres)	Docetaxel (79) Gefitinib (82)	NR	Age ≥18 years WHO PS 0-2 Histologically or cytologically confirmed NSCLC with stage IIIB or IV disease One previous platinum-based chemotherapy regimen Progressive or recurrent disease following previous chemotherapy
ISEL[25]	Randomised, multicentre international, double-blind, placebo controlled, phase III	28 countries (210 centres)	BSC (563) Gefitinib+BSC (1129)	7.2 months	Age ≥18 years WHO PS 0-3 Histologically or cytologically proven, locally advanced or metastatic NSCLC At least one previous platinum-based chemotherapy regimen
CheckMate 057[28]	Randomised, multicentre international, open-label, active-controlled, phase III study	22 countries (106 sites)	Nivolumab (292) Docetaxel (290)	30 months	Age ≥18 years Stage IIIB/Stage IV or recurrent or progressive non-squamous NSCLC ECOG PS 0-1 Failed at least one prior platinum-based doublet chemotherapy regimen
Study connected ONLY in network of all-comers NSQ NSCLC					
V-15-32[27]	Randomised, multicentre, open label, active-controlled, phase III study	Japan (50 sites)	Docetaxel (244) Gefitinib (245)	21 months	Age ≥20 years Histologically or cytologically confirmed NSCLC (stages IIIB to IV) Failure of prior treatment with one or two chemotherapy regimens (≥ 1 platinum-based regimen) Life expectancy of 3 months or greater WHO PS 0-2

ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; NR=not reported; NSQ=non-squamous; PS=performance status; WHO=World Health Organization
Source: CS, Table 23

4.3.2 Methodological approach to the indirect comparisons

The company performed the ITCs using the Bucher method,[40] as described in Appendix 7.2 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 5 and Figure 6, there were no closed loops in the either network of evidence and hence the ERG is satisfied that the modelling approach chosen by the company was appropriate.

ITCs often incorporate reported HRs from the included studies, and the outputs from these ITCs are estimated HRs for pairs of treatments which take into consideration both direct and indirect evidence. As there are no closed loops in the networks of evidence provided by the company, the HRs generated by the ITCs are based on indirect evidence only.

However, the company highlights that the validity of using HRs within ITCs relies on the assumption that the hazards of drugs within each study and across different studies included in the network of evidence are proportional. To test the assumption of PH, the company regenerated individual patient data from published K-M curves using methodology proposed by Guyot and colleagues.[41] The company inspected log-log plots (log cumulative hazard versus log time) and, if the curves for each treatment arm were approximately parallel, it was assumed that the assumption of PH was valid. The company also performed statistical tests, namely the Global Test for PH assumption,[35] and a supremum test for PH assumption.

The company states that if the PH assumption was violated for data taken from the included trials they would use differences in restricted mean survival time (RMST) instead of HRs in the ITCs as RMST is a measure of treatment effect which does not rely on the assumption of PH. This is based on work by Royston[42] in the analysis of OS in RCTs. This is the first time that the ERG have seen this measure of treatment effect used in an ITC. The ERG can think of no reason why it would not be appropriate to use this measure of treatment effect in an ITC and their approach using WinBUGs to fit the model sounds reasonable, although we do have very limited information in the CS about the actual analysis.

RMST is defined as the area under the survival curve up to the time t*, where t* is the follow-up period of clinical interest. From a clinical perspective, this measure can be interpreted as the 'life expectancy' between randomisation (t=0) and a particular time horizon (t=t*). The company chose t* to be the minimum follow-up time of all the trials included in the analysis. The company explains that the benefit of implementing this methodology is that the approach does not make any assumptions about the distribution of the data. The company used R to calculate RMST for each treatment arm, and the difference between the RMST in

the two arms, along with CIs, for each study included in the network of evidence. After calculating the RMST for each study, the company used WinBUGS to perform the ITCs, consequently estimating the RMST differences for treatments for which there is no direct evidence.

The results of the company assessments of PH for the included studies were not provided in the CS, and, instead of using the results of these assessments to determine whether to perform ITCs using HRs or RMST differences, the company performed each ITC using both HRs and RMST differences.

For the results of an ITC that uses HRs as data inputs to be credible, the assumption of PH must hold both within and across trials. As previously discussed in Section 4.2.4 of this ERG report, the results of the testing carried out by the company (see Appendix 10.2) indicate that the assumption of PH is violated for both OS and PFS data for CheckMate 057. As data from CheckMate 057 are used in every ITC, the mathematics used to calculate estimated HRs for indirect estimates of effect are fundamentally compromised. Consequently, the ERG is of the opinion that none of the ITC results that were generated using HRs (as opposed to RMST differences) are valid.

The company also provided the results of testing the PH assumption for the other trials included in the ITCs. However, as PH was violated for CheckMate 057, this rendered every ITC result for OS and PFS (which was generated using HRs) meaningless, and so there is no reason to consider PH for the other trials included in the ITCs. The ERG does not therefore report the HRs for any of these analyses and urges that any HRs reported in the CS are interpreted with extreme caution.

4.3.3 Characteristics of studies included in the indirect comparisons

The patient populations of the five trials[21,24-27] included in the networks of evidence differed due to differences in eligibility criteria; CheckMate 057 recruited previously treated patients with only non-squamous advanced and/or metastatic NSCLC, whereas the other four studies[24-27] included patients with both squamous and non-squamous NSCLC. Furthermore, CheckMate 057[21], ISEL,[25] ISTANA,[26] and V-15-32[27] recruited patients who had failed a platinum-based chemotherapy and had PS 0-1, PS 0-2, PS 0-3 and PS 0-2, respectively; however, LUME-Lung 1[24] included patients who had failed one line of chemotherapy and had a PS 0-1. In addition V-15-32[27] recruited patients from Japan who may have significantly different responses.

Baseline characteristics of the patients recruited to RCTs that were included in the ITCs are reported in Table 18 and Table 19.

Table 18 Baseline characteristics of studies for previously treated non-squamous NSCLC population

Study	Treatment arm	N	Smokers, n (%)				PS (ECOG*/WHO†), n (%)					
			Current	Former	Never	Current or former	PS 0	PS 0-1	PS 1	PS 2	PS 3	PS 2-3
Studies connected in BOTH networks (EGFR mutation-negative/unknown AND all-comers NSQ NSCLC)												
LUME-Lung 1[24] Adenocarcinoma population	Docetaxel	336	59 (17.6)	162 (48.2)	115 (34.2)	221 (65.8)	99 (29.5)	-	237 (70.5)			
	Docetaxel+ nintedanib	322	56 (17.4)	151 (46.9)	115 (35.7)	207 (64.3)	96 (29.8)	-	226 (70.2)			
ISTANA[26]	Docetaxel	79	0 (0.0)	43 (54.4)	36 (45.6)	43 (54.4)	3† (3.8)	-	71† (89.9)	5† (6.3)		
	Gefitinib	82	1 (1.2)	51 (62.2)	30 (36.6)	52 (63.4)	2† (2.4)	-	74† (90.2)	6† (7.3)		
ISEL[25]	BSC	563	97 (17)	340 (60)	125 (22)	437 (77)	70† (12)	-	318† (56)	145† (26)	29† (5)	
	Gefitinib+BSC	1129	201 (18)	678 (60)	250 (22)	879 (78)	140† (12)	-	598† (53)	332† (29)	55† (5)	
CheckMate 057[28]	Nivolumab	292	-	-	58 (19.9)	231 (79.1)	84 (28.8)	-	208 (71.2)		0 (0)	
	Docetaxel	290	-	-	60 (20.7)	227 (78.3)	95 (32.8)	-	193 (66.6)		1 (0.3)	
Study connected ONLY in network of all-comers NSQ NSCLC												
V-15-32[27]	Docetaxel	244	-	-	87 (35.7)	157 (64.3)		93* (38.1)	141* (57.8)	10* (4.1)		
	Gefitinib	245	-	-	71 (29)	174 (71)		85* (34.7)	149* (60.8)	11* (4.5)		

BSC=best supportive care; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; NSQ=non-squamous; PS=performance status; WHO=World Health Organization

* PS rated on the ECOG scale

† PS rated on the WHO scale

Source: CS, adapted from Table 24; data for the adenocarcinoma population from LUME-Lung 1[24] were taken from data published as part of the previous NICE appraisal (TA347)[43]

Table 19 Summary of baseline characteristics of studies for previously treated non-squamous NSCLC population and included in analysis

Study	Treatment arm	N	Disease stage (%)			EGFR mutation status	Histology	Median age (range), years	Male (%)
			Stage III	Stage IV	Stage III/ IV				
Studies connected in BOTH networks (EGFR mutation-negative/unknown AND all-comers NSQ NSCLC)									
LUME-Lung 1[24] Adenocarcinoma population	Docetaxel	336	NR	NR	NR	EGFR mutation-negative/unknown: 100%	NSQ: 100% SQ: 0%	Mean (SD): 58.6 (9.5)	61.9
	Docetaxel + nintedanib	322	NR	NR	NR		NSQ: 100% SQ: 0%	Mean (SD): 58.5 (10.1)	63
ISTANA[26]	Docetaxel	79	-	-	100	Unclear	NSQ: 86.3% SQ: 13.7%	58 (20-73)	57
	Gefitinib	82	-	-	100		NSQ: 79.3% SQ: 20.7%	57 (21-74)	67.1
ISEL[25]	BSC	563	39	50	-	EGFR mutation-negative/unknown: 87.9% EGFR mutation-positive: 12.1%	NSQ: 67% SQ: 33%	61 (31–87)	67
	Gefitinib + BSC	1129	44	47	-		NSQ: 65% SQ: 35%	62 (28–90)	67
CheckMate 057[28]	Nivolumab	292	6.8	93.2	-	EGFR mutation testing: N=212 EGFR mutation-positive: 20.7% EGFR mutation-negative/unknown: 79.3%	NSQ: 100%	61 (37-84)	51.7
	Docetaxel	290	8.3	91.7	-	EGFR mutation testing: N=210 EGFR mutation-positive: 18.1% EGFR mutation-negative/unknown: 79.9%	NSQ: 100%	64 (21-85)	57.9
Study connected ONLY in network of all-comers NSQ NSCLC									
V-15-32[27]	Docetaxel	244	20.5	61.5	-	EGFR mutation testing: N=54 EGFR mutation-positive: 54.4%	NSQ: 83.2% SQ: 16.8%	NR	61.9
	Gefitinib	245	19.2	64.9	-		NSQ: 84.9% SQ: 15.1%	NR	61.6

BSC=best supportive care; EGFR=epidermal growth factor receptor; NR=not reported; NSQ=non-squamous; SQ=squamous
Source: CS, adapted from Table 25; data for the adenocarcinoma population from LUME-Lung 1[24] were taken from data published as part of the previous NICE appraisal (TA347)[43]

Baseline characteristics for trials included in all-comers network

The ERG considered baseline characteristics for the included trials in order to determine whether performing an ITC for the all-comers population was appropriate.

The ERG notes that the company presented baseline characteristics for the whole trial population of LUME-Lung 1[24] in Table 24 of the CS, despite the fact that only data for the adenocarcinoma population were used in the ITC. In order to allow comparisons between the LUME-Lung 1[24] adenocarcinoma population and the other trials included in the ITC, the ERG presents baseline characteristics for the adenocarcinoma population for LUME-Lung 1[24] (Table 18). These data were published as part of a previous NICE appraisal (TA347).[43]

Due to differences in eligibility criteria, the proportions of patients with different types of ECOG PS varied considerably between the included trials. The trials also differed with regards to the smoking status of the patient populations.

Although only a small number of patients in V-15-32[27] had EGFR mutation status tested (54 patients out of 489), the results of this testing indicated that a large proportion of patients were EGFR mutation-positive (54.4%). The other trials all had large (≥75%) percentages of EGFR mutation-negative/unknown patients.

Perhaps the most important source of variability within the populations of the trials included in the all-comers network is the inclusion of both squamous and non-squamous patients in ISEL,[25] ISTANA,[26] and V-15-32.[27] The company states that subgroup data were provided for the non-squamous patients for the trials that included both squamous and non-squamous patients, but the data inputs provided by the company that were used in the ITCs were for the whole trial populations. The ERG notes that the trials which recruited both squamous and non-squamous patients recruited a majority of non-squamous patients, although the ERG is disappointed that the company did not list the variability in the proportion of non-squamous patients as a limitation of the ITCs, and the company did not consider whether it was appropriate to compare these trial populations to the trial population of CheckMate 057 which consisted of solely non-squamous patients.

The ERG notes that heterogeneity within the trials would be more likely to affect the ITC of nivolumab versus BSC than the ITC of nivolumab versus nintedanib+docetaxel. The main heterogeneity in the network is observed between the trials used to link BSC to nivolumab (i.e. CheckMate 057,[7] ISEL,[25] ISTANA,[26] and V-15-32[27]). The ERG is of the opinion that this heterogeneity ought to be considered when interpreting results presented for nivolumab versus BSC, although it is very difficult to assess how the overall treatment effect estimate

would be affected by these differences. The ERG advises that the results of the ITC for nivolumab versus BSC ought to be interpreted with caution.

Only two trials contribute evidence to the ITC of nivolumab versus nintedanib+docetaxel (CheckMate 057[7] and LUME-Lung 1[24]), and the ERG is of the opinion that baseline characteristics are fairly similar across these trials. CheckMate 057 included fewer male patients (51.7% in the nivolumab arm, 57.9% in the docetaxel arm) than LUME-Lung 1[24] (61.9% in the docetaxel arm, 63% in the docetaxel plus nintedanib arm). As male patients are expected to do slightly worse than females, this heterogeneity could favour nivolumab, although the ERG notes that the LUME-Lung 1[24] population consisted of solely EGFR mutation-negative/unknown patients, who are likely to have better treatment outcomes than a population consisting of both EGFR mutation-positive and -negative/unknown patients (CheckMate 057). Overall, the ERG does not consider differences between these two trials to be concerning. However, it is important to note that the ERG did not have access to data summarising the disease stage of patients in the adenocarcinoma population of the LUME-Lung 1 trial,[24] and so it is not possible to compare the patients of the adenocarcinoma subpopulation of LUME-Lung 1[24] and the patient population of CheckMate 057 in this respect.

Baseline characteristics for trials in EGFR mutation-negative/unknown network

No baseline characteristics were provided for the subpopulation of EGFR mutation-negative/unknown patients for any of the included trials. Following the company's response to the clarification letter, it became clear to the ERG that, with the exception of CheckMate 057, the company used data for the whole trial populations in the ITCs for EGFR mutation-negative/unknown patients. The company justified this approach by stating that in all of these trials, either the whole population was EGFR negative or the proportion of EGFR negative patients was ≥80% of the whole population.

The company used data for the EGFR mutation-negative/unknown subgroup of patients from CheckMate 057. However, there are no baseline characteristics presented for the subgroup of EGFR mutation-negative/unknown patients from CheckMate 057, and consequently it is not possible to assess whether the patient populations of the trials included in the EGFR mutation-negative/unknown network are comparable.

4.3.4 Assessment of risk of bias of the trials included in the indirect comparisons

The company conducted an assessment of the risk of bias of the studies included in the ITCs and the results presented in the CS and are shown in Appendix 10.4 of the ERG report and discussed below.

The CS indicates that it is unclear whether randomisation was carried out appropriately in ISTANA,[26] ISEL[25] and V-15-32[27] so it is not possible to assess whether there was a risk of bias. All studies were at low risk of bias for differences between the groups on prognostic factors at the outset of the studies.

Whilst LUME-Lung 1[24] and ISEL[25] were considered to be at low risk of bias, CheckMate 057,[28] ISTANA[26] and V-15-32[27] trials were considered to be at a high risk of bias for blinding due to being open-label trials. However, the ERG notes that due to the difference in the treatment schedules and AE profiles it would be challenging to compare any combination of these treatments with each other in a blinded manner.

Only ISTANA[26] did not report unexpected imbalances in drop-outs between groups and was therefore assessed to at high risk of bias for this item. There was no evidence to conclude whether all outcomes assessed were reported in the ISEL[25] trial so it was not possible to assess the risk of bias for this item. All trials were assessed as having low risk of bias for analysis using an ITT.

4.3.5 Results from the indirect comparisons

Individual study results

The results of the individual studies included in the ITCs were provided by the company (CS, Table 27). The ERG has updated Table 27 of the CS to correct minor errors which were identified as part of the clarification process; this table is provided in Appendix 10.5 of this ERG report.

Indirect treatment comparison results

The results of the ITCs carried out by the company are provided in Table 20.

As PH was violated for CheckMate 057, this rendered every ITC result for OS and PFS (which was generated using HRs) meaningless, and so there is no reason to consider PH for the other trials included in the ITCs. The ERG does not therefore report the HRs for any of these analyses and urges that any HRs reported in the CS are interpreted with extreme caution.

The results shown in Table 20 are slightly different to those shown in Table 28 of the CS, as the ERG has incorporated the updated ITC results, which use the updated data inputs. The ERG is satisfied that the company's approach was appropriate, and the results of the ITC are very similar when using either set of data inputs.

For OS in the all-comers patient population, no statistically significant differences between nivolumab and nintedanib+docetaxel were identified. Similarly, no statistically significant differences were found in terms of PFS or ORR. For AEs, no treatment benefit was observed for nivolumab in comparison to nintedanib+docetaxel when considering the outcome "any adverse event"; however, nivolumab was demonstrated to statistically significantly reduce the risk of Grade 3-4 AEs ([redacted]) (Table 20).

Considering the comparison of nivolumab and BSC in the all-comers patient population, nivolumab was shown to statistically significantly improve OS (RMST difference (95%CI); [redacted]) (Table 20).

For OS, PFS and ORR in the EGFR mutation-negative/unknown patient population, there were no statistically significant differences between nivolumab and nintedanib+docetaxel.

The comparison of nivolumab and BSC in the EGFR mutation-negative/unknown patient population failed to demonstrate any statistically significant differences in terms of OS (Table 20).

Table 20 Results of the indirect treatment comparison

Outcome	Nivolumab vs nintedanib+docetaxel	Nivolumab vs. BSC
Patient population: All-comers NSQ NSCLC		
OS RMST difference (95% CI); p value	[redacted]	[redacted]
PFS RMST difference (95% CI); p value	[redacted]	[redacted]
ORR RR (95% CI); p value	[redacted]	[redacted]
Any adverse event RR (95% CI); p value	[redacted]	[redacted]
Any Grade 3/4 adverse event RR (95% CI); p value	[redacted]	[redacted]
Patient population: EGFR mutation-negative/unknown NSQ NSCLC		
OS RMST difference (95% CI); p value	[redacted]	[redacted]
PFS RMST difference (95% CI); p value	[redacted]	
ORR RR (95% CI); p value	[redacted]	[redacted]

BSC=best supportive care; CI=confidence interval; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; NSQ=non-squamous; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RMST=restricted mean survival time; RR=relative risk
Source: CS, adapted from Table 28

Additional analysis requested by the ERG

The ERG noted that the ITC for nivolumab versus nintedanib+docetaxel used data from the LUME-Lung 1[24] second-line patient population, and CheckMate 057 second and third-line patient population. The ERG therefore requested that the company perform an indirect comparison of nivolumab versus nintedanib+docetaxel using data only from the second-line population from CheckMate 057. The results of this analysis are provided in Appendix 10.6. The ERG is satisfied that the results of the ITC for nivolumab+docetaxel are robust; results generated by the additional analysis requested by the ERG are in accordance with those from the original analysis.

ERG critique of the company's results from the ITCs

The ERG's main concern when considering the results of the ITCs is that none of the results of the ITCs which were performed using HRs (as opposed to RMST differences) are valid.

The ERG has not previously seen RMST differences used as the measure of effect in an ITC. The ERG can think of no reason why it would not be appropriate to use this measure of treatment effect in an ITC, although the ERG would be more confident in the validity of the approach of the company had provided detailed justification for the use of RMST in ITCs, including references to published articles describing the methodology used, and an explanation of strengths and limitations of the approach. The ERG notes that these analyses are sometimes based on reasonably short follow-up periods, as shown in Table 21.

For the comparison of nivolumab versus BSC (both all-comers and EGFR mutation-negative/unknown networks), OS data are truncated for inclusion in the ITC at 13 months, as this is the minimum follow-up time of ISEL.[25] Each of the other studies had a minimum follow-up time of at least 25 months for this outcome. Similarly, for the comparison of nivolumab versus nintedanib+docetaxel (both all-comers and EGFR mutation-negative/unknown networks), PFS data are truncated for inclusion in the ITC at 12 months, as this is the minimum follow-up time of LUME-Lung 1.[24] Data from CheckMate 057 also contributed to this ITC and this trial had a minimum follow-up time of 25 months. The ERG is of the opinion that the company applied an appropriate method to overcome the problem of non-PH, but the RMST method is limited in that long-term data cannot be incorporated into the ITCs even if available.

Table 21 Minimum follow-up for each ITC

	All-comers network		EGFR mutation-negative/unknown network	
	OS	**PFS**	**OS**	**PFS**
Nivolumab versus nintedanib+docetaxel	25 months	12 months	28 months	12 months
Nivolumab versus BSC	13 months	N/A	13 months	N/A

BSC=best supportive care; EGFR= epidermal growth factor receptor; N/A=not applicable; OS=overall survival; PFS=progression-free survival

The ERG's interpretation of the ITC results which were calculated using RMST differences (or risk ratios in the case of ORR and AE outcomes) is as follows:

- In the all-comers patient population, no statistically significant differences between nivolumab and nintedanib+docetaxel were found for OS, PFS, ORR or "any AE". Nivolumab was found to statistically significantly reduce the risk of Grade 3/4 AEs in comparison to nintedanib+docetaxel
- In the all-comers patient population, nivolumab was shown to statistically significantly improve OS in comparison to BSC.
- In the EGFR mutation-negative/unknown patient population, no statistically significant differences between nivolumab and nintedanib+docetaxel were found for OS, PFS, or ORR.
- In the EGFR mutation-negative/unknown patient population, no statistically significant differences were observed in terms of OS between nivolumab and BSC.

The ERG noted that variability within the trials would be more likely to affect the indirect comparison of nivolumab versus BSC than the indirect comparison of nivolumab versus nintedanib+docetaxel (see Section 4.3.3). However, it is very difficult to assess how the overall treatment effect estimates would be affected by heterogeneity. The ERG notes that a statistically significant treatment benefit was observed for nivolumab in comparison to BSC in terms of OS for the all-comers network, but not for the EGFR mutation-negative/unknown network. This result is somewhat surprising in that EGFR mutation-negative/unknown patients might be expected to respond better to nivolumab than patients in the all-comers population. This unexpected result could be a consequence of heterogeneity within one or both networks of evidence, which decreases the validity of indirect estimates of treatment effect.

Finally, the ERG notes that it is not possible to assess whether the patient populations of the trials included in the EGFR mutation-negative/unknown network are comparable, since no baseline characteristics for the EGFR mutation-negative/unknown subgroup of CheckMate

057 were presented. Consequently, it is possible that there may be important differences between this subpopulation and the trial populations of other trials included in the EGFR mutation-negative/unknown network. This issue introduces uncertainty as to the validity of estimates of treatment effect generated for this network.

4.4 Summary and critique of supportive evidence from non-randomised studies

In addition to the Phase III RCT (CheckMate 057), evidence from two non-RCTs was also submitted by the company: a Phase IIIb/IV, open-label study (CheckMate 153[22]) and a single-arm Phase I dose-escalation study (CheckMate 003[23]). The characteristics and findings relating to these trials are reported in the CS in Section 4.11.

4.5 Conclusions of the clinical effectiveness section

The primary data provided in the CS are derived from CheckMate 057 and an ITC that is limited by the use of HRs and a lack of data to allow for comparison with all of relative comparators listed in the scope. Comparison is therefore limited to nivolumab with docetaxel, nintedanib+docetaxel and BSC.

CheckMate 057 is a well conducted trial however the use of HRs in the analysis of the data cannot be considered a reliable estimate of treatment effectiveness as the CS points out that the proportional hazards assumption is violated for both OS and PFS. This limitation is also true of the ITC where only RMST analysis should be considered. The ITC is also limited by the differences in the patient populations of patients included in the analysis (e.g. inclusion of patients with squamous disease, Asian population, length of follow-up etc.) Since it is expected that nintedanib+docetaxel will replace the use of docetaxel alone in the treatment of these patents then consideration of the comparison of nivolumab to this combination treatment is important. The results of the ITC show no difference in terms of OS, PFS, ORR or AE in the 'all comer' or EGFR mutation-negative/unknown populations. The comparison with BSC provides mixed results demonstrating the effectiveness of nivolumab versus BSC in the all-comers group but not in the EGFR mutation-negative/unknown patients, raising concerns that there were differences in the patient populations in the trials used in the ITC.

The CS indicates that the AE experienced by patients receiving nivolumab will be fewer than those experienced by patients receiving nintedanib+docetaxel. The ERG is of the opinion that although the comparative data are limited that patients receiving docetaxel do have a higher rate of Grade 3-4 AEs and it would be expected this would be at least the same when docetaxel was given in combination with nintedanib.

The company makes a claim that OS in the patients receiving docetaxel in CheckMate 057 is longer then would be expected. Examination of data from other similar trials does not substantiate this claim. The CS also makes a claim that the pseudo progression seen in patients receiving nivolumab would have an effect on OS. The ERG is not convinced that the data presented support this claim.

Subgroup analyses suggest that nivolumab is statistically significantly more effective in patients with higher PD-L1 expression levels than those with lower PD-L1 expression levels. The report is however somewhat inconsistent with regards to where all patients should therefore be tested for PD-L1.

5 COST EFFECTIVENESS

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 provided an electronic version of the economic model which was developed in Microsoft Excel.

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Objective of cost effectiveness review

The company performed a search to identify economic evaluations, resource use and costs and utility values. The full search strategies are documented in Appendix 11 of the CS and are outlined in Section 5.1.1. The search was performed in February 2015 using the following databases: MEDLINE; MEDLINE in Process; EMBASE; EconLIT, NHSEED, CENTRAL and HTAD. The reported population terms and drug names in the database strategies were considered to be comprehensive by the ERG. Both an economics search filter and a health related quality of life (HRQoL) search filter were added to the search, and consequently the results were not limited to cost effectiveness alone. The searches carried out in EconLit included only NSCLC search terms; the ERG deems this approach to be appropriate due to the small numbers of studies retrieved from these databases. It is not documented whether any further hand searches were carried out as part of the cost effectiveness searches. The same search strategy was used for the measurement and valuation of health effects searches.

5.1.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria that were used to facilitate study selection are presented in Table 22. The ERG is satisfied that these criteria are relevant to the decision problem.

Table 22 Inclusion/exclusion criteria for the company's cost effectiveness review

	Inclusion criteria	Exclusion criteria
Population	Adults diagnosed with locally advanced or metastatic NSCLC previously treated with at least one previous line of chemotherapy	Patients aged <18 years Patients with stage I-IIIa disease Chemotherapy treatment-naïve patients
Intervention	Nivolumab	Studies investigating first-line treatment for NSCLC Studies assessing nivolumab as an adjuvant or neoadjuvant therapy Studies evaluating nivolumab 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
Comparator	Any pharmacological intervention Placebo BSC Afatinib Docetaxel Erlotinib Gefitinib Nintedanib (in combination with docetaxel) Pemetrexed monotherapy Ceritinib Crizotinib Platinum-based chemotherapy in combination with gemcitabine, vinorelbine, pemetrexed, or a taxane	Non-pharmacological interventions, other than BSC
Outcome	All reported outcomes	-
Study design 1 (S1)*	All economic evaluation studies based on: Cost-effectiveness analysis Cost-utility analysis Cost-minimisation analysis Budget-impact models	Studies reporting only cost and resource use data where no formal economic analysis has been undertaken
Study design 2 (S2)*	Randomised controlled trials Database studies Prospective observational studies Retrospective observational studies	Animal/in vitro studies Single-arm studies Studies with no subgroup data for disease and adult population Reviews, letters to the editors and editorials Conference abstracts prior to 2012
Line of therapy	Second- or further-line of therapy	First-line of therapy
Search timeframe	2000 to 2015 (last 15 years)	Prior to 2000
Language	Only studies with the full-text published in English included	Studies with the full-text published in languages other than English

BSC=best supportive care; NSCLC=non-small cell lung cancer
*Within the single systematic review, two sets of study design criteria (S1 and S2) 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
Source: CS, Table 42

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 non-squamous only population and, furthermore, no studies considered treatment with nivolumab. The company identified four relevant appraisals (Crizotinib [TA296[44]], Erlotinib [TA162[45]], Erlotinib and gefitinib [Review of TA162 and TA175)[46]] and Nintedanib [TA379[43]]) and these were used to inform the development of the company economic model (Table 44 of the CS). Two relevant UK-based cost effectiveness studies[47,48] were also identified by the search. Both studies included patients with NSCLC who had been previously treated (CS, Table 43); one study[47] compared docetaxel with BSC and the other study[48] compared erlotinib with docetaxel. Holmes[47] reported an incremental cost per life year gained (LYG) for docetaxel versus BSC of £13,863. Lewis[48] found erlotinib to be dominant when compared with docetaxel. The models described in these two studies[47,48] and the four relevant models[43-46] submitted previously as part of technology appraisals, all used a three-state partitioned survival model representing progression-free (PF) disease, progressive disease (PD) and death.

5.1.4 Findings from the cost effectiveness review

The company did not identify any studies that evaluated the cost effectiveness of nivolumab compared to any comparator in a non-squamous patient population. Summary details relating to the two UK-based published cost effectiveness studies[47,48] and four published NICE technology appraisals[43-46] considered to be relevant to the company's review question are reported in the CS (Tables 43-44).

5.2 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria and is confident that the company did not miss any relevant published papers at the time of submission. The ERG considers the wider search for published economic literature (e.g. inclusion of 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 non-squamous NSCLC.

5.3 ERG summary and critique of the economic evaluation submitted by the company

5.3.1 Model structure

The company developed a cohort-based partitioned survival model comprising three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. The de novo economic 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 patients with advanced NSCLC (including nivolumab [after chemotherapy] for patients with squamous NSCLC[49] and other metastatic cancers (e.g. Nintedanib TA347,[43] Erlotinib TA258[50] and Bevacizumab TA212[51]). A schematic of the company's model is shown in Figure 7.

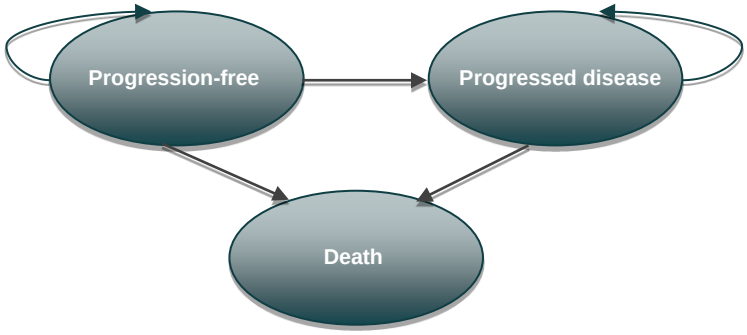


Figure 7 Schematic of company's model

Source: CS, Figure 26

The base case evaluates the cost effectiveness of nivolumab compared with (i) docetaxel and (ii) nintedanib+docetaxel. These two comparators represent the current standard of care in the second-line setting in the UK NHS. Patients who have failed platinum-based chemotherapy enter the model in the PF health state. Patients who remain in PF are treated with nivolumab, docetaxel or nintedanib+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. Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and quality adjusted life years (QALYs) per cycle. In the model, cycle length is 1 week to accommodate the different dosing regimens of nivolumab (every 2 weeks) and docetaxel (every 3 weeks). All patients are treated until treatment discontinuation, which may be beyond progression, and this is consistent with the CheckMate 057 protocol.[52]

In the company model the PF health state occupancy is modelled using time to treatment discontinuation (TTD), rather than PFS. This means that costs and utilities are based on actual treatment duration. The ERG does not recommend the use of TTD data for the estimation of treatment benefit/utilities.

5.3.2 Population

The economic evaluation considers previously treated adult patients with advanced or metastatic non-squamous NSCLC, which is consistent with the decision problem, expected marketing authorisation and population included in CheckMate 057. This patient population is a subgroup of the population described in the final NICE scope.

5.3.3 Interventions and comparators

In the model, nivolumab treatment is implemented 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. The company also compares nivolumab with nintedanib+docetaxel, nintedanib is taken as two tablets per day on a 21-day cycle and docetaxel is 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 non-squamous NSCLC in the UK,[21] the company assumes that it is the treatment most likely to be displaced by the introduction of nivolumab.

Subsequent treatments

In the model it is assumed that nivolumab and docetaxel are second-line treatments and that patients can only receive one further line of therapy following progression (third-line therapy). However, the company did not provide details about the duration of subsequent treatments used in CheckMate 057. The duration of third-line therapy was derived from real world data (RWD) as reported in an observational study (CA209-116[53]) in which treatment patterns, outcomes and healthcare resource use in patients with advanced NSCLC in Europe were investigated. In the model, the time until treatment discontinuation in patients in a third-line setting is reported to be [redacted] days.

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 a

previous NICE STA[49] in this disease area (Table 45 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; a half-cycle correction is implemented in the model.

5.3.5 Treatment effectiveness and extrapolation: nivolumab versus docetaxel

The company economic model relies on patient level data from CheckMate 057. 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 TTD data from the trial was necessary to enable the partitioned survival method to be used. Extrapolation involved the identification of suitable parametric survival models for OS and TTD data.

Overall survival

Log-cumulative hazards, log-cumulative odds and standardised normal curve plots were generated to determine whether patient level data from CheckMate 057 indicated proportional hazards. The analyses that were carried out by the company confirmed that the assumption of proportional hazards did not hold for OS. Therefore, both independent survival models and single survival models adjusted for shape and scale were then assessed. The Akaike Information Criterion and Bayesian Information Criterion goodness-of-fit values for the selected parametric distributions and long-term clinical plausability of the extrapolated model were used to establish the best fitting survival model. As stated by the company (CS, p149), the long-term clinical plausibility of the extrapolated model was based on validation against available nivolumab clinical study data with longer follow-up than CheckMate 057: CheckMate 003,[54] the National Lung Cancer Audit (NLCA) registry[10] (UK) and input from UK clinicians. NLCA data[10] were available for up to 5 years.

According to the company, in terms of statistical fit, the three best-fitting parametric survival models for nivolumab are the 2-knot spline, log-normal and generalised gamma distributions. Correspondingly, the three best-fitting parametric survival models are the gamma, generalised gamma and 1-knot spline distributions for docetaxel. Based on all of the evidence (statistical and visual fit, validation against CheckMate 003[54] and NLCA data[10] clinical input and NICE DSU guidance[55]), the generalised gamma model was used in the company base case for OS extrapolation of nivolumab and docetaxel.

Time to treatment discontinuation

The choice of a parametric survival model for TTD was informed by assessment of whether the assumption of proportional hazards was violated. This was performed by visual inspection of the log-cumulative hazards, log-cumulative odds, and standardised normal curve plots. The results of the Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time indicated that the null hypothesis for proportional hazards should be rejected ($p<0.05$).

In terms of statistical fit, the two best-fitting parametric survival models for nivolumab are the 1-knot spline odds and generalised gamma. Correspondingly, the two best-fitting parametric survival models are the generalised gamma and gamma distribution for docetaxel. The company determined that the generalised gamma model should be used as the base case for TTD extrapolation for nivolumab and docetaxel (Table 23) on the grounds that the generalised gamma distribution provided a good fit for both treatment arms in terms of goodness-of-fit statistics and internal validation against long-term nivolumab clinical study data (CheckMate 003[56]). The company also noted that using the generalised gamma model maintained consistency between the functional forms used for OS and TTD extrapolation.

Table 23 Summary of survival distributions for TTD and OS used in the base case

Survival models explored	Best-fitting parametric curve
Time to treatment discontinuation	
Base case	Docetaxel: Generalised gamma Nivolumab: Generalised gamma
Scenario analysis	Docetaxel: Gamma Nivolumab: 1-knot spline odds
Overall survival	
Base case	Docetaxel: Generalised gamma Nivolumab: Generalised gamma
Scenario analysis	Docetaxel: Gamma Nivolumab: 2-knot spline hazards

Source: CS, Table 52

Nivolumab versus nintedanib+docetaxel comparison

K-M graphs from the LUME-Lung 1[24] trial (nintedanib+docetaxel versus docetaxel+placebo) were digitised by the company to estimate proxy patient-level data. Specifically, data for the adenocarcinoma population were used in the analysis. According to the company, it is indicated that there is no difference in OS between nintedanib+docetaxel versus docetaxel+placebo up to 6 months, thus the HR is assumed to be 1 to this time point. An estimated HR of 0.75 was assumed for ≥6 months. For PFS, a HR of 1 is assumed up to 2

months and a HR of 0.98 is assumed for ≥ 2 months. Table 24 summarises the output of this analysis.

Table 24 Summary of OS and PFS hazard ratios for nintedanib+docetaxel

Efficacy	HR	95% CI
OS after 6 months	0.75	(0.60 to 0.93)
PFS after 2 months	0.98	(0.73 to 1.33)

CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival
Source: CS, Table 74

In the economic model, the HRs applied to the docetaxel data to estimate the nintedanib+docetaxel patient flows, according to the relevant time points, are outlined in Table 24.

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. The utility values incorporated into the model are those derived from CheckMate 057. Utility data were collected in the trial using the EuroQol-5D preference-based health state utility questionnaire (EQ-5D Utility Index). The schedule of EQ-5D assessments is outlined in Table 25.

Table 25 Schedule of EQ-5D assessments in CheckMate 057

EQ-5D assessment schedule	On-study assessment			Follow-up assessment (visit 1 and 2)	Survival assessment (beyond 100 days from the last study dose)
	Every 4 weeks for the first 6 months	Every 3 weeks for the first 6 months	Every 6 Weeks thereafter	Within the first 100 days from the last dose of study	Every 3 months for the first 12 months, and every 6 months thereafter
Nivolumab	✓		✓	✓	✓
Docetaxel		✓	✓	✓	✓

EQ-5D=EuroQol 5-Dimension
Source: CS, Table 55

In all, 82.2% of nivolumab patients and 76.6% of docetaxel patients completed the EQ-5D assessment at baseline. For baseline and at least one post-baseline visit, completion rates fell to 70.5% and 69.7% for nivolumab and docetaxel, respectively. No adjustments were made for missing data when analysing the EQ-5D data. Data from screening visits (up to 28 days before) were used in place of missing baseline data.

The mean utility values derived from patients with advanced NSCLC based on the analysis of CheckMate 057 (using a UK scoring algorithm[57]) are 0.688 (PD) and 0.739 (PF) with an overall utility of 0.728 across all disease states. The HRQoL of patients with advanced NSCLC is lower than the mean utility value of 0.86 that is derived from a representative sample of adults drawn from a national Health Survey of England in 2008.[58] The utility values used in the economic model are summarised in Table 26.

Table 26 UK-specific mean EQ-5D values by health state

Tumour response category (N=number of assessments)	UK (Mean)	Standard deviation	95% CI
Overall (N=1132)	0.728	NA	NA
PD (N=219)	0.688	0.298	0.665 to 0.712
PF (including SD/PR/CR) (N=913)	0.739	0.233	0.729 to 0.748

CI=confidence interval; CR=complete response; NA=not available; PD=progressive disease; PF=progression-free; PR=partial response; SD=stable disease; UK=United Kingdom
Sources: CS, Table 56

Adverse events

The economic model incorporates the quality of life impact of treatment related AEs of Grade 3 or higher severity which occurred in ≥2% of patients in CheckMate 057. The disutility per episode for the included AEs is shown in Table 27. The expected disutility per patient was calculated according to the incidence rates of the included AEs from CheckMate 057 according to treatment arm, this was applied separately in the first cycle only (i.e. without discounting) as a single disutility quantum. Disutility values could not be identified for all AEs; therefore, in the base case, where information was not available, a disutility of 0 was assumed. In addition to the AE disutility applied in the first cycle, the company applied the disutility of each AE separately.

Table 27 Disutilities of AEs

Adverse event	Disutility	Reference
Fatigue	-0.07346	Nafees 2008[59]
Asthenia	-0.07346	Nafees 2008[59]
Pain	0	Assumption
Dyspnoea	-0.050	Doyle 2008[60]
Pleural effusion	0	Assumption
Hyperglycemia	0	Assumption
Pneumonia	-0.008	Marti 2013[61]
Neutrophil count decreased	0	Assumption
White blood cell count decreased	-0.05	NICE 2015[43]
Anaemia	-0.07346	Nafees 2008[59]
Neutropenia	-0.08973	Nafees 2008[59]
Febrile neutropenia	-0.09002	Nafees 2008[59]
Leukopenia	-0.08973	Nafees 2008[59]
Diarrhoea	-0.0468	Nafees 2008[59]
Increased ALT	-0.05	NICE 2015[43]
Increased AST	0	Assumption
Hyponatraemia	0	Assumption

ALT=alanine Aminotransferase; AST=aspartate Transaminase
Source: CS, Table 57

The AE data in the economic model for nintedanib+docetaxel were taken directly from the LUME-lung 1[24] trial. Table 28 presents the proportion of patients experiencing Grade 3-4 AEs (≥2% incidence).

5.3.7 Resources and costs

Intervention costs

The drug acquisition costs by pack/vial size and the acquisition costs of each treatment cycle for the treatments are presented in Table 29 and Table 30 respectively.

Table 28 AEs included in the economic model based on LUME-Lung 1 (Grade 3 and 4 severity)

Type of AE	Rate for nintedanib+docetaxel
Fatigue	5.5%
Asthenia	2.0%
Pain	0.0%
Dyspnoea	4.9%
Pleural effusion	1.0%
Hyperglycemia	1.1%
Pneumonia	2.6%
Neutrophil count decreased	32.0%
White blood cell count decreased	16.4%
Anaemia	1.1%
Neutropenia	12.1%
Febrile neutropenia	7.0%
Leukopenia	2.9%
Diarrhoea	6.5%
Increased ALT	7.8%
Increased AST	3.4%
Hyponatraemia	2.1%

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate transaminase
Source: CS, Table 75, Reck 2014[24]

Table 29 Drug acquisition costs (initial treatments)

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 60)
		10ml	£1,097.00 (£10.98/mg)	
Docetaxel	10mg/ml	2ml	£7.45 (£0.37/mg)	eMit[62]
		8ml	£25.73 (£0.32/mg)	
		16ml	£35.35 (£0.22/mg)	
Dexamethasone	-	100 tablets	£5.16 cost per 21-day cycle	eMit[62]
Nintedanib	150mg	60 tablets	£2,151.10	PharmaTimes[63]

BNF=British National Formulary; NICE=National Institute for Health and Care Excellence; UK=United Kingdom
Source: CS, Table 60

Table 30 Drug acquisition cost per dose (initial treatments)

Drug	Total dose per administration	No. of vials per packs	Method of administration	Total drug cost per dose	Frequency of administration
Nivolumab	3mg/kg	1.19 × 10-ml vial*+ 1.84 × 4-ml vial	IV; no vial sharing (i.e. round up to nearest full vials)	£2,538.25	Every 2 weeks
Docetaxel	75mg/m^2	1.79 × 2-ml + 0.65 × 8 ml + 0.35 × 16-ml* + dexamethasone	IV; no vial sharing (i.e. round up to nearest full vials)	£47.59	Every 3 weeks
Nintedanib + docetaxel	-	2 tablets per day × 21 days plus the cost per dose of docetaxel	Oral	£1,553.29	2 tablets a day for 21 days =1 dose

IV=Intravenous
*The 4-ml vial (nivolumab) and 16-ml vial (docetaxel) are used in the base case because these are the smallest and cheapest vial sizes, respectively
Source: CS, Table 61

Subsequent treatments

The model includes costs of subsequent treatments for patients with PD based on the distribution of subsequent therapies observed in CheckMate 057. Table 31 presents drug acquisition costs per dose for these subsequent treatments. The treatment duration for all subsequent therapies is [redacted], based on RWD collected in an observational study (CA209-116[53]) in which the treatment patterns, resource use and outcomes of patients with advanced NSCLC in Europe were explored. The company made an assumption that the pooled RWD collected from European countries were applicable to clinical practice in the UK.

Table 31 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
Pemetrexed	500mg/m^2	2.15 × 500-ml vials	IV; no vial sharing (i.e. round up to nearest full vials)	£1,723.02	Every 3 weeks
Carboplatin	400mg/m^2	0.80 × £3.43 + 1.22 × £7.69 + 1.15 × £20.17	IV; no vial sharing (i.e. round up to nearest full vials)	£35.42	Every 4 weeks
Gemcitabine	1,000mg/m^2	1.44 × 200mg + 5.63 1,000mg	IV; no vial sharing (i.e. round up to nearest full vials)	£56.20	Every 4 weeks (once per week for 3 weeks, followed by 1 week off treatment)
Docetaxel	75mg/m^2	1.79 × 2-ml + 0.65 × 8-ml+ 0.35 × 16-ml + dexamethasone	IV; no vial sharing (i.e. round up to nearest full vials)	£47.59	Every 3 weeks
Erlotinib	150mg	1/30 pack (30 × 150mg)	Oral; vial sharing is N/A	£54.38	Daily

IV=Intravenous; N/A=not applicable
Source: CS, Table 63

Treatment administration costs

The costs of treatment administration for nivolumab and docetaxel, as applied in the model, are shown in Table 32.

Table 32 Cost per administration

Treatment	Type of administration		Currency code	Cost per administration*	Source
Nivolumab	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z	£167.34	NHS reference costs 2013-2014[64]
Docetaxel	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z	£167.34	NHS reference costs 2013-2014[64]

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.
Source: CS, Table 64

Health care costs

Patient monitoring, disease management and terminal care costs are provided in Table 33. A one-off, end of life/terminal care cost is applied to patients who enter the death state. These weighted costs reflect treatment received in various care settings.

Table 33 Health care costs

Type of cost	Health state	Cost*
Monitoring cost – nivolumab, docetaxel or nintedanib+docetaxel	Progression-free	£151.89 per 4 weeks
Disease management	Progression-free	£313.55 per 4 weeks
Disease management	Progressed disease	£766.62 per 4 weeks
Terminal care	Death	£3,628.70 (one off)

*2015 National Reference Costs for unit costs were unavailable at the time of submission, the company inflated costs to June 2015 values
Source: Adapted from CS, Tables 65-69

Adverse event costs

The base case analysis includes all Grade 3-5 AEs (regardless of causality) with ≥2% incidence in the nivolumab or docetaxel arms of CheckMate 057. AE costs and management costs per episode were sourced from NHS Reference Costs[65] guided by the currency codes used in recent NICE submissions in NSCLC and melanoma.[9,43,46] A summary of costs is presented in Table 34.

Table 34 Cost of adverse events

AEs from CheckMate 057	Cost per episode*	Mean number of episodes per AE treatment course	Source
Fatigue	£3,015.13	1	NHS Reference Costs 2013-2014[64]
Asthenia	£3,015.13	1	NHS Reference Costs 2013-2014[64]
Pain	£122.00	1	NHS Reference Costs 2013-2014[64]
Dyspnoea	£0.00	1	Assumption based on ipilimumab NICE STA submission for melanoma[9]
Pleural effusion	£553.00	1	NHS Reference Costs 2013-2014[64]
Hyperglycemia	£652.00	1	NHS Reference Costs 2013-2014[64]
Pneumonia	£1,822.85	1	NHS Reference Costs 2013-2014[64]
Neutrophil count decreased	£0.00	1	Assumption
White blood cell count decreased	£423.00	1	NICE 2015[43]
Anaemia	£978.00	1	NICE 2015[43]
Neutropenia	£354.72	1	NHS Reference Costs 2013-2014[64]
Febrile neutropenia	£5,489.94	1	Erlotinib and gefitinib (post-chemotherapy) MTA (rev TA162, TA175) [ID620]
Leukopenia	£354.72	1	Assumed to be same as neutropenia based on medical opinion
Diarrhoea	£1,796.00	1	NICE 2015[43]
Increased ALT	£587.00	1	NICE 2015[43]
Increased AST	£336.00	1	NICE 2015[43]
Hyponatraemia	£652.00	1	Assumed to be same as hyperglycaemia based on medical opinion

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate transaminase; ID=in development; MTA=multiple technology appraisal; NHS=National Health Service; TA=technology appraisal
*All adverse event costs originating from pre-2015 sources are inflated to June 2015 values
Source: CS, Table 71

5.3.8 Cost effectiveness results

Base case results

The base case analysis was based on the generalised gamma curves for all extrapolations (OS and TTD). Life years were undiscounted. In comparison to docetaxel, nivolumab generated 0.73 incremental QALYs and 1.15 incremental life years, and the nivolumab-treated cohort incurred an increase in total costs. The incremental cost effectiveness ratio (ICER) was £103,589 per QALY gained. Total costs, LYG, QALYs, and incremental cost per QALY gained for nivolumab versus docetaxel are presented in Table 35.

In comparison to nintedanib+docetaxel, nivolumab generated 0.49 incremental QALYs and 0.80 incremental life years with a higher total cost. The ICER was £126,861 per QALY gained. Expected QALYs for nivolumab, docetaxel and nintedanib+docetaxel disaggregated

by health state are shown in Table 36 and Table 37. Predicted (per patient) resource use costs included in the company model are presented in Table 38 and Table 39.

Table 35 Base case results

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	93,306	2.24	1.42				
Docetaxel	17,854	1.09	0.70	75,452	1.15	0.73	103,589
Nintedanib +docetaxel	30,708	1.44	0.93	62,598	0.80	0.49	126,861

LYG=life year gained; QALY=quality adjusted life year
Source: CS, Table 76

Table 36 Summary of QALY gain per patient by health state - nivolumab vs. docetaxel

Health state	QALY intervention (nivolumab)	QALY comparator (docetaxel)	Incremental QALYs	% absolute incremental QALYs
PF	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

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 79

Table 37 Summary of QALY gain per patient by health state - nivolumab vs. nintedanib+docetaxel

Health state	QALY intervention (nivolumab)	QALY comparator (nintedanib+docetaxel)	Incremental QALYs	% absolute incremental QALYs
PF	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

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 80

Table 38 Discounted cost per patient (disaggregated) - nivolumab vs. docetaxel

Health state	Cost intervention (nivolumab)	Cost comparator (docetaxel)	Incremental costs	% absolute incremental costs
Disease management cost: PF	[redacted]	[redacted]	[redacted]	[redacted]
Disease management cost: PD*	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Total treatment cost	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; PD=progressed disease; PF=progression-free
*PD includes the costs of managing patients who have progressed and end-of-life and terminal care. No costs are assigned to the death state
Source: CS, Table 80

Table 39 Discounted cost per patient (disaggregated) - nivolumab vs. nintedanib+docetaxel

Health state	Cost intervention (nivolumab)	Cost comparator (nintedanib+docetaxel)	Incremental costs	% absolute incremental costs
Disease management cost: PF	[redacted]	[redacted]	[redacted]	[redacted]
Disease management cost: PD*	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Total treatment cost	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE=adverse event; PD=progressed disease; PF=progression-free
*PD includes the costs of managing patients who have progressed and end-of-life and terminal care. No costs are assigned to the death state
Source: CS, Table 81

5.3.9 Sensitivity analyses

Deterministic sensitivity analysis

One-way sensitivity analyses of nivolumab versus docetaxel and nivolumab versus nintedanib+docetaxel were undertaken by varying cost, utility and OS base case parameter values by their confidence intervals or +/-20%, based on data availability (Table 40 and Table 41).

Table 40 Results of deterministic analysis vs. docetaxel

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		75,452	0.73	103,589
Discount rate: costs	Lower	85,895	0.73	117,928
	Higher	69,973	0.73	96,068
Discount rate: outcomes	Lower	75,452	0.88	85,753
	Higher	75,452	0.65	116,472
Average body weight	Lower	63,650	0.73	87,386
	Higher	87,528	0.73	120,169
BSA	Lower	75,500	0.73	103,655
	Higher	75,360	0.73	103,463
				Costs
Cost: PF state	Lower	74,908	0.73	102,843
	Higher	75,995	0.73	104,335
Cost: PD state	Lower	74,911	0.73	102,848
	Higher	75,992	0.73	104,331
Terminal cost	Lower	75,481	0.73	103,630
	Higher	75,422	0.73	103,549
Administration cost: nivolumab	Lower	74,567	0.73	102,375
	Higher	76,336	0.73	104,804
Administration cost: docetaxel	Lower	75,639	0.73	103,847
	Higher	75,264	0.73	103,331
Monitoring cost: nivolumab	Lower	75,054	0.73	103,043
	Higher	75,849	0.73	104,135
Monitoring cost: docetaxel	Lower	75,572	0.73	103,755
	Higher	75,331	0.73	103,424
				Outcomes
Utility weight, PFS	Lower	75,452	0.72	104,546
	Higher	75,452	0.73	102,743
Utility weight, PD	Lower	75,452	0.72	104,484
	Higher	75,452	0.73	102,672

BSA=body surface area; PD=progressed disease; PF=progression-free; PFS=progression-free survival; QALY =quality adjusted life year
Source: CS, Table 104

Table 41 Results of deterministic analysis versus nintedanib+docetaxel

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		62,598	0.49	126,861
Discount rate: costs	Lower	72,736	0.49	147,407
	Higher	57,308	0.49	116,141
Discount rate: outcomes	Lower	62,598	0.63	99,830
	Higher	62,598	0.42	147,671
Average body weight	Lower	50,796	0.49	102,943
	Higher	74,674	0.49	151,335
BSA	Lower	62,646	0.49	126,959
	Higher	62,506	0.49	126,676
Costs				
Cost: PF state	Lower	62,058	0.49	125,767
	Higher	63,138	0.49	127,956
Cost: PD state	Lower	62,686	0.49	127,040
	Higher	62,510	0.49	126,683
Terminal cost	Lower	62,663	0.49	126,993
	Higher	62,533	0.49	126,730
Administration cost: nivolumab	Lower	61,713	0.49	125,069
	Higher	63,482	0.49	128,654
Administration cost: docetaxel	Lower	62,809	0.49	127,289
	Higher	62,387	0.49	126,433
Monitoring cost: nivolumab	Lower	62,200	0.49	126,055
	Higher	62,996	0.49	127,668
Monitoring cost: docetaxel	Lower	62,734	0.49	127,137
	Higher	62,462	0.49	126,585
Outcomes				
Utility weight, PFS	Lower	62,598	0.49	128,588
	Higher	62,598	0.50	125,347
Utility weight, PD	Lower	62,598	0.49	126,601
	Higher	62,598	0.49	127,134
Survival outcomes				
HR on PFS: nintedanib+docetaxel	Lower	60,246	0.49	123,209
	Higher	64,293	0.50	129,442
HR on OS: nintedanib +docetaxel	Lower	59,328	0.28	214,630
	Higher	65,217	0.66	98,353

BSA=body surface area; PD=progressed disease; PF=progression-free; PFS=progression-free survival; QALY=quality adjusted life year
Source: CS, Table 105

Scenario analyses

The scenario analyses involved varying the survival modelling approaches applied to OS and TTD data and duration of treatment. With regards to the alternative treatment duration scenarios, treatment stopping rules were implemented by terminating all treatment-related costs (i.e. acquisition, administration and monitoring) at either 1 or 2 years. The treatment stopping rule was applied in order to represent patients who experienced a durable response i.e. maintenance of clinical benefit after treatment discontinuation prior to progression. The influence of each change on the size of ICER per QALY gained is presented in Table 42.

Table 42 Scenario analyses results

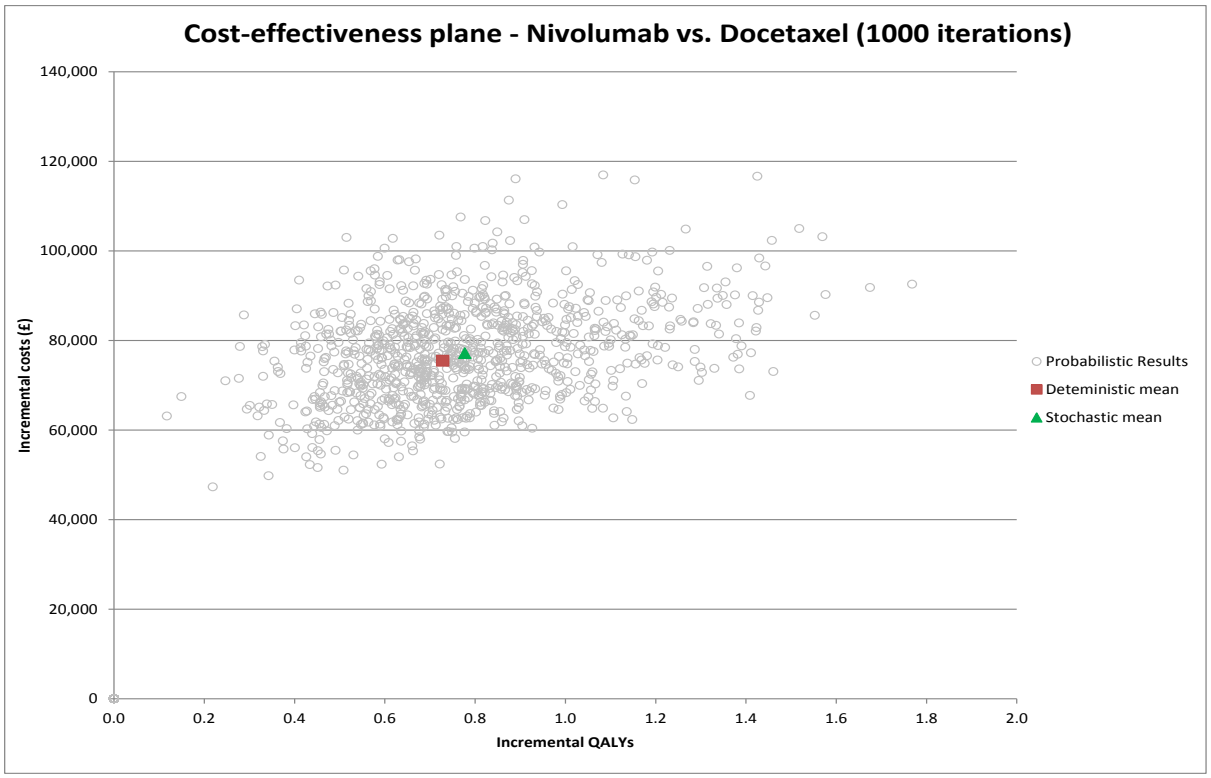
Description	ICER per QALY gained
Base case – nivolumab vs. docetaxel	£103,589
Base case – nivolumab vs. nintedanib+docetaxel	£126,861
Survival analysis - OS	
2-knot spline hazards model for nivolumab and gamma distribution for docetaxel – nivolumab vs. docetaxel	£144,594
2-knot spline hazards model for nivolumab and gamma distribution for docetaxel– nivolumab vs. nintedanib+docetaxel	£195,348
Survival analysis - TTD	
1-knot spline hazards model for nivolumab and gamma distribution for docetaxel – nivolumab vs. docetaxel	£120,773
1-knot spline hazards model for nivolumab and gamma distribution for docetaxel – nivolumab vs. nintedanib+docetaxel	£149,112
Duration of treatment	
1-year treatment stopping rule for nivolumab - nivolumab vs. docetaxel	£46,860
1-year treatment stopping rule for nivolumab - nivolumab vs. nintedanib+docetaxel	£43,122
2-year treatment stopping rule for nivolumab - nivolumab vs. docetaxel	£60,955
2-year treatment stopping rule for nivolumab - nivolumab vs. nintedanib+docetaxel	£63,928

ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation
Source: CS, adapted from Tables 108, 111, 114, 117

Probabilistic sensitivity analysis

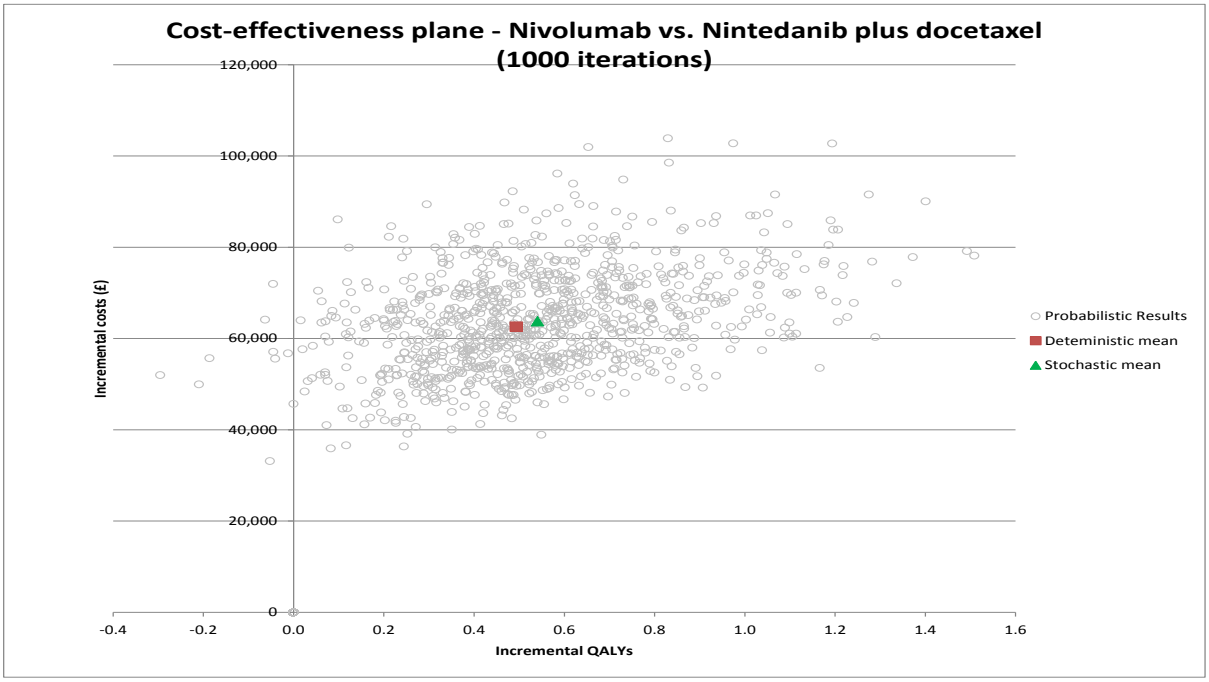
The company undertook probabilistic sensitivity analysis (PSA) to derive the mean ICER per QALY gained for nivolumab versus docetaxel and nivolumab versus nintedanib+docetaxel. The PSA was run for 1000 iterations. The probabilistic ICER versus docetaxel is £99,291 per QALY gained compared with £103,589 per QALY gained in the deterministic analysis. The probabilistic ICER versus nintedanib+docetaxel is £111,934 per QALY gained compared with £126,861 per QALY gained in the deterministic analysis. For these comparisons, the

cost effectiveness planes are shown in Figure 8 and Figure 9 and the cost effectiveness acceptability curve for both comparators is shown in Figure 10.



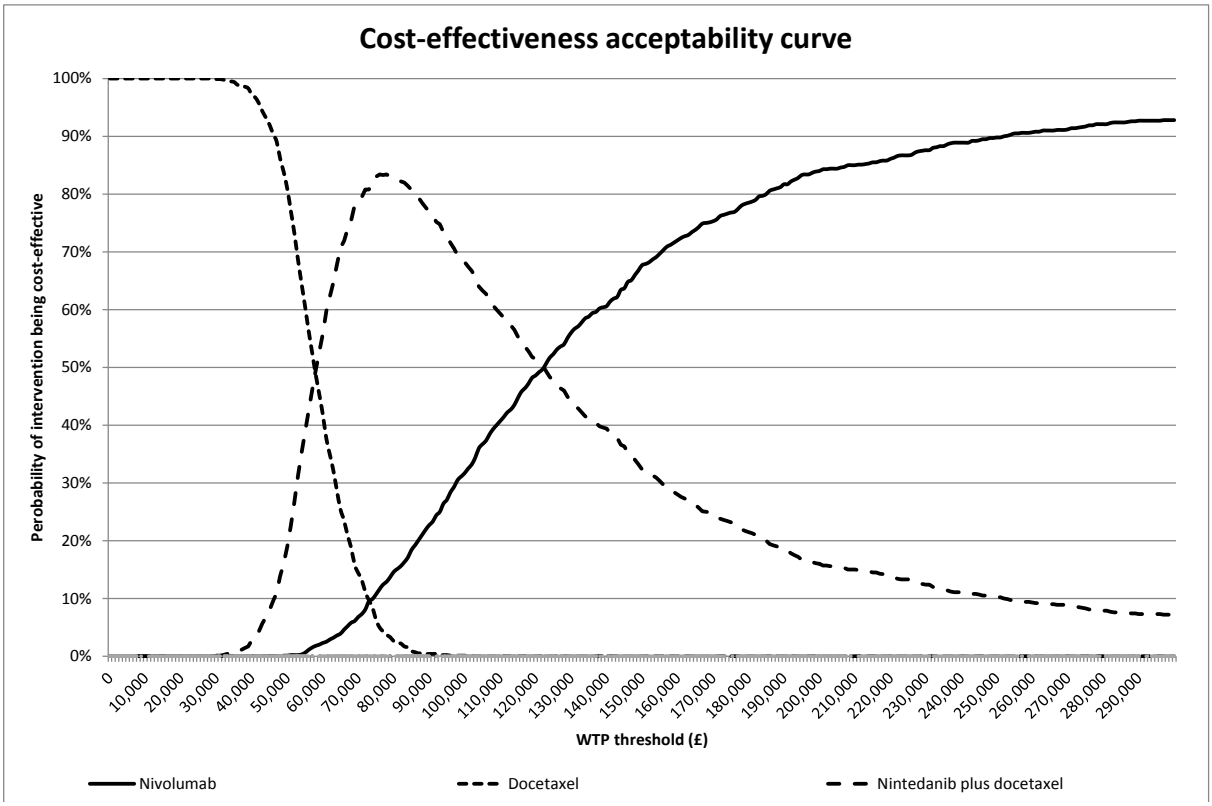
QALY=quality adjusted life year
Source: CS, Figure 43

Figure 8 Scatter plot-cost effectiveness of nivolumab vs. docetaxel (1,000 iterations)



QALY=quality adjusted life year
Source: CS, Figure 44

Figure 9 Scatter plot for cost effectiveness of nivolumab vs. nintedanib+docetaxel (1,000 iterations)



WTP=willingness to pay
Source: CS, Figure 45

Figure 10 Cost effectiveness acceptability curve of nivolumab vs. docetaxel and nintedanib+docetaxel

5.3.10 Model validation and face validity check

The company states that their survival models were validated against data from CheckMate 057,[28] CheckMate 003[54] and the NLCA dataset.[10] In addition, during model development, external clinical and health economic experts attended four workshops and provided advice during ad hoc consultations.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

5.4.1 NICE reference case and Drummond critical appraisal

A summary of the checklists for the reference case and the Drummond critical appraisal are presented in Table 43 and Table 44.

Table 43 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial. BSC was not subject to a full economic evaluation
Perspective costs	NHS and PSS	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
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
Form 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 outcomes	Based on systematic review	Yes – data primarily taken from CheckMate 057
Outcome measure	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
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Benefits and costs have been discounted at the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Partial. NHS costs, valued at relevant prices, have been used. PSS costs are not included in the model

EQ-5D=EuroQol 5-dimension; 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

Table 44 Critical appraisal checklist for the 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	Limited data available from Checkmate 057
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?	Yes	-
Were the cost and consequences valued credibly?	Partially	The ERG considers that the company's OS and PFS/TTD 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
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

ICER=incremental cost effectiveness ratio; PFS=progression-free survival; TTD= time to treatment discontinuation

5.5 The company model

The company's Microsoft Excel spreadsheet model is constructed according to conventional practice and is generally implemented correctly. The company is to be commended for taking previous ERG comments into account regarding the implementation of certain features of the model.

5.5.1 Health-state modelling: key issues

The elements of the company's cost effectiveness evidence that cause most concern to the ERG relate to the modelling of patients in two health states: PFS and post-progression survival (PPS). In the model, PPS is based on the modelling of PFS and OS and it is assumed that PPS = OS-PFS. The ERG considers the modelling of PFS, PPS and OS to be flawed for both the intervention and the comparators. The issues become more problematic when nivolumab is compared with nintedanib+docetaxel rather than when compared with

docetaxel monotherapy. The ERG's proposed amendments to the company model have a substantial impact on the size of each of the estimated ICERs per QALY gained.

The specific issues of concern identified by the ERG relate to the modelling of each health state and are compounded by the results of the ERG's examination of subgroups of patients within the group of patients treated with nivolumab; these subgroups have not been discussed in the CS. The ERG identified two distinct patient subgroups according to whether patients received treatment with nivolumab post-progression. Information describing the baseline characteristics of the patient subgroups was not available to the ERG at the time of analysis. Therefore, the ERG cannot ascertain whether there are fundamental differences between the groups other than that some patients received treatment with nivolumab after progression (PPTx) and other patients did not receive nivolumab after progression (no-PPTx).

The specific survival modelling issues identified by the ERG are as follows:

- the interdependence in the model between OS, PFS and all-cause mortality rates results in implausible projections for nivolumab PFS in particular, but also casts doubt on the reliability of the model used to estimate nivolumab OS
- survival gain is predominantly accrued in the PFS state for nivolumab in the company model, whereas the trial evidence suggests that nivolumab has a substantial post-progression benefit over docetaxel. This is particularly true for the PPTx patient subgroup
- the gamma parametric model chosen to model OS for nivolumab is not a good fit to the K-M data from CheckMate 057. The CheckMate 003[23] data used to validate the nivolumab OS model are inappropriate as the survival profiles are different
- TTD data have been used instead of PFS data in all parts of the company model. There are two key issues. First, the projection of TTD data as a proxy for PFS data is implausibly long and results in 85% of patients being still alive at 20 years, remaining progression-free and being on treatment. Second, the ERG considers that TTD data should only be used for estimating costs and not for estimating QALYs accruing in the different health states
-

- the piecewise proportional hazards assumption is not supported for OS or PFS in the LUME-Lung 1[24] trial, which invalidates the company's indirect method of comparing nivolumab with nintedanib+docetaxel.

The ERG deals with several of these issues using its preferred method of modelling survival i.e. using as much direct trial (K-M) data as possible, and only projecting future survival for the subgroup of patients remaining at risk towards the end of the reported trial data. This method ensures that as much of the available trial evidence as possible is used and limits uncertainty to the projection period only.

Other issues identified by the ERG relate to the use of utility values from CheckMate 057, an error in the calculation of nivolumab dosing and the timing of treatment administration costs. The ERG has also performed a sensitivity analysis based on the company's 1- and 2-year stopping rule scenarios.

5.5.2 Nivolumab treatment subgroups

The protocol[52] for the pivotal CheckMate 057 trial notes that there is accumulating evidence that a minority of patients treated with immunotherapy may derive clinical benefit despite exhibiting initial evidence of progressed disease. As a result, patients in the trial were permitted to continue on study treatment beyond progression (as defined by RECIST 1.1) as long as:

- they continued to derive clinical benefit from nivolumab (as assessed by investigator) and did not have rapidly progressing disease;
- they tolerated the drug;
- they had stable PS;
- the intervention to prevent serious complications of disease progression would not be delayed and the subject had provided written consent.

Further progression was defined as an additional 10% increase in tumour volume from the time of the initial progression, at which point treatment was discontinued permanently.

During the clarification process, the ERG requested details of the number of patients treated beyond progression. The ERG also requested survival data split by whether nivolumab patients received treatment-post progression. The ERG did not request clarification data on the baseline characteristics of the different nivolumab treatment subgroups, so is unable to provide the results of further analyses based on more detailed patient information.

As stated in the clarification response, during CheckMate 057, 25% of all nivolumab patients (n=72) had received treatment beyond progression by the 18-month data lock, and 22.5% (n=16) of these patients met the criteria for 'non-conventional benefit'. Non-conventional benefiters are subjects whose best confirmed objective response was not PR/CR and who met at least one of the following:

- appearance of a new lesion followed by decrease from baseline of at least 10% in sum of target lesions; or
- initial increase from nadir >=20% in sum of target lesions followed by reduction from baseline of at least 30%; or
- initial increase from nadir >=20% in sum of target lesions or appearance of new lesion followed by at least 2 tumour assessments showing no further progression defined as 10% additional increase in sum of target lesions and new lesions.

Based on the proportion of nivolumab patients who had received treatment beyond progression at the time of the 18-month data lock, the ERG has assumed that 25% of patients treated with nivolumab are permitted to continue treatment beyond progression. This assumption affects the analysis of PPS and OS, but not PFS.

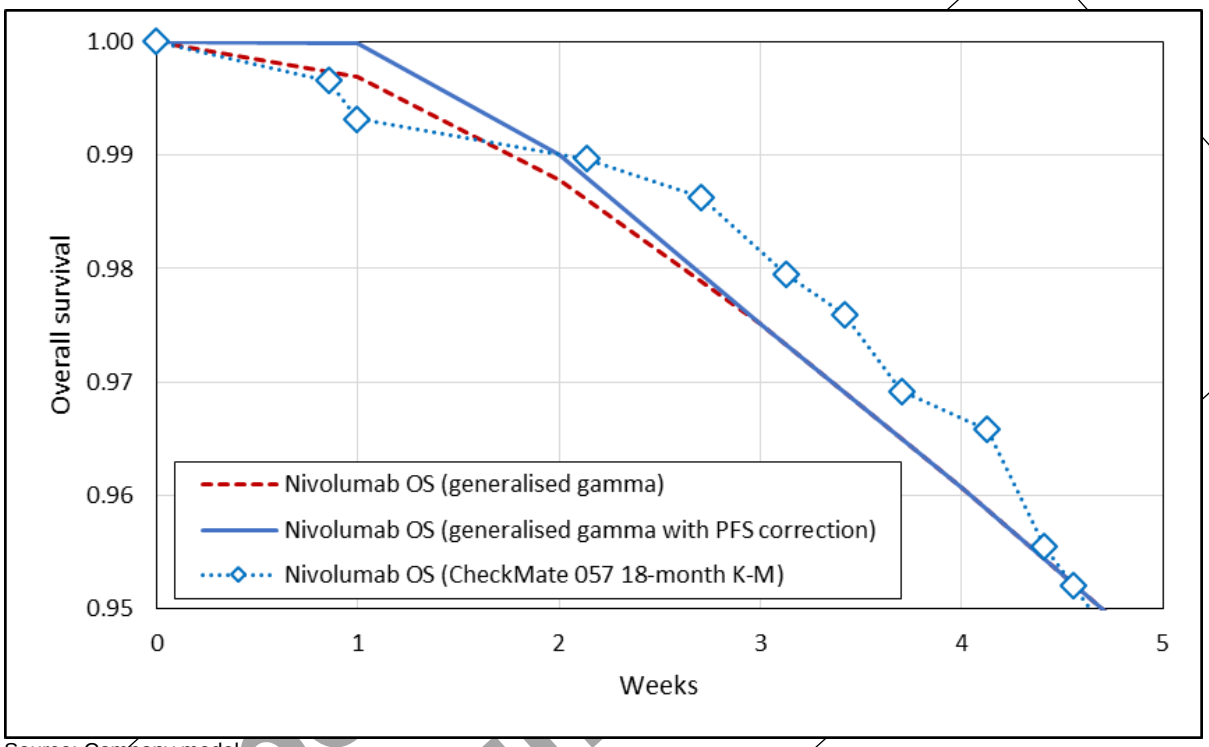
It is not valid to split the PFS K-M data according to whether nivolumab patients were treated beyond progression, as progression is a prerequisite of belonging to the PPTx group. Membership of the post-progression treatment subgroups is decided once a patient has left the progression-free state, so it is not appropriate to reverse-assign them to either the PPTx or no-PPTx group whilst in PFS. If other characteristics were identified that could predict whether a patient would receive treatment beyond progression whilst the patient was still progression-free, then the split would be valid. The ERG has not had access to detailed patient data that might be able to identify such patients before they progress.

5.5.3 Interdependence of health-state models

The company model is built with two 'check and substitute' mechanisms that link PFS, OS and all-cause mortality rates in a way that is not credible and undermines the projection of PFS and OS, particularly for patients receiving nivolumab.

First, OS is linked with PFS to ensure that PFS is never greater than OS for any treatment in the company model. Should the modelled curves result in a greater value for PFS than OS in any given week, the PFS value is used instead of the OS value. It can be seen in Figure 11 that the distribution used to model nivolumab OS produces lower values than the distribution used to model nivolumab PFS in the first 2 weeks. The company model then substitutes PFS

values for OS in the first 2 weeks so that there are not more people in PFS than people who are alive. The choice of parametric distribution for either PFS or OS (or both) is therefore inappropriate, as their combination produces implausible values and cannot be used without adjustment. Figure 11 also emphasises the uncertainty in the fit of the generalised gamma curve to the K-M data during this early period.

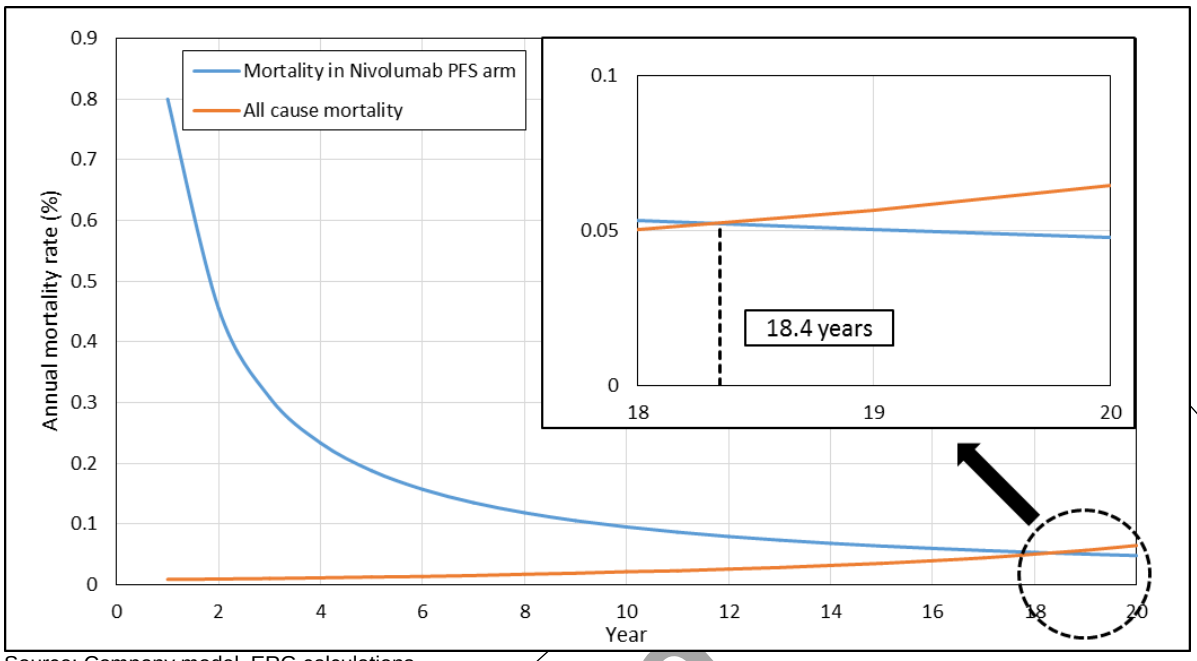


Source: Company model

Figure 11 Nivolumab OS with modelled generalised gamma curve, PFS correction and CheckMate 057 18-month K-M data

Second, the nivolumab arm is subject to a 'check and substitute' mechanism to ensure that disease specific mortality rates do not fall below all-cause mortality rates. Projections for both PFS and OS are compared to age- and sex- adjusted all-cause mortality rates and, should the latter be greater than the modelled rates, a substitution is made.

Figure 12 shows that the gamma model used by the company to model PFS for patients treated with nivolumab projects annual mortality rates that fall below all-cause mortality rates 18.4 years after patients begin treatment. Hence, the model forecasts that any patient who remains in PFS for 18.4 years will never progress and is essentially cured of the disease. This is a very strong assumption for the company to make without providing supporting clinical evidence.



Source: Company model, ERG calculations

Figure 12 Relationship between nivolumab PFS and all-cause annual mortality rates in the company model

5.5.4 Post-progression survival: nivolumab and docetaxel

When compared with docetaxel, the company model estimates that patients treated with nivolumab accrue 31% of mean survival gain during PPS; this 31% gain equates to a survival gain of 4.3 months.

On inspection of the cohort trace for nivolumab (Figure 13), it is clear that the proportion of survival gain attributable to PPS is influenced considerably by the implausibly long PFS tail in the nivolumab arm. In the company model, PFS is modelled with a tail so long that 85% of the nivolumab patients who are still alive at 20 years are in PFS and are still receiving treatment. In comparison, almost all of the patients treated with docetaxel (>99.9%) are estimated to have left the progression-free state by 1.8 years when only 17% of these patients are still alive.

Source: CS, Figure 40

Figure 13 Cohort trace for nivolumab up to 20 years (company model base case analysis)

The ERG considers the PPS estimates from the model to be unreliable as a consequence of a flawed approach to modelling PFS. The ERG therefore requested PPS K-M data from CheckMate 057 to perform an independent analysis.

Examination of the PPS data at the time of the 18-month data lock shows that there is little difference in survival rates for all patients in the nivolumab and docetaxel arms immediately after progression, the curves then separate around 5 months and then converge again at around 20 months (Figure 14). This implies that, compared to docetaxel, nivolumab has only a small incremental effect on PPS. However, the amalgamated all-patient nivolumab PPS data conceal substantial differences between the PPTx and the no-PPTx subgroups. PPS for patients treated with nivolumab until disease progression have PPS indistinguishable from patients treated with docetaxel (log-rank test, p=0.84), whereas patients treated with nivolumab beyond progression have a much better chance of survival post-progression than other patients treated with nivolumab or patients treated with docetaxel (Figure 15).

Source: Clarification response-question B1c

Figure 14 Nivolumab (all patients) vs. docetaxel PPS K-M (18-month data cut)

PPTx=Received treatment post progression; no PPTx=Did not receive treatment post progression
Source: Clarification response-question B1g

Figure 15 Nivolumab (PPTx patients), nivolumab (no PPTx patients) and docetaxel PPS K-M data (18-month data cut)

The effect of these differences in PPS between the PPTx and no-PPTx nivolumab subgroups versus docetaxel depends on the proportion of patients receiving each treatment who die in PFS and on the proportion of patients in each of the nivolumab subgroups.

5.5.5 Overall survival: nivolumab versus docetaxel

The company employed an independent-curve approach to modelling OS for nivolumab and docetaxel, as it noted that proportional hazards models and single survival models were not appropriate due to the crossing of the nivolumab and docetaxel OS curves of CheckMate 057 at around 7 months. The company explored the use of a number of OS models and concluded that separate generalised gamma models had the most appropriate fit to both the nivolumab and docetaxel arms of the trial.

The ERG has identified three flaws in the company approach to modelling OS for patients in the nivolumab arm:

- the chosen gamma curve systematically underestimates most of the K-M data and so represents a poor fit to the nivolumab data from CheckMate 057
- the K-M data from CheckMate 003[23] Phase 1b clinical trial that were used to validate the projection exhibit a different survival profile to the data from CheckMate 057
- the modelled OS curve in the company model does not relate appropriately to the modelled PFS curve, as noted in Section 5.5.3 of this ERG report.

Inspection of the company model OS curve against the 18-month K-M data for nivolumab shows that the fitted distribution systematically underestimates the trial data from 7 months to 20 months (Figure 16). This means that the fitted curve has not adequately incorporated all of the evidence on survival from CheckMate 057 for nivolumab patients who live beyond 7 months and relies too heavily on the pattern of survival during the first 7 months from randomisation. It is desirable to use all of the available clinical data when projecting survival. However, it is not always possible to fit a single parametric curve to the K-M data from time 0 without systematically misrepresenting that data to some extent. The principle objective of fitting a curve to K-M data is to be able to project a trend beyond the limits of available evidence, so it is preferable to closely model trends that are established later in the data and trends that might reasonably be expected to continue in the long-term rather than to seek a

parametric distribution that fits well to earlier K-M data but does not adequately capture the later evidence.

Source: Clarification response-question B1a, company model

Figure 16 Nivolumab OS: 18-month K-M data vs. company model

At the time of writing the CS, the company had only 12 months of data with which to project 20 years of survival. However, the company was able to provide the ERG with 18 months of data during the clarification process. The company attempted to mitigate the uncertainty inherent in extrapolating immature data by comparing potential OS models to other clinical studies and to RWD, namely the single-arm, Phase 1b CheckMate 003[23] trial and the UK's NLCA database.[10]

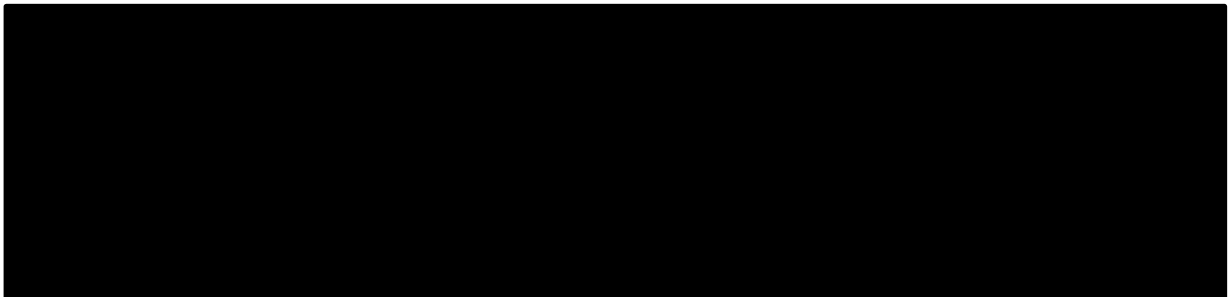
Figure 17 compares the K-M OS data from the CheckMate 057[28] and CheckMate 003[23] trials. It is clear from this plot that the survival profiles differ markedly between the two trials from around 7 months. The ERG therefore considers CheckMate 003[23] trial data to be unsuitable for validating projections based on data from CheckMate 057.

Source: Clarification response-question B1a, BMS 2015h[54]

Figure 17 Nivolumab OS K-M data from CheckMate 057 and CheckMate 003

It is good practice wherever possible to use the same functional form to model survival in both the intervention and comparator arms. So, although the company's generalised gamma model appears to be a better fit to the docetaxel 18-month OS data from CheckMate 057 than it is to the nivolumab K-M OS data, the ERG re-analysed the K-M OS data for both arms of CheckMate 057 to investigate alternative methods of extrapolating survival.

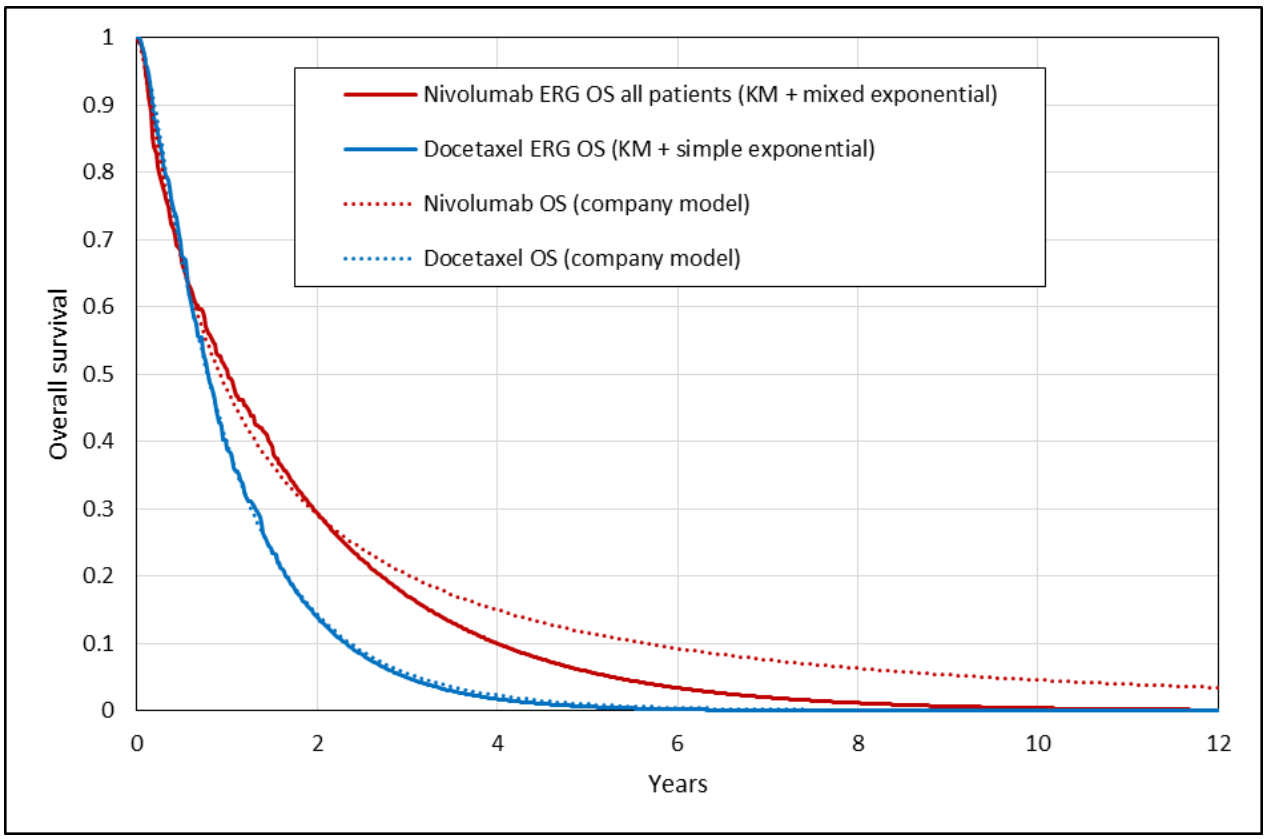
The ERG examined the cumulative hazard plot of the 18-month OS K-M data from CheckMate 057 (Figure 18). It is clear that both of the nivolumab subgroups (PPTx and no-PPTx) and the survival of patients in the docetaxel arm can be satisfactorily modelled using simple exponential distributions; from around 8 months for the nivolumab PPTx patients and docetaxel patients, and from 12 months for the no-PPTx patients. Long-term hazards in the nivolumab subgroups are very similar and much of the difference in survival occurs before 10 months.



Source: Adapted from clarification response-questions B1a & B1e

Figure 18 Cumulative hazard plot of OS K-M data from CheckMate 057 (18-month data cut)

As exponential models fit well to OS K-M data for both nivolumab subgroups, the ERG built a mixed exponential model based on 25% of patients receiving nivolumab beyond progression to project OS for the full nivolumab cohort. The ERG then appended the mixed exponential model to the K-M data for the full nivolumab cohort and modelled the docetaxel arm using K-M data followed by a simple exponential projection (Figure 19).



Source: Company model, clarification response-question B1a

Figure 19 Nivolumab and docetaxel OS: ERG model and company model

When the ERG compared its alternative projections for nivolumab OS to the three best-fitting survival models from the CS, it noted that its exponential extrapolation produced similar values to the company's 2-knot spline model (Figure 20). This is not unexpected as the spline model is a piecewise model that projects exponentially beyond the limit of the K-M data. The company reported that the 2-knot spline model had the best statistical fit of all of the models that were explored, but rejected this model on the basis that it projected lower OS rates at 2, 3 and 4 years than the K-M data from CheckMate 003[23] trial.

Source: Company model, clarification response-question B1a

Figure 20 Nivolumab OS ERG mixed exponential extrapolation and company 2-knot spline model

The company model projects an implausibly long PFS tail for patients receiving nivolumab, with 85% of the patients who are still alive at 20 years still being in PFS. It can be seen from Figure 21 that the ERG's amended OS projection dips below the company's PFS projections at approximately 5 years. The model's 'check and substitute' mechanism discussed in Section 5.5.3 is activated at this point, which artificially increases the ERG's OS projections to ensure that OS is not below PFS. It also means that implementing the ERG's alternative OS projections in isolation in the company model results in there being no patients in the PD state from 5 years onwards, so all patients who had progressed before 5 years have died and no further patients progress. These are purely functions of the interaction between the ERG's and company's projections, and the ERG does not consider them to be plausible clinical scenarios.

Source: Company model, ERG calculations

Figure 21 Effect of company's nivolumab PFS model on ERG nivolumab OS model

Applying the ERG's exponential projections to both the nivolumab and docetaxel arms from 7 months to 20 years reduces OS gain in the company model by 58% to 5.8 months. The estimated ICER per QALY gained is increased by £40,395 to £143,984.

5.5.6 Progression-free survival and time to treatment discontinuation: nivolumab versus docetaxel

The company does not use PFS data from CheckMate 057 in its model. The company uses TTD data from CheckMate 057 as a proxy for PFS data in order to be able to capture the extra treatment received by nivolumab patients who were treated beyond progression. However, the base case model that the company uses to project TTD data for both nivolumab and docetaxel is a poor fit to the available K-M data for both TTD and PFS and is not an appropriate surrogate for either.

The company concluded that a generalised gamma model was the most appropriate fit to the TTD K-M data in both the nivolumab and docetaxel arms. Figure 22 compares the generalised gamma curves used in the company model with the TTD K-M data from the 18-

month data lock provided by the company during the clarification process. It is clear that the company model is a poor fit to the TTD data and substantially overestimates time on treatment in the early part of the model for patients in both trial arms.

Source: Company model, clarification response-question B1d

Figure 22 TTD K-M data and company model for nivolumab and docetaxel

The CS did not include any PFS projections based on PFS K-M data from CheckMate 057 as the number of patients in PFS was estimated from projections of TTD K-M data. When the company's TTD models are compared against the PFS K-M data for both nivolumab and docetaxel, it is clear that the gamma curves are again inappropriate. Figure 23 shows that the TTD model used to estimate PFS for nivolumab overestimates almost all of the data and captures only a few of the final points. Conversely, the company TTD model serves to underestimate PFS for docetaxel.

Source: Company model, clarification response-question B1b

Figure 23 PFS K-M data and company model for nivolumab and docetaxel

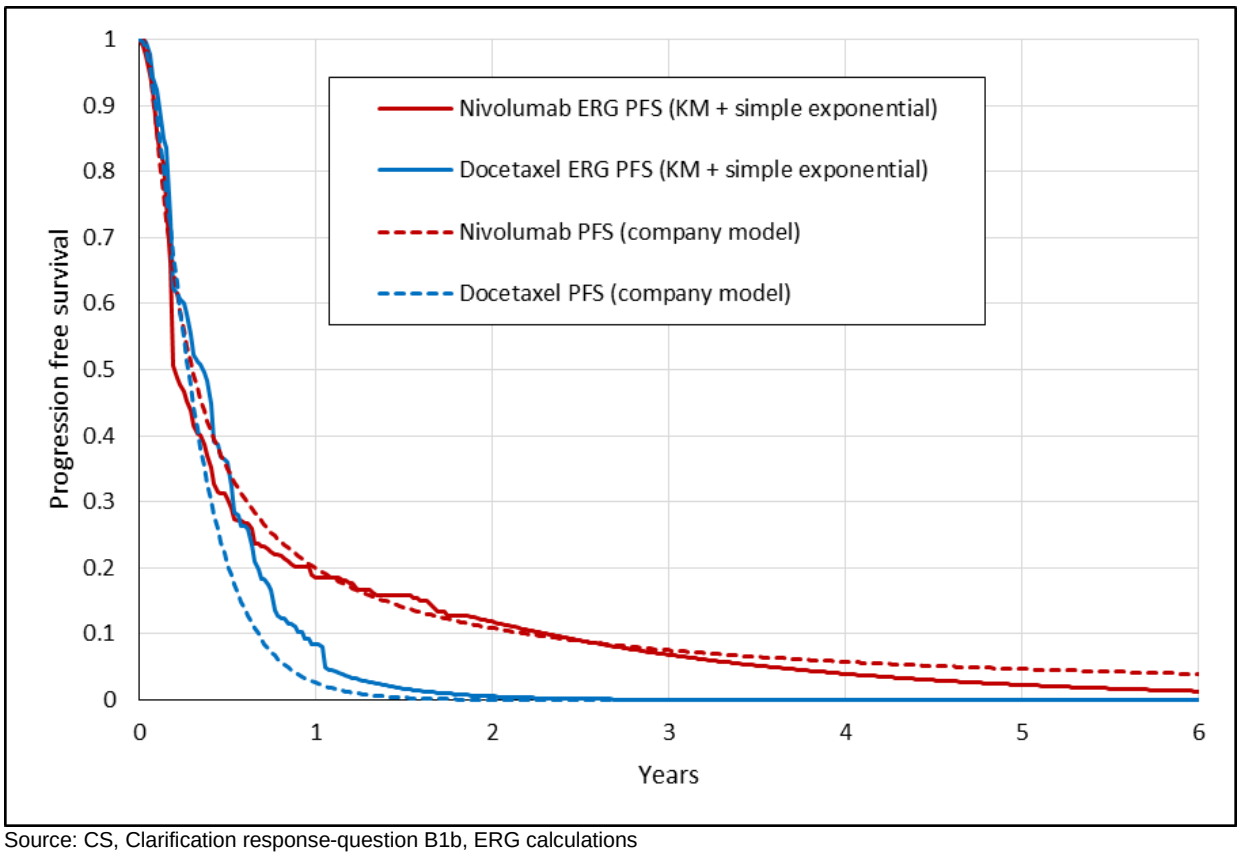
Progression-free survival projections

A cumulative hazard plot from 3 months indicates that nivolumab PFS hazards are constant from around 8 months; an exponential curve is therefore an appropriate method of projecting PFS for nivolumab in the long-term (Figure 24). Docetaxel PFS also exhibits constant hazards from around 8 months onwards, allowing exponential projections to be fitted to the end of the trial data.

Source: Adapted from clarification response-question B1b

Figure 24 Cumulative hazard plot of nivolumab and docetaxel PFS KM data (CheckMate 057)

Figure 25 compares the ERG's preferred PFS models for nivolumab and docetaxel with the company's generalised gamma model. The ERG's models decrease PFS gain in the company model by 57.9% to 4 months, as nivolumab PFS is reduced by shortening the long tail and docetaxel PFS is increased primarily in the first year.



Source: CS, Clarification response-question B1b, ERG calculations

Figure 25 ERG and company PFS projections for nivolumab and docetaxel

Using the ERG's PFS projections instead of the company TTD projections in the company model reduces the size of the ICER per QALY gained by £22,649 to £80,940 due to decreases in treatment acquisition, treatment administration and treatment monitoring costs.

Time to treatment discontinuation projections

Inspection of Figure 26 shows nivolumab TTD and PFS data to be very similar, particularly after 3 months; however, the ERG considers it appropriate to capture the differences between the PFS and TTD K-M data because of their relevance to treatment cost (TTD) and QALY (PFS) calculations.

Source: Clarification response-question B1b and B1d, ERG calculations

Figure 26 Nivolumab PFS and TTD K-M data and long-term trends

All patients in the docetaxel arm of CheckMate 057 had finished treatment by the time of the 18-month data cut (Figure 27). This means that no projections were necessary to estimate TTD for docetaxel, as the area under the K-M curve provides the best estimate of mean treatment duration for all of these patients.

Source: Clarification response-question B1d, ERG calculations

Figure 27 ERG TTD for nivolumab and docetaxel

The ERG's TTD estimates decrease the projected time that patients spend receiving nivolumab from 14.5 months to 10.3 months and the time that patients spend receiving docetaxel from 5 months to 4.2 months.

Using the ERG's TTD projections instead of the company TTD projections in the company model reduces the size of the ICER per QALY gained by £22,077 to £81,513 due to proportionately greater decreases in treatment acquisition, treatment administration and treatment monitoring costs for nivolumab.

5.5.7 Overall survival: nivolumab versus nintedanib+docetaxel

There is no direct clinical evidence to compare nivolumab with nintedanib in combination with docetaxel (nintedanib+docetaxel) for patients with progressed non-squamous lung cancer. The company notes that it was not possible to carry out a conventional ITC for the comparison of nivolumab versus nintedanib+docetaxel as the standard proportional hazards assumption was shown in TA347[43] not to hold for OS in the LUME-Lung 1[24] trial for the adenocarcinoma population.

The company analysed K-M OS data for the adenocarcinoma subgroup digitised from the published LUME-Lung 1 trial[24] and concluded that the OS K-M data for nintedanib+docetaxel

versus docetaxel+placebo had a 2-part proportional-hazard profile; i.e. there was no difference between the two treatments up to 6 months (HR=1) and this was followed by a separation of the curves showing benefit for nintedanib+docetaxel (HR=0.75).

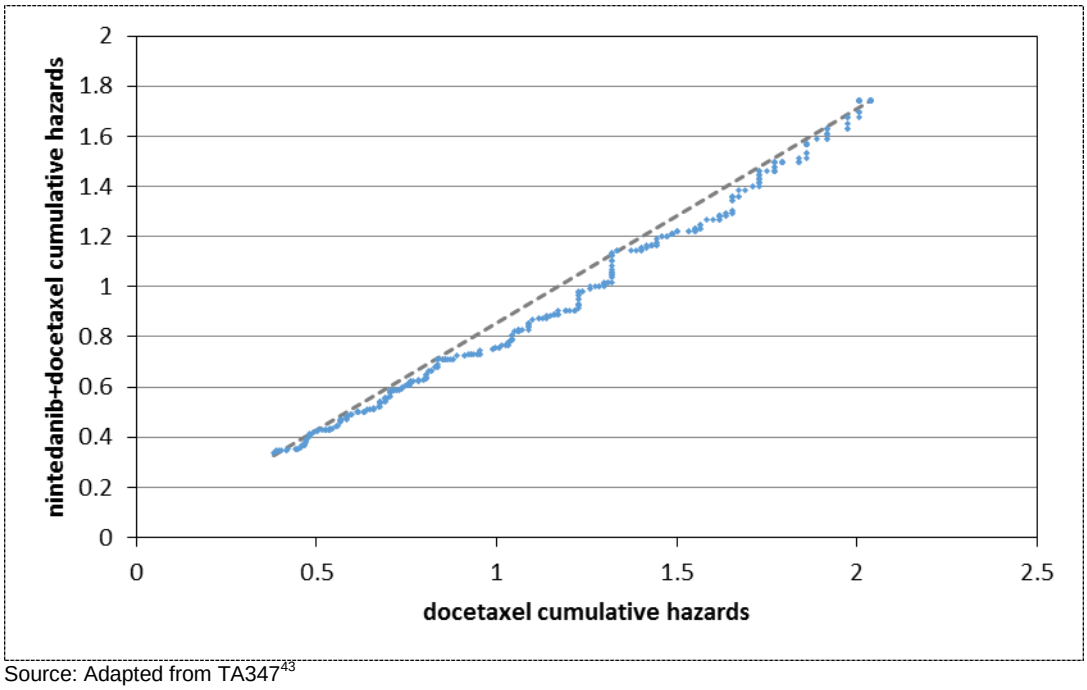
This approach relies on the proportional hazards assumption holding between 0 and 6 months, and again from 6 months onwards. In the CS there was no evidence presented to suggest that these proportional hazards assumptions had been tested by the company in any way beyond a visual inspection of the OS curves. The ERG independently digitised published data from TA347,[43] which contains more mature OS data from the LUME-Lung 1[24] trial than have been included in the CS, in order to estimate the proxy patient-level data required to test the proportional hazards assumptions.

Figure 28 shows an H-H plot of the docetaxel versus nintedanib+docetaxel arms of the LUME-Lung 1[24] trial from 6 months to 30 months. Points are dotted randomly around a line joining the first and last points in an H-H plot if hazards are proportional in the two arms. However, Figure 28 shows that the data points curve systematically below the line. This indicates that the docetaxel hazard is diverging from the nintedanib+docetaxel hazard, so the hazard ratio is increasing. The proportional hazards assumption is therefore not valid (Lee & Pirie, p value=0.0235). The ERG thus investigated alternative ways to compare nivolumab with nintedanib+docetaxel.

The ERG is of the opinion that baseline characteristics are fairly similar between the docetaxel arms of the CheckMate 057[28] and LUME-Lung 1[24] (adenocarcinoma population) trials. This means that, if there is sufficient evidence to suggest that the (comparator) docetaxel arms of the CheckMate 057[28] and LUME-Lung 1[24] trials are equivalent, the intervention arms of both trials (nivolumab and nintedanib+docetaxel) may be compared without adjustment. However, it is important to note that the ERG did not have access to data summarising the disease stage of patients in the adenocarcinoma population of the LUME-Lung 1 trial,[24] d so it is not possible to compare the two trials in this respect.

The ERG compared digitised K-M OS data for the adenocarcinoma population in the docetaxel+placebo arm of the LUME-Lung 1[24] trial with OS data from the docetaxel arm of the CheckMate 057 trial to investigate whether the OS outcomes for patients receiving docetaxel were significantly different in the two trials. The ERG concluded, by visual inspection of Figure 29 and by statistical test, that the docetaxel-treated populations from the two trials could be treated as equal. The ERG thus considers it is credible to compare

unadjusted nintedanib+docetaxel OS data from the LUME-Lung 1[24] trial with nivolumab OS data from the CheckMate 057 trial.



Source: Adapted from TA347[43]

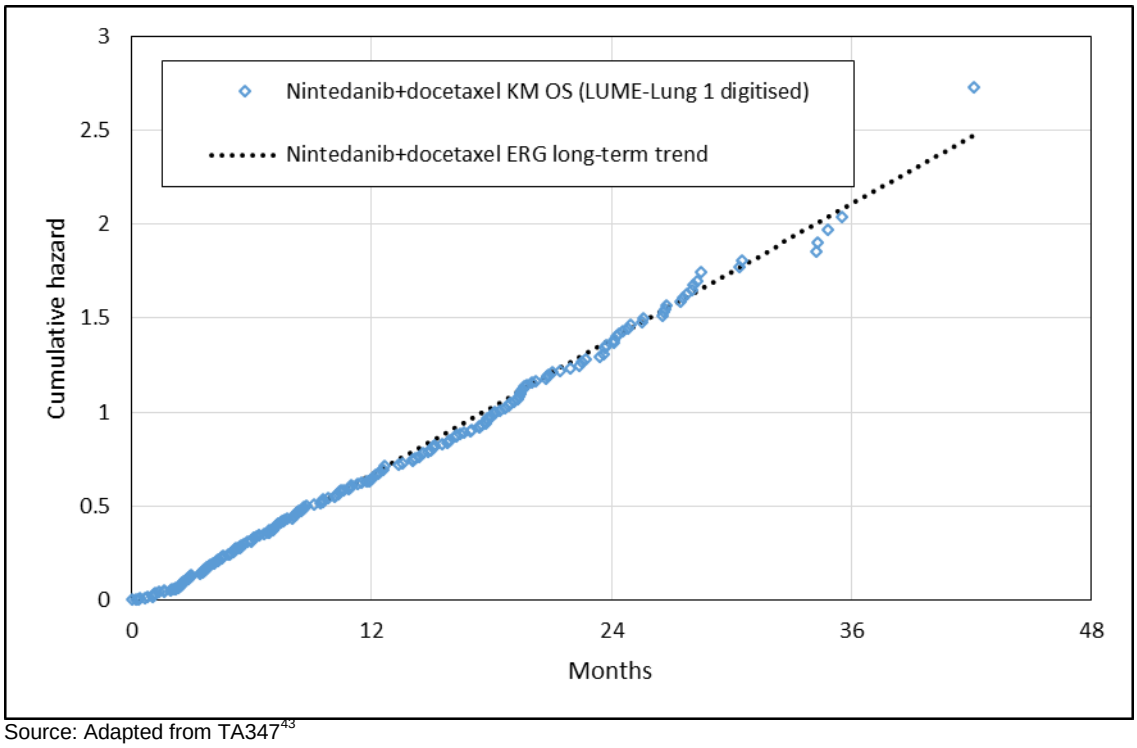
Figure 28 H-H plot of nintedanib+docetaxel OS vs. docetaxel OS (6 to 30) months

[redacted]

Figure 29 OS in docetaxel arms of CheckMate 057 and LUME-Lung 1 trials

Inspection of the cumulative hazard plot of the nintedanib+docetaxel OS K-M data from the LUME-Lung 1[24] trial (Figure 30) shows that a simple linear trend is established by 300 days

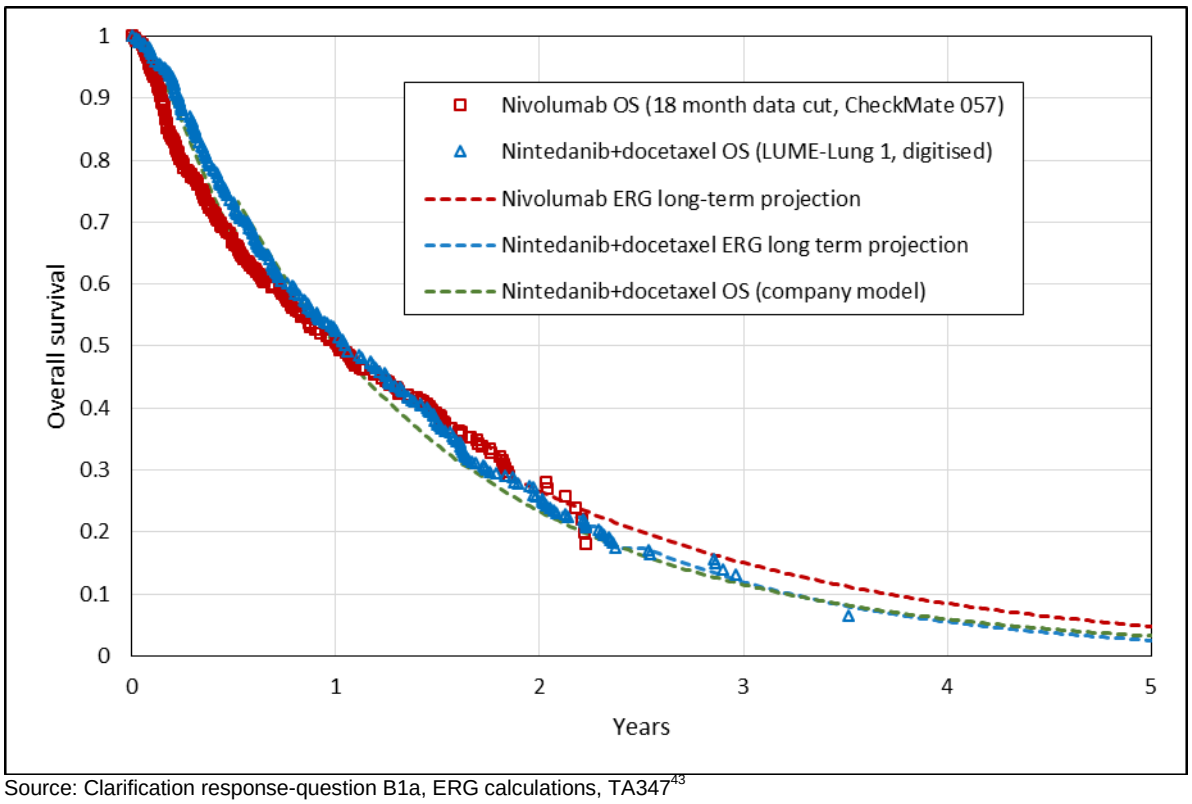
and continues indefinitely. This indicates that OS can be estimated by use of a simple exponential projective model beyond the limits of the K-M data (i.e. there is a constant hazard irrespective of time).



Source: Adapted from TA347[43]

Figure 30 Nintedanib OS from LUME-Lung 1 trial

A comparison of the nintedanib+docetaxel K-M OS data from LUME-Lung 1[24] trial and the K-M data for nivolumab from CheckMate 057 reveals very little difference in OS between the two treatments. When appropriate exponential long-term projections (see Section 5.5.5 for an explanation of the nivolumab OS projection) are applied to both arms (Figure 31), survival gain for nivolumab versus nintedanib+docetaxel is reduced in the company model by 70% to 3.1 months due to the reduction in nivolumab OS. The ERG and company projections for nintedanib+docetaxel OS result in very similar values. The estimated size of the ICER per QALY gained increases by £121,977 to £248,838 due to a substantial decrease in the incremental life years gained.



Source: Clarification response-question B1a, ERG calculations, TA347[43]

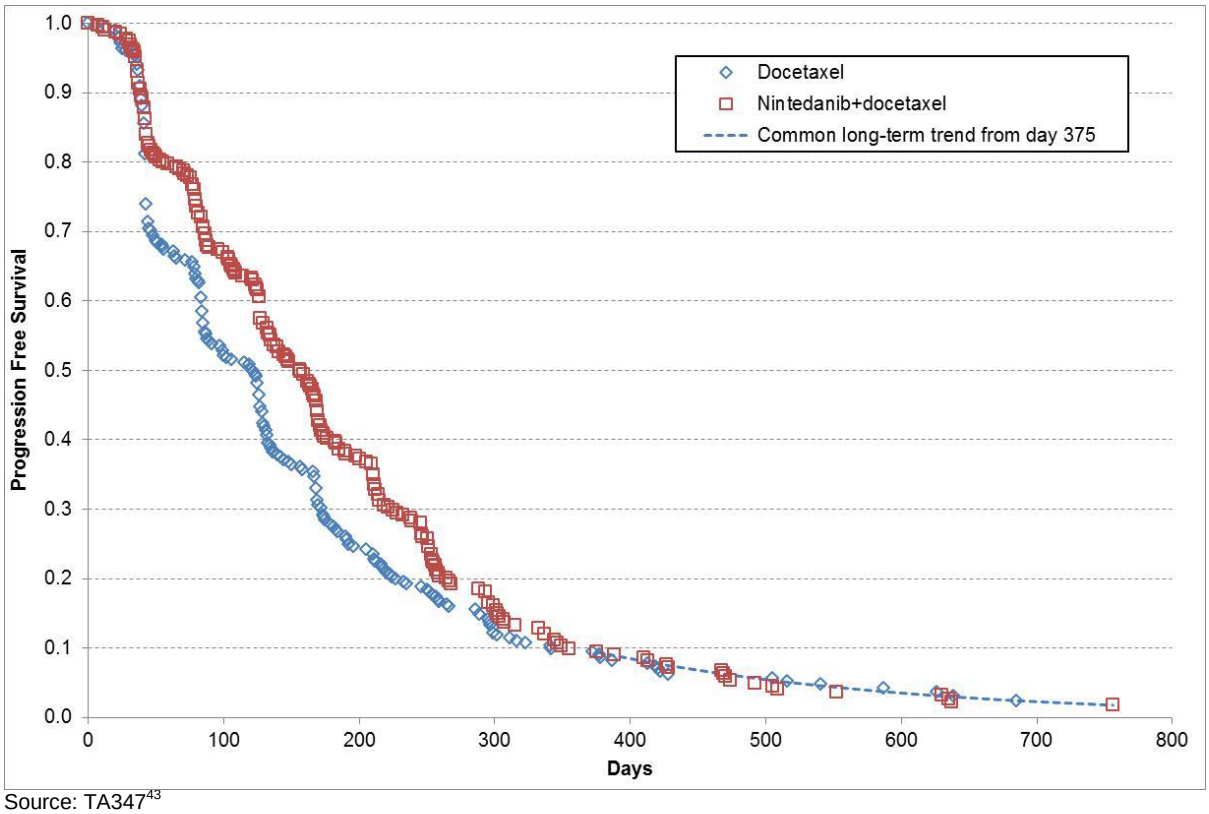
Figure 31 Nivolumab and nintedanib+docetaxel OS K-M data plus ERG projections

5.5.8 Progression-free survival: nivolumab versus nintedanib+docetaxel

When modelling PFS for patients treated with nintedanib+docetaxel, the company analysed digitised K-M data for the adenocarcinoma subgroup from the LUME-Lung 1[24] trial to compare outcomes in the nintedanib+docetaxel and docetaxel+placebo arms. The company concluded that PFS in the LUME-Lung 1[24] trial could also be described as a two-part proportional-hazard profile: equal in both arms to 2 months, then a HR of 0.98 from 2 months onwards. The company applied this two-part profile to the docetaxel TTD data from CheckMate 057 in order to model PFS for nintedanib+docetaxel. This approach again relies on the proportional hazards assumption holding independently in the two stages identified by the company.

The ERG report for TA347[43] contains more mature PFS data from the LUME-Lung 1[24] trial than have been included in the CS. Figure 32 shows that the early delay in progression for some patients receiving nintedanib+docetaxel (where the PFS curves begin to separate at around 6 weeks or 42 days) progressively dissipates over the course of a few months. The curves then converge at around 1 year, when the PFS experiences of patients in both arms of the LUME-Lung 1[24] trial are indistinguishable. Since the two arms are clearly separated in

the early part of the plot yet identical by 1 year, the HRs cannot be constant over time and the proportional hazards assumption - even from 2 months onwards - is invalidated.



Source: TA347[43]

Figure 32 PFS for the nintedanib+docetaxel and docetaxel arms (adenocarcinoma only) from LUME-Lung 1

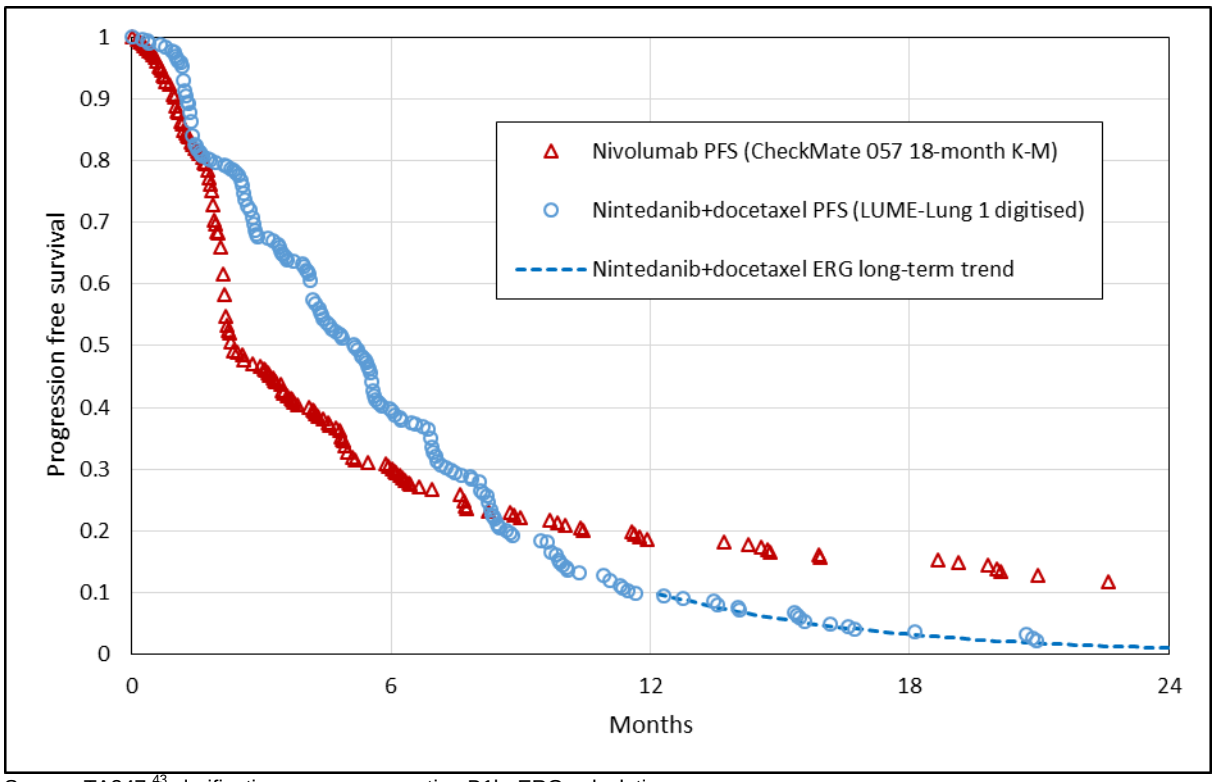
The ERG examined PFS data from the LUME-Lung 1[24] and CheckMate 057[28] trials to investigate whether PFS outcomes in the docetaxel arms were demonstrably different between the studies. Visual inspection of Figure 33 suggests that there is very little to separate the unadjusted K-M PFS data from the docetaxel arms of the two trials and this is confirmed by statistical testing. Since the PFS outcomes in the comparator arms from the two trials may be treated as equivalent, the ERG deems it is credible to compare the unadjusted nintedanib+docetaxel K-M PFS data from the LUME-Lung 1[24] trial with nivolumab K-M PFS data from CheckMate 057.

Figure 33 Docetaxel PFS in CheckMate 057 and LUME-Lung 1

The ERG used unadjusted nintedanib+docetaxel K-M PFS data from LUME-Lung 1 [TA347][43] to 375 days. Since the nintedanib+docetaxel and docetaxel arms of the LUME-Lung 1 trial[24] converge and the docetaxel arms of the CheckMate 057[28] and LUME-Lung 1[24] trials can be considered equivalent, the ERG applied the long-term trend from the docetaxel arm of CheckMate 057 to project PFS for nintedanib+docetaxel (Figure 34).

Using the ERG's preferred PFS models for nivolumab and nintedanib+docetaxel reduces nivolumab PFS gain over nintedanib+docetaxel in the company model by 42.3% to 5.8 months.

Amending the model to use the ERG's PFS estimates for nivolumab and for nintedanib+docetaxel reduces the ICER per QALY gained by £39,660 to £87,202 due to a proportionately greater reduction in treatment costs for nivolumab. Amending the model to use the ERG's TTD estimates for nivolumab, and the ERG's PFS projection for nintedanib+docetaxel reduces the size of the ICER per QALY gained versus nintedanib+docetaxel by £38,714 to £88,147, again due to a proportionately greater reduction in treatment costs for nivolumab.



Source: TA347,[43] clarification response-question B1b, ERG calculations

Figure 34 Nivolumab vs. nintedanib+docetaxel PFS

5.5.9 Calculating costs and QALYs using PFS and TTD

The company used TTD to represent time spent on treatment and time spent in PFS for all treatments compared in the company model. The ERG considers this approach to be flawed, as it can misrepresent the incremental costs and QALYs of treatments and their comparators.

Some costs that patients accrue are linked to the treatment they receive (i.e. treatment acquisition, treatment administration and treatment monitoring) and some are connected to their health state (i.e. disease-management costs). Some QALYs that patients accrue are linked to the treatment they receive (i.e. treatment-related AE disutilities) and some are connected to their health state (i.e. health state utilities). Therefore the ERG considers it preferable to use PFS and PPS when possible to estimate the costs and QALYs associated with health states and TTD to estimate costs and QALYs associated with treatment and has investigated the effect of using this approach on cost effectiveness estimates.

TTD data are also available for nintedanib+docetaxel from the LUME-Lung 1 trial [TA347];[43] however, it was not possible to use them in the company model. The company economic model does not have the facility to accommodate separate calculations for TTD for the two

elements of the nintedanib+docetaxel combination therapy, so the ERG used PFS as a proxy to model treatment-related costs for nintedanib+docetaxel. The projected costs of the nintedanib+docetaxel comparator in the ERG's revised ICER per QALY gained should thus be treated with caution.

Using the ERG's preferred models for PFS and TTD for nivolumab and docetaxel in the relevant parts of the economic model decreases the size of the ICER per QALY gained versus docetaxel by £19,996 to £83,594. Using the ERG's preferred models for PFS and TTD for nivolumab and for PFS for nintedanib+docetaxel reduces the size of the ICER per QALY gained versus nintedanib+docetaxel by £39,491 to £87,371.

5.5.10 Nivolumab dosing calculations

The company has used a log-normal distribution of body weight, weighted by sex, to calculate the average number of doses of nivolumab received by patients. Whilst the method is robust, the company has made a mistake when implementing the method in the model, which leads to a small overestimate in the average cost per dose of nivolumab.

The ERG has corrected the body weight calculation error, which decreases the average cost per full dose of nivolumab by £50.84 to £2,487.41. This amendment results in a £1,855 reduction in the size of the ICER per QALY gained versus docetaxel to £101,734 and a £2,738 reduction in the size of the ICER per QALY gained versus nintedanib+docetaxel to £124,123.

5.5.11 Treatment administration costs

The company model correctly estimates costs for the intervention and comparators based on the number of patients in treatment at the start of any given cycle. However, administration costs are calculated based on the number of patients in treatment mid-cycle. Given that treatment is acquired and administered at the same time, administration costs should also be calculated at the start of the cycle. The ERG has amended this oversight in the company model. Calculating administration costs at the beginning of the cycle reduces the size of the ICER per QALY gained versus docetaxel by £1,187 to £102,403 and increases the estimated ICER per QALY gained versus nintedanib+docetaxel by £26 to £126,887.

5.5.12 Health state utilities

The ERG identified several limitations with regard to completion rates and the health state utility estimates associated with the EQ-5D data collected during CheckMate 057. 73.9% of randomised patients completed the EQ-5D assessment at baseline. Despite 81.6% of participants being alive at week 12, the respective completion rates at this time point were 40.8% and 38.9% for nivolumab and docetaxel patients. The corresponding completion rates for nivolumab and docetaxel arms at 24 weeks were 26.9% and 14.8% while 69.4% of patients in CheckMate 057 were still alive.

It is likely that patients' decisions to continue completing the EQ-5D questionnaire throughout the trial period have been subject to various influences. Even if the possible self-selecting behaviour and response bias attributable to patients that completed the EQ-5D questionnaire were to be ignored, the ERG remains concerned that the characteristics of patients who completed the EQ-5D instrument are unlikely to match the characteristics of the initial trial population. Improvements in observed mean utility scores over time were observed (ERG report, Appendix 11.3). However, the ERG considers that the substantial differences deemed attributable to nivolumab treatment compared with docetaxel treatment cannot be considered reliable. The ERG considers it is likely that patients who continue to complete HRQoL assessments are those with better health status and higher ECOG PS scores than non-respondents. An important implication of this finding is that self-selection is likely to cause health state utility values to be overestimated. This phenomenon was previously observed in the NICE appraisal for nivolumab and squamous NSCLC patients.[49]

Health state utility values from CheckMate 057 indicate that patients in the PF health state have a mean utility score of 0.739 compared with patients in PD who have a mean utility score of 0.688. The ERG analysis of EQ-5D data by region provided utility estimates of 0.735 and 0.654 for the corresponding PF and PD states in European patients. Testing the effect of EQ-5D values obtained exclusively from European patients, as carried out by the ERG (Appendix 10.7), results in a slight increase in the overall ICERs per QALY gained when comparing nivolumab with both comparators.

The effects of using alternative utility values from (i) the study by Nafees et al[59] and (ii) a combination of EQ-5D values from CheckMate 057 with a Dutch lung cancer study by van den Hout et al[66] were investigated by the ERG.

Nafees et al[59] obtained utility values for health states describing second-line treatments for NSCLC from UK participants using a Standard Gamble (SG) approach. Values from the Nafees et al[59] study were previously used for patients treated with second-line chemotherapy in a systematic review and economic evaluation of first-line chemotherapy for NSCLC.[67] Substituting 0.65 for the PF state and 0.43 for the PD state into the company model reduced the incremental QALYs gained per patient for nivolumab versus docetaxel by 18%, and increased the size of the estimated ICER per QALY gained by £22,347 to £125,936. For nivolumab versus nintedanib+docetaxel, incremental QALYs gained per patient are reduced by 8% and the estimated ICER per QALY gained increases by £13,537 to £140,399.

In Holland, van den Hout et al[66] studied alternative palliative radiotherapy delivery models for patients with NSCLC. EQ-5D utility values were obtained using a UK valuation set over 52 weeks. The ERG has estimated patient utility in the PPS state to be 0.545 using stable data from this Dutch trial for both treatment arms. The ERG has also calculated an additional disutility associated with the terminal care phase. The company model structure does not capture terminal disutility therefore the ERG applied an adjustment to the stable PPS utility value to spread terminal disutility over the mean duration of PPS from CheckMate 057. This adjustment resulted in a utility value for PD of 0.476. Taking into account the increasing EQ-5D utility estimates over time in CheckMate 057, the ERG has selected early EQ-5D assessment results where participant responses were most stable i.e. limited analysis of overall EQ-5D values for the PF state during the first 12 weeks after randomisation for European patients alone. This method generated a utility value for the PF health state of 0.713. The implementation of these alternative utility values in the company model reduced the incremental QALYs gained per patient for nivolumab versus docetaxel by 10.2% and increased the estimated ICER per QALY gained by £11,853 to £115,443. For nivolumab versus nintedanib+docetaxel, the incremental QALYs gained per patient decreased by 1.4% and the estimated ICER per QALY gained increased by £2,055 to £128,916.

The utility values calculated from van den Hout et al[66] and CheckMate 057 are the ERG's preferred values, as they take into account terminal disutility, which is not otherwise accounted for in the company model. The alternative utility values considered by the ERG are outlined in Table 45.

Table 45 UK-specific mean EQ-5D values by source

Source	PF Mean	PD Mean
CheckMate 057 – all patients	0.739	0.688
CheckMate 057 – European patients	0.735	0.654
Nafees study[59]	0.65	0.43
CheckMate 057 & van den Hout study[66]	0.713	0.476

ICER=incremental cost effectiveness ratio; PD=progressed disease; PF=progression free
Source: Clarification response – Tables 4-7, Nafees 2009,[59] van den Hout 2006[66]

5.5.13 Adverse event utility decrements

In the company model, 17 AEs are selected to represent the effects of AEs on health-related utility. Disutility estimates associated with the selected AEs were derived from the following sources: the Nafees study[59] for fatigue, asthenia, anaemia, neutropenia, febrile neutropenia, leukopenia and diarrhoea, a study by Marti et al[68] for pneumonia, a study by Doyle, Lloyd and Walker[60] for dyspnoea and a previous Technology Appraisal[43] for white blood cell count and increased ALT. Utility values were unavailable for pain, pleural effusion, decreased neutrophil count, increased aspartate transaminase and hyponatraemia and the company therefore assumed that a disutility of 0 was associated with these AEs. The study by Marti et al[68] included a standard gamble exercise involving South and Central American parents of hospitalised children aged 3 to 36 months, and considered the disutility of a 7 day stay in hospital followed by recovery to full health. The relevance of utility values estimated in this study to elderly patients with metastatic lung cancer undergoing second-line chemotherapy is therefore questionable. The Doyle, Lloyd and Walker study[60] was less sophisticated than the study carried out by Nafees et al[59] and included only three symptoms and omitted PD. The ERG considers that the company's approach i.e. combining a single estimated parameter value from the Doyle, Lloyd and Walker model[60] with parameters from the study by Nafees et al[59] and from a previous appraisal,[43] is inconsistent and is therefore inappropriate.

The ERG is concerned that the estimated disutility effect of AEs in the model is necessarily understated to an unknown extent. The company applied utility decrements to AEs by multiplying the Grade 3 or 4 AE incidence rates (≥2%) of selected AEs from CheckMate 057 with the corresponding disutility values and summing them to a single disutility quantum for each treatment. Disutilities associated with AEs are applied only once during the first cycle of the company model. This technique assumes that patients suffering an AE only suffer a

single episode due to the use of incidence rates per person rather than use of event rates. Additionally, the ERG considers the assumption that all AEs and any consequent effects on patient health last no longer than 1 week in the model to lack validity. Moreover, the disutility of each AE was applied separately in the model thus introducing a potential for interaction or double counting when multiple AEs occur concurrently. The ERG is not able to assess the potential size of these problems due to lack of data, but this is not expected to have a substantial effect on the model results.

5.5.14 1- and 2- year stopping rules

The company has conducted sensitivity analyses in which medical dose caps are applied to treatment with nivolumab. These caps halt all treatment-related costs (i.e. acquisition, administration and monitoring) at either 1 or 2 years, but assume clinical efficacy across treatments and the costs and disutlilties associated with AEs remain equal to those experienced with uncapped treatments.

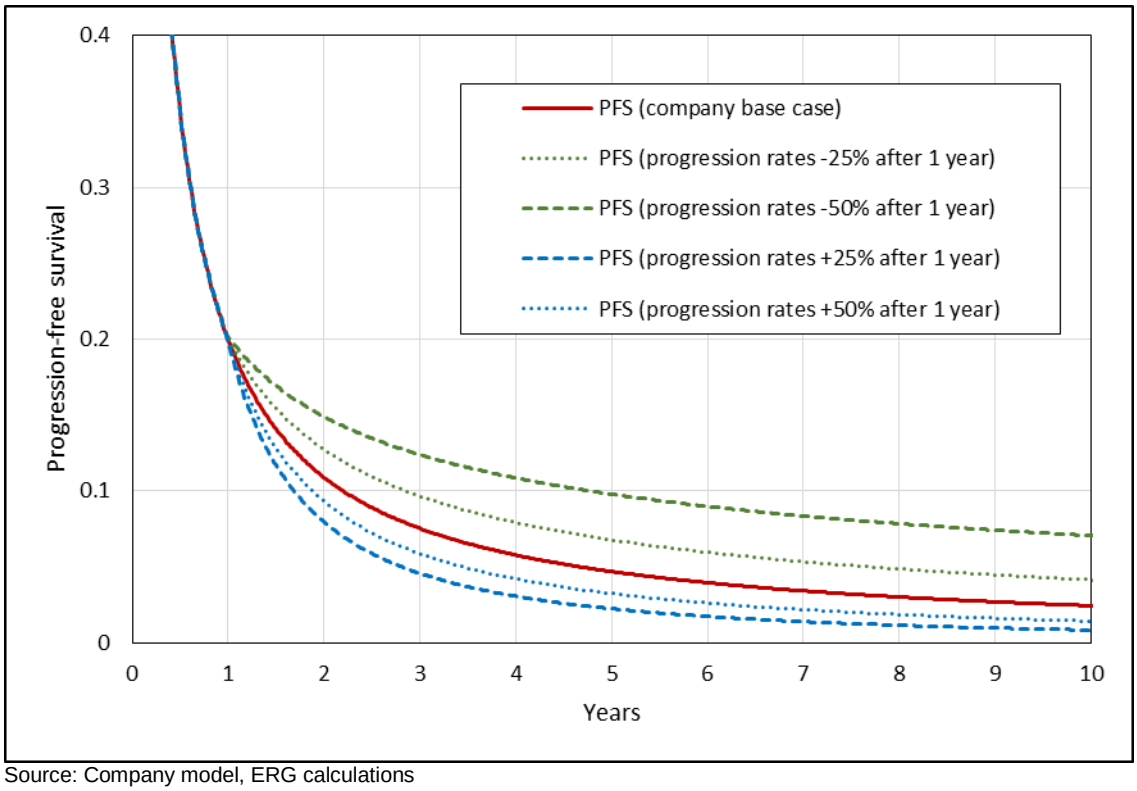
Evidence is currently lacking for the duration of benefit beyond an imposed treatment cap. The company references two trials whose results suggest that a durable benefit might be feasible for some patients who stop treatment with nivolumab before disease progression: the Phase Ib CheckMate 003[23] trial and the Phase IIIb/IV CheckMate 153[22] safety study.

CheckMate 003[23] implemented a 96-week (1.8 year) stopping rule and results from the September 2014 data analysis indicate that some patients who responded to treatment and were still in PFS at 96 weeks continued to respond to treatment. Data on post-treatment benefit in this study is limited to those patients who experienced either a CR or a PR. According to the CS (Figure 48), 13 patients with non-squamous NSCLC experienced a response in CheckMate 003[23] and one patient was still receiving treatment at the 96 week cut off. Three non-squamous patients (23%) had a response that lasted beyond 96 weeks.

Results from the CheckMate 003[23] trial indicate possible ongoing benefit for some patients who stop treatment before disease progression. However, there are insufficient data available from this trial to enable robust modelling of PFS or OS if treatment with nivolumab were to be capped at 1 or 2 years.

The CheckMate 153[22] trial randomised patients who were still in PFS at 1 year to either stop nivolumab or to continue nivolumab treatment until progression. Detailed survival data from CheckMate 153[22] trial were not available to the ERG at the time of writing the ERG report.

There is a lack of data describing the clinical effect of stopping treatment with nivolumab before progression. The ERG investigated the sensitivity of the estimated ICERs per QALY gained to 25% and 50% increases and decreases in nivolumab progression rates and mortality rates (which affect PFS and OS) after treatment is halted at 1 or 2 years. An example of the effect of varying progression rates on PFS is shown in Figure 35.



Source: Company model, ERG calculations

Figure 35 Nivolumab PFS with varying mortality rates after 1 year

The ERG explored scenarios where progression and mortality rates for nivolumab either increased or decreased after treatment was capped at 1 or 2 years. The ERG scenarios were included to investigate the potential effect on cost effectiveness of changes in clinical efficacy due to capped treatment with nivolumab. The ERG scenarios did not investigate the potential effect of changes to costs and disutilities associated with AEs as a result of capping treatment.

The company base case ICER per QALY gained with a 1-year medical dose cap is £46,860 for nivolumab versus docetaxel. This ICER per QALY gained ranges from £26,521 to £85,844 when varying progression and mortality rates were applied. The company base case ICER per QALY gained with a 2-year medical dose cap is £60,955 for nivolumab

versus docetaxel. This ICER per QALY gained ranges from £39,690 to £135,323 when varying progression and mortality rates were applied.

The company base case ICER per QALY gained with a 1-year medical dose cap is £43,122 for nivolumab versus nintedanib+docetaxel. This ICER per QALY gained ranges from £21,942 to £140,494 when varying progression and mortality rates were applied. The company base case ICER per QALY gained with a 2-year medical dose cap is £63,928 for nivolumab versus nintedanib+docetaxel. This ICER per QALY gained ranges from £36,366 to £198,460 when varying progression and mortality rates were applied.

The full results of the ERG's analysis of the sensitivity of the 1- and 2-year medical dose caps to changes in the progression and mortality rates for nivolumab patients are given in Appendix 10.8

5.6 Conclusions of the cost effectiveness section

The various changes implemented by the ERG for the comparison of nivolumab versus docetaxel and for nivolumab versus nintedanib+docetaxel yield a mixture of effects. When implemented individually, these revisions both increase and decrease the size of the ICERs per QALY gained. However, the combined effect of all of the ERG's preferred changes yields a revised base case ICER of £165,234 per QALY gained for nivolumab versus docetaxel and of £293,232 for nivolumab versus nintedanib+docetaxel.

The ERG considers that the company's base case results substantially underestimate the size of the most probable ICER per QALY gained for both nivolumab versus docetaxel and nivolumab versus nintedanib+docetaxel in previously treated patients with non-squamous NSCLC.

6 IMPACT ON THE ICER OF ADDITIONAL ERG ANALYSES

The ERG has made the following changes to the submitted company model to address the points raised in Section 5:

- use of ERG preferred OS estimates (R1)
- use of ERG preferred PFS estimates (R2)
- use of ERG preferred treatment duration estimates (based on TTD) for nivolumab and docetaxel (R3)
- application of ERG preferred PFS and TTD estimates to relevant cost and QALY categories for nivolumab and docetaxel (R4)

- ERG TTD for nivolumab and ERG PFS for nintedanib+docetaxel (R5)
- ERG PFS for nivolumab disease costs and QALYs, ERG TTD for nivolumab treatment costs and AEs; ERG PFS for nintedanib+docetaxel disease costs and QALYs (R6)
- nivolumab dosing calculations (R7)
- treatment administration costs at the start of each cycle (R8)
- use of preferred health state utility values (R9)
- use of health state utility values from study by Nafees[59] (R10).

Details of all Microsoft Excel revisions made by the ERG to the company's model are presented in Appendix 10.8 of this report.

6.1.1 Summary of ERG revisions to company model

The cost effectiveness results obtained by applying each of the ERG's model revisions for nivolumab versus docetaxel are shown in Table 46 and Table 47.

Revisions R2 and R3 (shaded rows) are superseded by R4 for nivolumab versus docetaxel, and revisions R2 and R5 (shaded rows) are superseded by R6 for nivolumab versus nintedanib+docetaxel.

The ERG's revised base case analysis (Scenario B) yields an ICER per QALY gained of £165,234 for nivolumab versus docetaxel, which is £61,644 per QALY gained higher than the company's original ICER. The ERG's revised base case for the comparison of nivolumab and docetaxel generates both incremental costs (-£22,109) and benefits (-0.41 QALYs) that are lower than those generated by the company.

The ERG's revised base case analysis (Scenario C) yields an ICER per QALY gained of £293,232 for nivolumab versus nintedanib+docetaxel, which is £166,370 per QALY gained higher than the company's original ICER. The ERG's revised base case for the comparison of nivolumab and docetaxel generates both incremental costs (-£27,482) and benefits (-0.37 QALYs) that are lower than those generated by the company.

Table 46 Cost effectiveness (nivolumab vs. docetaxel): ERG revisions to company base case

Model scenario ERG revision	Nivolumab			Docetaxel			Incremental			ICER	ICER
	Cost £	QALYs	Life years	Cost £	QALYs	Life years	Cost £	QALYs	Life years	£/QALY[+]	Change
A. Company base case	***93,306***	***1.424***	***2.243***	***17,854***	***0.696***	***1.095***	***+75,452***	***+0.728***	***+1.149***	***103,589***	**-**
R1) ERG OS	89,873	1.184	1.806	17,666	0.683	1.072	+72,207	+0.501	+0.734	143,984	**+40,395**
R2) ERG PFS	76,044	1.410	2.243	18,715	0.702	1.095	+57,328	+0.708	+1.149	80,940	**-22,649**
R3) ERG TTD	76,568	1.411	2.243	17,991	0.693	1.095	+58,577	0.719	+1.149	81,513	**-22,077**
R4) ERG PFS for disease costs and QALYs, ERG TTD for treatment costs and AEs	76,123	1.410	2.243	16,915	0.702	1.095	+59208	+0.708	+1.149	83,594	-19996
R7) Nivolumab dosing calculations	91,955	1.424	2.243	17,854	0.696	1.095	+74,100	+0.728	+1.149	101,734	**-1,855**
R8) Treatment administration costed at start of cycle	93,347	1.424	2.243	18,759	0.696	1.095	+74,587	+0.728	+1.149	102,403	**-1,187**
R9) ERG utility values (Van den Hout[66] + CheckMate 057)	93,306	1.186	2.243	17,854	0.532	1.095	+75,452	+0.654	+1.149	115,443	**+11,853**
R10) Utility values from study by Nafees[59]	93,306	1.076	2.243	17,854	0.477	1.095	+75,452	+0.599	+1.149	125,936	**+22,347**
B. ERG revised base case A+R1, R4, R7:R9	***70,124***	***0.870***	***1.806***	***16,781***	***0.547***	***1.072***	***+53,343***	***+0.323***	***+0.734***	***165,234***	***+61,644***

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; TTD=time to treatment discontinuation
R2 and R3 (shaded) are superseded by R4
* Interpret with caution due to interdependence of nivolumab ERG OS and company PFS projection in the company model
[+] Rounding errors account for difference between ICERs calculated using the incremental cost and QALY values given in the table and ICERs in this column

Table 47 Cost effectiveness results (nivolumab vs. nintedanib+docetaxel): ERG revisions to company base case

Model scenario ERG revision	**Nivolumab**			**Nintedanib+docetaxel**			**Incremental**			**ICER**	**ICER**
	Cost £	**QALYs**	**Life years**	**Cost £**	**QALYs**	**Life years**	**Cost £**	**QALYs**	**Life years**	**£/QALY[+]**	**Change**
A. Company base case	***93,306***	***1.424***	***2.243***	***30,708***	***0.931***	***1.440***	***+62,598***	***+0.493***	***+0.803***	***£126,861***	**-**
R1) ERG OS	89,873	1.184	1.806	30,709	0.946	1.457	+59,164	+0.238	+0.349	248,838	**+121,977**
R2) ERG PFS	76,044	1.410	2.243	34,974	0.939	1.440	+41,069	+0.471	+0.803	87,202	**-39,660**
R5) ERG TTD for nivolumab treatment costs and AEs, ERG PFS for nintedanib+docetaxel disease costs and QALYs	76,568	1.411	2.243	34,974	0.939	1.440	+41,593	+0.472	+0.803	88,147	**- 38,714**
R6) ERG PFS for nivolumab disease costs and QALYs, ERG TTD for nivolumab treatment costs and AEs; ERG PFS for nintedanib+docetaxel disease costs and QALYs	76,123	1.410	2.243	34,974	0.939	1.440	+41149	+0.471	+0.803	87,371	-39491
R7) Nivolumab dosing calculations	91,955	1.424	2.243	30,708	0.931	1.440	+61,247	+0.493	+0.803	124,123	**-2,738**
R8) Treatment administration costed at start of cycle	93,347	1.424	2.243	30,736	0.931	1.440	+62,611	+0.493	+0.803	126,887	**+26**
R9) ERG utility values (Van den Hout[66] + CheckMate 057)	93,306	1.186	2.243	30,708	0.700	1.440	+62,598	+0.486	+0.803	128,916	**+2,055**
R10) Utility values from Nafees[59]	93,306	1.076	2.243	30,708	0.630	1.440	+62,598	+0.446	+0.803	140,399	**+13,537**
C. ERG revised base case A+R1, R6:R9	***70,124***	***0.870***	***1.806***	***35,007***	***0.750***	***1.457***	***+35,116***	***+0.120***	***+0.349***	***£293,232***	***+166,370***

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
R2 and R5 (shaded) are superseded by R6
* Interpret with caution due to interdependence of nivolumab ERG OS and company PFS projection in the company model
[+] Rounding errors account for difference between ICERs calculated using the incremental cost and QALY values given in the table and ICERs in this column

7 END OF LIFE

The company makes a case that nivolumab fulfils the criteria set by NICE for end of life treatment. Namely:

- the life expectancy of the patient population was short (median life expectancy <24 months)
- the number of patients who would be eligible for the treatment is small
- the increase in mean OS is >3 months.

The details of the company's case for nivolumab meeting the NICE end of life criteria are outlined in Table 48.

Table 48 Company 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.[10]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The proportional hazards assumption used in the published OS analysis has been shown not to hold (CS, Section 4.10). Therefore, mean OS from the cost effectiveness model may be considered more appropriate. This estimates mean OS, over the model time horizon of 20 years, to be 26.8 months for nivolumab compared with 13.09 months for docetaxel. This means that nivolumab is anticipated to extend life by greater than 3 months compared with docetaxel.
The treatment is licensed or otherwise indicated for small patient populations	The non-squamous NSCLC patient population potentially eligible for nivolumab treatment is expected to be very small (estimated 1413 patients). Nivolumab is also indicated for the treatment of advanced (unresectable or metastatic) squamous NSCLC in adults. The expected number of eligible patients for which nivolumab is being appraised in that submission is 853. 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 1304.

Source: CS, Table 40

Abbreviations: NHS = National Health Service; NSCLC = Non-Small Cell Lung Cancer

The ERG agrees that patients with advanced NSCLC have a short life expectancy of less than 24 months and that the total number of patients who would be eligible for the treatment is small. It also considers that nivolumab offers an extension to life of more than 3 months in comparison with docetaxel, but of just over 3 months in comparison with nintedanib+docetaxel; the ERG estimates a mean gain of 5.8 months for nivolumab versus docetaxel and a mean gain of 3.1 months for nivolumab versus nintedanib+docetaxel.

The ERG also agrees that nivolumab is licensed for a small patient population. Overall, the ERG considers that the combination of nivolumab meets NICE's end of life criteria.

8 OVERALL CONCLUSIONS

8.1 Strengths of the clinical and cost effectiveness evidence

- Checkmate 057 is a good quality trial providing direct evidence of effectiveness of nivolumab versus docetaxel in relation to OS and demonstrating an acceptable AE profile.

- 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 similar treatments in a number of previous NICE STAs

- The decision model submitted by the company is generally implemented to a good standard.

8.2 Weaknesses and areas of uncertainty

- The validity of all assessed outcomes is limited by the fact that the proportional hazards assumption has been violated

- The comparison with all comparators in the original scope is limited by the available direct and indirect evidence.

Issues common to the modelling of nivolumab, docetaxel and nintedanib+docetaxel

- QALY calculations in the company model are linked to the time patients spend on treatment and not to their health state, which is incorrect

- The utility data used by the company lack credibility

- The model calculates treatment administration costs mid-treatment cycle when they should be applied at the start of the cycle, when treatment is received.

Issues specific to the modelling of nivolumab

- The method employed by the company to project nivolumab OS results in the model does not adequately represent the existing trial evidence from CheckMate 057

- The company's PFS model projects a small minority of patients treated with nivolumab to remain progression free throughout the lifetime of the model and to constitute 85% of those patients still alive after 20 years. It also predicts that any patient treated with nivolumab who is still in PFS by 18.4 years is cured of the disease and will never progress. The ERG considers both these outcomes to be implausible

- The company model creates an interdependence between OS and PFS projections that results in some values from the parametric OS model for nivolumab being replaced by PFS values to ensure that PFS is never greater than OS. This indicates that at least one of the parametric models (PFS or OS) used for nivolumab is inappropriate

- In the company model, one-third of the survival gain (nivolumab versus docetaxel) occurs post-progression, but this does not take into account the subgroup of nivolumab patients treated beyond progression who continue to accrue extra survival benefit, whether

due to extra treatment or other factors. ERG analysis suggests that post-progression survival constitutes 52% of survival gain when 25% of patients are treated beyond progression

- The nivolumab dosing calculations undertaken by the company are inaccurate.

Issues specific to the modelling of nintedanib+docetaxel

- The proportional hazards assumptions required to validate the company's indirect method of comparing nivolumab with nintedanib+docetaxel do not hold.

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10 APPENDICES

10.1 CheckMate 057 eligibility criteria

Table 49 Inclusion/exclusion criteria for entry into CheckMate 057

	CheckMate 057 eligibility criteria
Inclusion criteria	• Patients with histologically or cytologically documented locally advanced non-squamous NSCLC who presented with stage IIIb/ stage IV or recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease) • ECOG PS ≤ 1 • Patients must have had measurable disease by computed tomography or magnetic resonance imaging per RECIST 1.1 criteria; radiographic tumour assessment was 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. • Patients who received study therapy after acceptable prior therapy as specified below: • Patients who received study therapy as second-line of treatment: • Patients must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. • First-line therapy was defined as therapy used to treat advanced disease. Each subsequent line of therapy was preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity did not define the start of a new line of therapy. Patients must have received at least two cycles of platinum doublet-based chemotherapy before discontinuation for toxicity. Experimental therapies, when given as separate regimen, were considered as separate line of therapy. Maintenance therapy following platinum doublet-based chemotherapy was not considered as a separate regimen of therapy and could include continuation of one or more of the agents used in the first-line therapy regimen or switch to another non–cross-resistant agent. The initiation of maintenance therapy required the lack of progressive disease with front-line therapy. Treatment given for locally advanced disease was not considered as a line of therapy for advanced disease. Patients with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemo-radiation 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 who received platinum-containing adjuvant, neoadjuvant or definitive chemo-radiation therapy given for locally advanced disease and who developed recurrent (local or metastatic) disease within 6 months of completing therapy were eligible. Adjuvant or neoadjuvant platinum-based chemotherapy (after surgery and/or radiation therapy) followed by recurrent or metastatic disease within 6 months of completing therapy was considered as first-line therapy for advanced disease. • Patients who received study therapy as third-line of treatment must have experienced disease recurrence or progression during or after a separate EGFR or ALK TKI regimen in addition to one prior platinum doublet-based chemotherapy regimen (regardless of order of administration). • Patients who received an EGFR-TKI (erlotinib, gefitinib or experimental) in addition to a platinum doublet-based chemotherapy must have had a tumour with a known activating EGFR mutation. Patients with a tumour with EGFR mutation-negative/unknown status who received an EGFR-TKI after failure of a prior platinum doublet-based chemotherapy were excluded. • Patients who received an ALK inhibitor (crizotinib or experimental) in addition to a platinum doublet-based chemotherapy must have had a tumour with a known ALK translocation.

	• 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.
Exclusion criteria	• Patients with untreated CNS metastases were to be excluded. Patients were eligible if CNS metastases had been treated and the patient 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. • Any serious or uncontrolled medical disorder or active infection with hepatitis or human immunodeficiency virus that may have been reactivated. • Other active malignancy requiring concurrent intervention. • Patients with previous malignancies (except non-melanoma skin cancers and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma or breast) were excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy was required or anticipated to be required during the study period. • Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg 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. • 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. • All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. • Prior therapy with anti-tumour vaccines or other immuno-stimulatory anti-tumour agents. • 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 with docetaxel. • Patients with interstitial lung disease that was symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity. • Patients were to have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

ECOG PS=Eastern Cooperative Oncology Group performance status; RECIST 1.1=Response Evaluation in Solid Tumours; EGFR=epidermal growth factor receptor; ALK=anaplastic lymphoma kinase; TKI=tyrosine kinase inhibitor; CNS=central nervous system; NCI CTCAE= National Cancer Institute Cancer Therapy Evaluation Program; PD-1= programmed death-1; PD-L1= programmed death-ligand 1; PD-L2= programmed death-ligand 2

10.2 PH assumption testing of CheckMate 057

- **Overall survival**

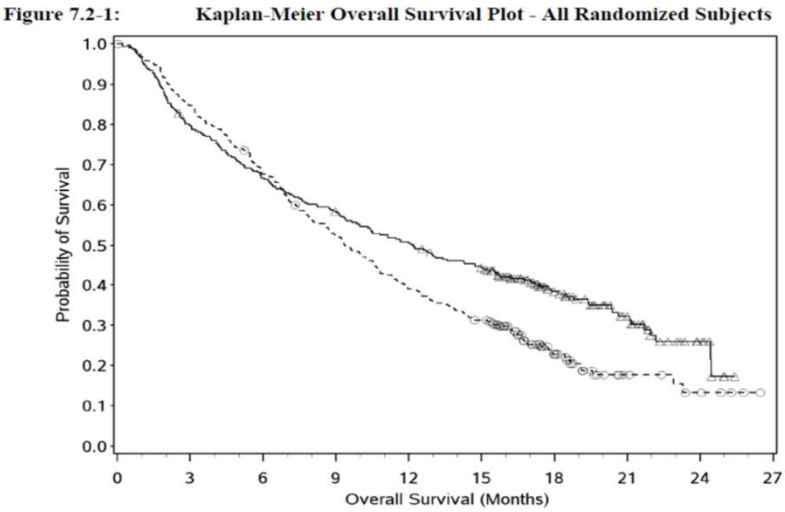


Figure 36 K-M curve of OS

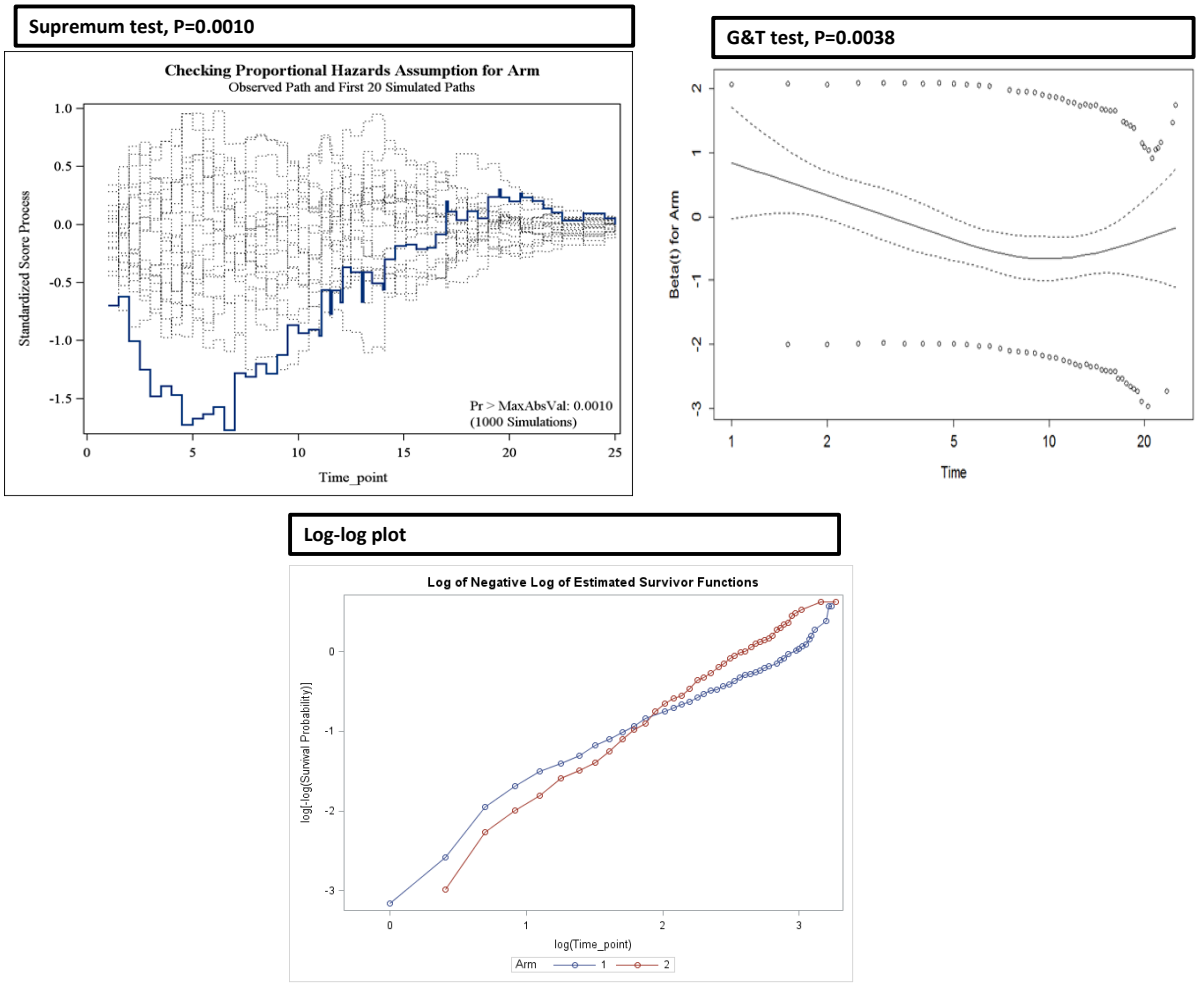


Figure 37 PH assumption tests-OS

- **PFS survival**

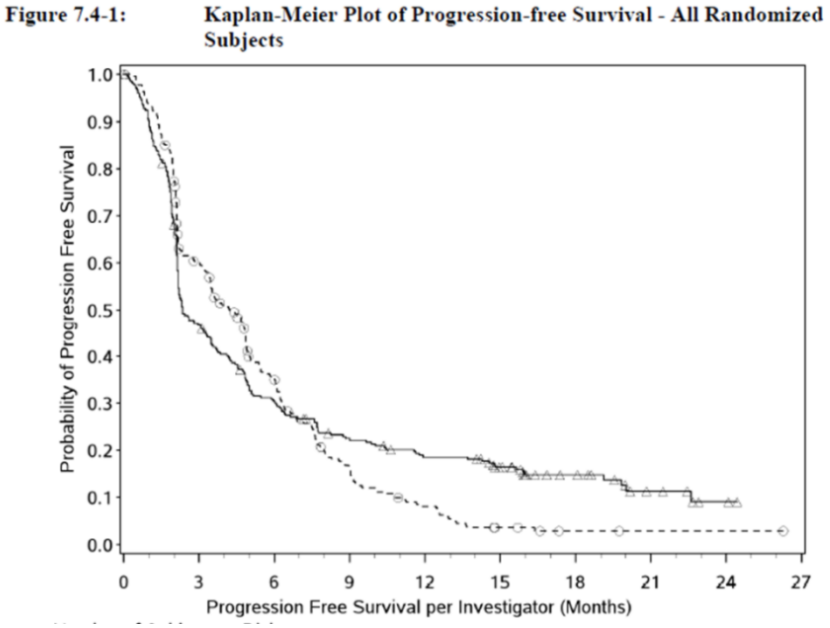


Figure 38 K-M Curve of PFS

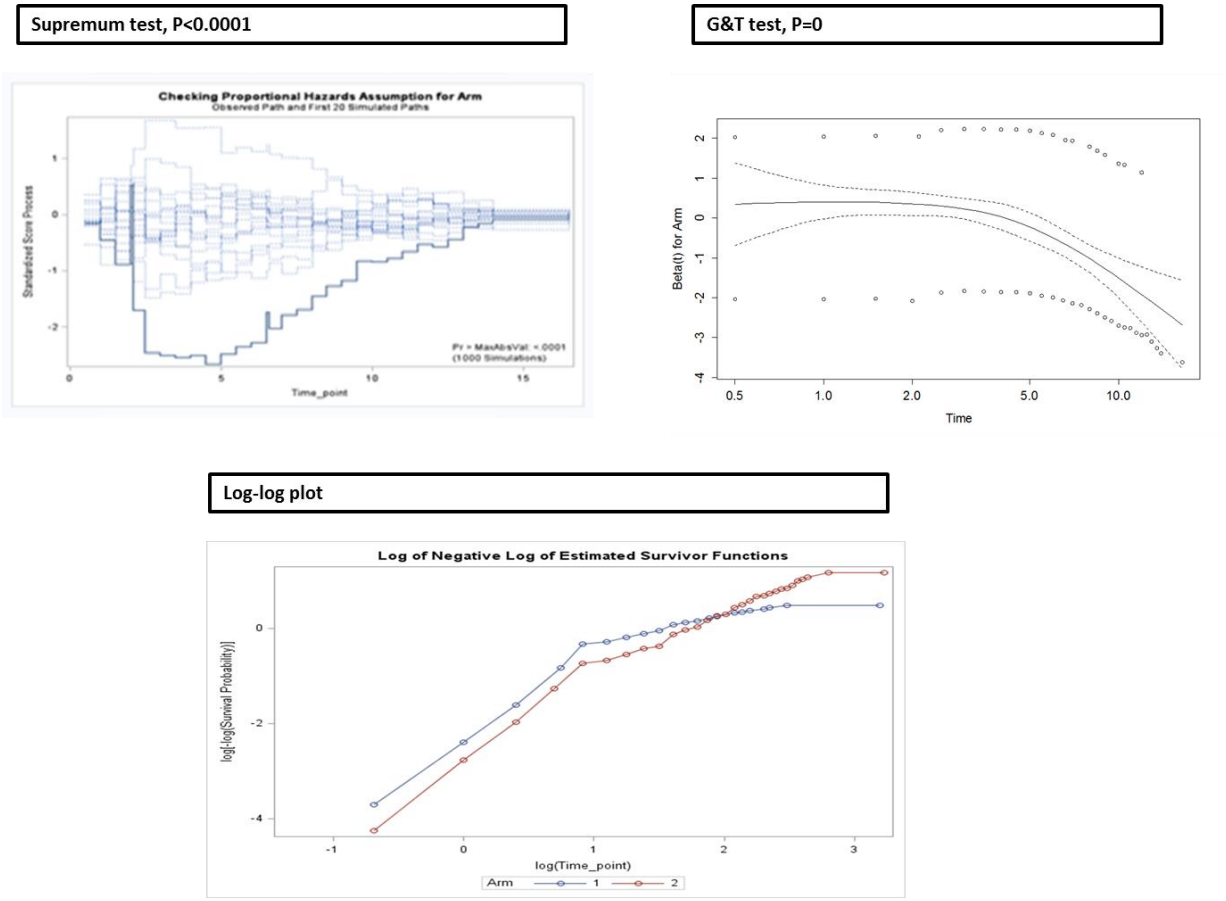


Figure 39 PH assumption tests - PFS

10.3 Subgroup analyses on 18 month data

Table 50 CheckMate 057: Treatment effect on OS in predefined subsets: 18-month data cut

Subset	N	HR, nivolumab vs. docetaxel (95% CI)	Test for interaction P value
Prior use of maintenance therapy			0.7577
Yes	233	0.78 (0.58 to 1.06)	
No	349	0.71 (0.56 to 0.91)	
Line of therapy			0.0431
Second-line	514	0.68 (0.56 to 0.83)	
Third-line/other	68	1.29 (0.74 to 2.25)	
Region			0.0006
US/Canada	215	0.54 (0.39 to 0.74)	
Europe	269	0.74 (0.57 to 0.98)	
Rest of World	98	1.54 (0.96 to 2.48)	
Age categorisation (years)			0.9960
<65	339	0.77 (0.60 to 0.99)	
≥65 and <75	200	0.68 (0.49 to 0.93)	
≥75	43	0.76 (0.37 to 1.56)	
Sex			0.3484
Male	319	0.69 (0.53 to 0.89)	
Female	263	0.82 (0.62 to 1.08)	
Race			
White	533	0.72 (0.59 to 0.88)	
Baseline ECOG PS			0.5236
0	179	0.63 (0.44 to 0.90)	
≥1	402	0.78 (0.62 to 0.97)	
Smoking status			0.0446
Yes	458	0.66 (0.54 to 0.82)	
Other	124	1.08 (0.70 to 1.65)	
EGFR mutation status			0.4689
Positive	82	1.12 (0.67 to 1.86)	
Not detected	342	0.64 (0.50 to 0.82)	
Not reported	158	0.76 (0.53 to 1.09)	
ALK translocation status			0.2970
Positive	13	0.50 (0.12 to 2.04)	
Not detected	254	0.71 (0.53 to 0.94)	
Not reported	315	0.79 (0.61 to 1.02)	
KRAS mutation status			0.9695
Positive	28	0.57 (0.32 to 1.02)	
Not detected	60	0.96 (0.65 to 1.43)	
Not reported	204	0.71 (0.56 to 0.89)	
MET receptor status			
Not reported	566	0.72 (0.59 to 0.87)	
Cell type			0.2536
Adenocarcinoma	541	0.76 (0.63 to 0.93)	
Other	41	0.51 (0.25 to 1.02)	

Subset	N	HR, nivolumab vs. docetaxel (95% CI)	Test for interaction P value
Time from diagnosis to randomisation			0.6366
<1 year	350	0.78 (0.62 to 0.99)	
Other	232	0.68 (0.50 to 0.92)	
Time from completion of most recent regimen to randomisation			0.2018
<3 months	364	0.82 (0.65 to 1.04)	
3-6 months	114	0.76 (0.49 to 1.16)	
>6 months	103	0.46 (0.28 to 0.76)	
Prior neo-adjuvant			0.8844
Yes	19	0.76 (0.26 to 2.21)	
No	563	0.74 (0.61 to 0.89)	
Prior adjuvant			0.5121
Yes	42	0.92 (0.45 to 1.87)	
No	540	0.73 (0.60 to 0.89)	
CNS metastases			0.3246
Yes	69	0.98 (0.59 to 1.65)	
No	513	0.71 (0.58 to 0.87)	

ALK=anaplastic lymphoma kinase; CI=confidence interval; CNS=central nervous system; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; HR=hazard ratio; KRAS=kirsten rat sarcoma 2 viral oncogene homolog; MET=mesenchymal epithelial transition; OS=overall survival; US=United States
Source: Company response to the ERG clarification letter, Table 2

10.4 Quality assessment of RCTs included in the ITC

Table 51 Summary of quality assessment of RCTs included in the analysis

Study ID	Jadad[1] [8] score	AC 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?
LUME-Lung 1[24]	4	A	Low risk; Randomisation was carried out appropriately as treatment was assigned by IVRS or IWRS. Allocation concealment was adequate.	Low risk; Demographics and baseline characteristics were well balanced between the two treatment	Low risk; This was a double-blind study. Patients and investigators were masked to assignment, and none of the individuals directly involved in the conduct and analysis of the study had access to treatment allocation before the final database lock	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were adequately reported at data cut-off	Low risk; Author has measured all the outcomes that have been reported in published protocol land in clinical study registry.	Low risk; The efficacy and safety analysis was done using ITT/mITT population
ISTANA[26]	1	B	Not clear; This was a randomised study but the method of randomisation was not reported. Allocation concealment was also not reported	Low risk; The treatment groups were well balanced for baseline characteristics, with the exception of slightly fewer females (33% versus 43%) and never-smokers (37% versus 46%) in the gefitinib treatment group than in the docetaxel group.	High risk: This was an open-label study	High Risk: Withdrawals were not reported.	Low risk; The author analysed all the primary outcomes in this final analysis as described in the protocol and the clinical study registry.	Low risk; ITT and mITT population was analysed for efficacy and safety outcomes
ISEL[25]	4	A	Not clear; This was a	Low risk; The baseline	Low risk; This was a	Low risk;	Not clear; There	Low risk; The safety

Study ID	Jadad[1][8] score	AC 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?
			randomised study and the randomisation was carried out by minimisation method.	characteristics of the two treatment arms were well balanced.	double-blind study and the details of blinding were reported. Physically identical tablets and packaging, assigned by the central registration and randomisation centre were used to ensure masking of both patients and investigators.	Withdrawals and reasons for withdrawals were reported	was no evidence to conclude whether all outcomes assessed were reported or not	and efficacy analysis was done using ITT/mITT population
CheckMate 057[28]	3	A	Low risk; the patients were randomised to the two active treatments using IVRS; Allocation concealment was adequate.	Low risk; the baseline characters in the two treatment arms were well balanced.	High risk; the study was conducted as an open-label study.	Low risk; study withdrawals were adequately reported.	Low risk; the authors measured all outcomes as reported in the protocol.	Low risk; the efficacy and safety analysis were performed using ITT and mITT analysis respectively.
V-15-32[27]	2	B	Not clear; This was a randomised study but the method of randomisation was not reported	Low risk; Treatment groups were generally well balanced for baseline demographics except for some small imbalances in smoking history (7% fewer never-smokers and 10% more ex-smokers in the gefitinib arm)	High risk; This was an open-label study	Low risk; The withdrawals and the specific reasons for withdrawal were reported	Low risk; There was a published protocol that describes that the author has measured all the outcomes that have been reported	Low risk; ITT population was considered for both safety and efficacy analysis

AC=allocation concealment; ITT=Intent-to-Treat; IVRS=interactive voice response system; IWRS=interactive web-based response system; mITT=modified Intent-to-Treat
Note: The Jadad Score is used to assess quality of RCTs, allocating them a score between 0 (very poor) and 5 (rigorous) .
Source: CS, adapted from Table 25

10.5 Outcomes data used in indirect treatment comparisons

Table 52 Summary of data from studies reporting data for pre-treated non-squamous NSCLC population and included in analysis

Study ID (acronym)	Treatment (N)	ORR, n (%)	OS (HR) (95% CI)	OS (RMST; Mean (SE; 95% CI) (months)	PFS HR (95% CI)	PFS (RMST; months)	Any adverse event	Any Grade 3/4 adverse event
Studies connected in BOTH networks (EGFR mutation-negative/unknown AND all-comers NSQ NSCLC)								
LUME-Lung 1[24]	Docetaxel (659) Results presented for adenocarcinoma subgroup (n=336)	12 (3.6%)	0.83 (0.70 to 0.99)	For all-comers at tau=13 months: 9.313 (0.228; 8.866 to 9.76). For EGFR mutation-negative/unknown at tau=28 months: 13.213 (0.512; 12.211 to 14.216).	0.77 (0.62 to 0.96)	For all-comers at tau=12 months: 4.173 (0.241; 3.70 to 4.645)	314/333 (94%)	228/333 (68%)
	Docetaxel+nintedanib (655) Results presented for adenocarcinoma subgroup (n=322)	15 (4.7%)		For all-comers at tau=13 months: 9.726 (0.241; 9.253 to 10.2). For EGFR mutation-negative/unknown at tau=28 months: 14.767 (0. 565; 13.659 to 15.874).		For all-comers at tau=12 months: 4.826 (0.258; 4.32 to 5.332)	308/320 (96%)	243/320 (76%)
ISTANA[26]	Docetaxel (79)	6 (7.6%)	0.87 (0.61 to 1.24)	For all-comers at tau=13 months: 9.743 (0.495; 8.772 to 10.713)	0.634 (0.459 to 0.875)	NR	NR	NR
	Gefitinib (82)	23 (28%)		For all-comers at tau=13 months: 9.949 (0.482; 9.004 to 10.90)		NR	NR	NR
ISEL[25]	BSC (563)	NR	0.84 (0.68 to 1.03)	For all-comers at tau=13 months: 6.752 (0.314; 6.138 to 7.367)	NR	NR	NR	NR
	Gefitinib	NR		For all-comers at tau=13		NR	NR	NR

Study ID (acronym)	Treatment (N)	ORR, n (%)	OS (HR) (95% CI)	OS (RMST; Mean (SE; 95% CI) (months)	PFS HR (95% CI)	PFS (RMST; months)	Any adverse event	Any Grade 3/4 adverse event
	+BSC (1,129)			months: 7.508 (0.233; 7.052 to 7.963)				
CheckMate 057	Nivolumab (292)	All-comers NSQ NSCLC: 56 (19.2%) Pooled EGFR mutation-negative/unknown NSCLC: 51 (21%)	All-comers NSQ NSCLC: 0.73 (0.59 to 0.89) Pooled EGFR mutation-negative/unknown NSCLC: 0.69 (0.56 to 0.85)*	For all-comers at tau=13 months: 9.108 (0.273; 8.572 to 9.463) For EGFR mutation-negative/unknown at tau=28 months: 14.976 (0.665; 13.673 to 16.28)	All-comers NSQ NSCLC: 0.92 (0.77 to 1.11) Pooled EGFR mutation negative/unknown NSCLC: 0.83 (0.68 to 1.02)*	For all-comers at tau=12 months: 5.116 (0.251; 4.624 to 5.696) For EGFR mutation-negative/unknown at tau=12 months: 6.336 (0.364; 5.622 to 7.05)	280 (98%)	132 (46%)[ł]
	Docetaxel (290)	All-comers NSQ NSCLC: 36 (12.4%) Pooled EGFR mutation-negative/unknown NSCLC: 30 (12%)		For all-comers at tau=13 months: 8.894 (0.251; 8.402 to 9.386) For negative/unknown at tau=28 months: 12.325 (0.599; 11.151 to 13.498)		For all-comers at tau=12 months: 5.263 (0.221; 4.831 to 5.696) For EGFR mutation-negative/unknown at tau=12 months: 5.684 (0.303; 5.09 to 6.277)	265 (99%)	180 (67%)[ł]
Study connected ONLY in network of all-comers NSQ NSCLC								
V-15-32[27]	Docetaxel (244)	24 (9.8%)	1.01 (0.87 to 1.27)	For all-comers at tau=13 months: 10.323 (0.240; 9.853 to 10.793)	0.89 (0.73 to 1.09)	NR	236 (99%)	195 (82%)
	Gefitinib (245)	45 (18.4%)		For all-comers at tau=13 months: 9.432 (0.275; 8.893 to 9.971)		NR	242 (99%)	99 (41%)

CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; NR=not reported; NSCLC=non-small cell lung cancer; NSQ=non-squamous; ORR=objective response rate, OS=overall survival; PFS=progression-free survival; RMST=restricted mean survival time; SE=standard error; tau=truncation time

*These data inputs are different to those presented in Table 27 of the CS; these are updated data inputs (from an additional analysis conducted by the company) which are more appropriate for use in the ITC

[†]These data were not provided in Table 27 of the CS, but the ERG observed that results for the any Grade 3/4 adverse event were reported in the ITC and so the ERG requested the data inputs as part of the clarification process

Source: CS, adapted from Table 27

10.6 Indirect comparison of nivolumab versus nintedanib+docetaxel for the second-line population only

Outcome	Nivolumab vs. nintedanib+docetaxel
Patient population: All-comers NSQ NSCLC	
OS (RMST difference (95% CI]; p value)	[redacted]
PFS (RMST difference [95% CI]; p value)	[redacted]
ORR (RR [95% CI]; p value)	[redacted]
Any adverse event (RR [95% CI]; p value)	[redacted]
Any Grade 3/4 adverse event (RR [95% CI]; p value)	[redacted]
Patient population: EGFR mutation-negative/unknown NSQ NSCLC	
OS (RMST difference [95% CI]; p value)	[redacted]
PFS (RMST difference [95% CI]; p value)	[redacted]
ORR (RR [95% CI]; p value)	[redacted]

CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RMST=restricted mean survival time; RR=relative risk

10.7 Health state utility

Table 53 UK-specific mean EQ-5D values by region

Region	Overall Mean	95% CI	PF Mean	95% CI	PD Mean	95% CI	ICER
USA & Canada (n=215)	0.751	0.747, 0.755	0.758	0.753, 0.763	0.730	0.723, 0.738	£100,279
Europe (n=268)	0.716	0.716, 0.717	0.735	0.732, 0.739	0.654	0.648, 0.661	£105,307
Other (n=99)	0.713	0.712, 0.715	0.717	0.715, 0.720	0.699	0.689, 0.708	£105,278

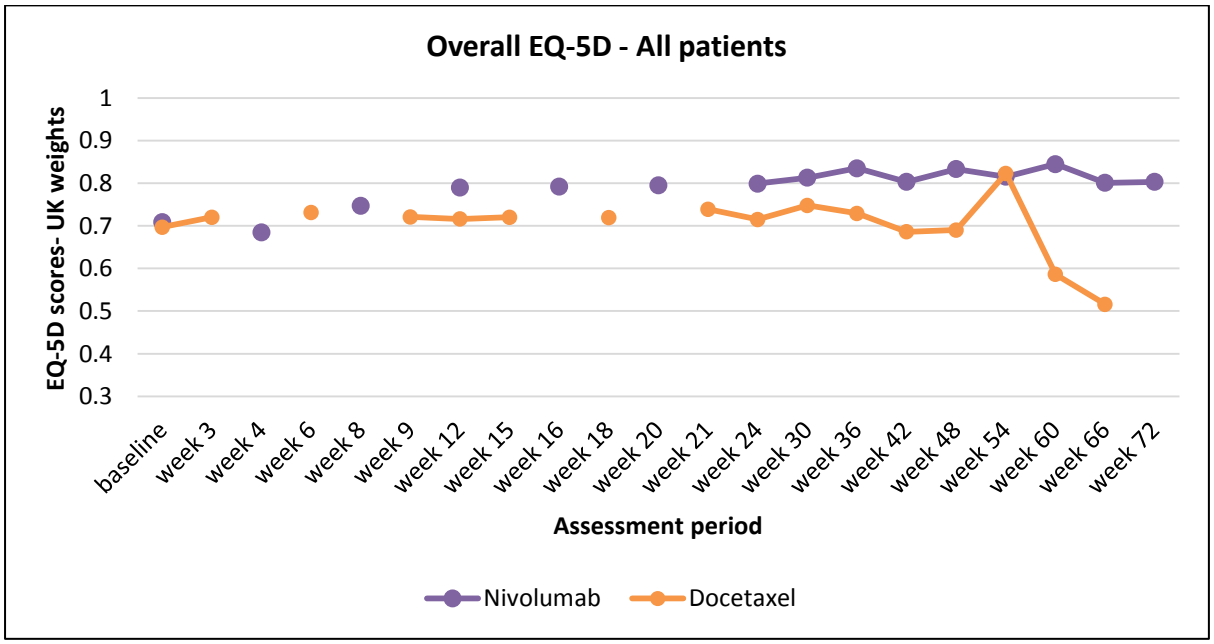
CI=confidence interval; ICER=incremental cost effectiveness ratio; PD=progressed disease; PF=progression free
Source: adapted from company's response to clarification letter, Tables 4-7

Table 54 UK-specific mean EQ-5D values by treatment arm and region

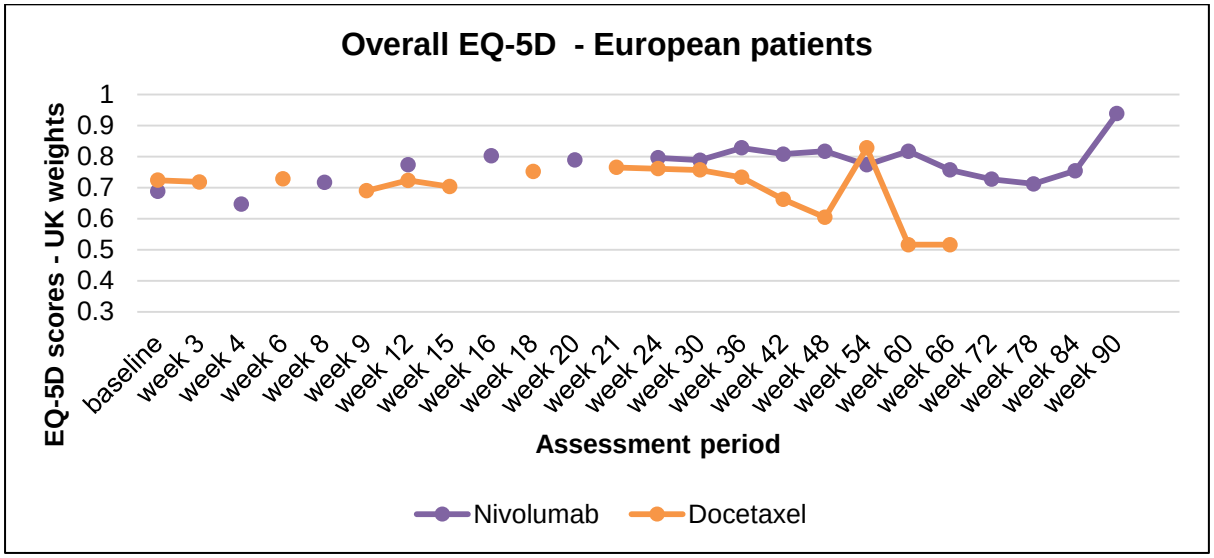
Region	Overall Mean	PF Mean	PF Mean
All			
Nivolumab	0.749	0.761	0.716
Docetaxel	0.705	0.716	0.650
USA & Canada (n=215)			
Nivolumab	0.784	0.791	0.755
Docetaxel	0.698	0.709	0.681
Europe (n=268)			
Nivolumab	0.725	0.743	0.682
Docetaxel	0.707	0.729	0.605

Other (n=99)			
Nivolumab	0.726	0.727	0.723
Docetaxel	0.703	0.711	0.644

PD= progressed disease; PF=progression-free
Source: adapted from company's response to clarification letter, Tables 4-7



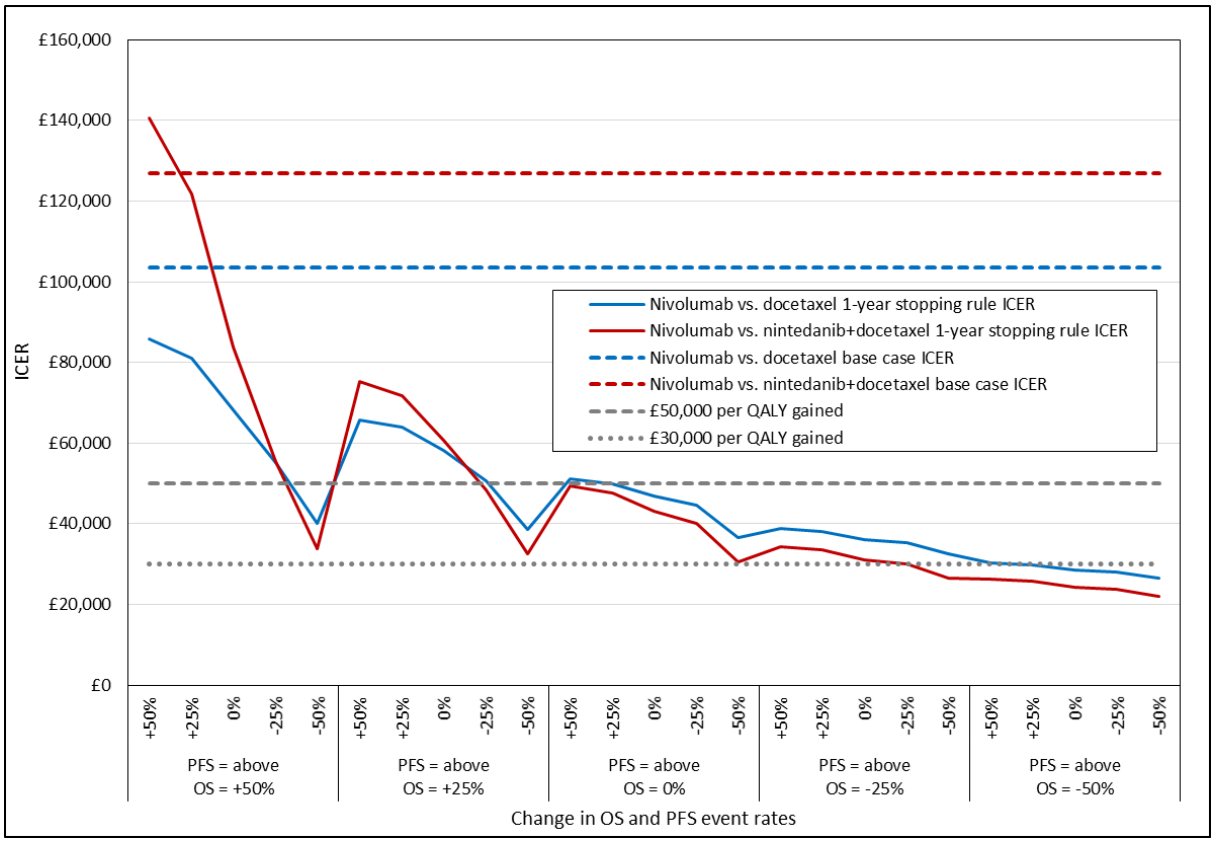
EQ-5D=EuroQol 5-dimension
Source: Company's response to clarification letter, Table 4
Figure 40 UK-specific mean EQ-5D for all patients



EQ-5D=EuroQol 5-dimension
Source: Company's response to clarification letter, Tables 5-7
Figure 41 UK-specific mean EQ-5D for European patients

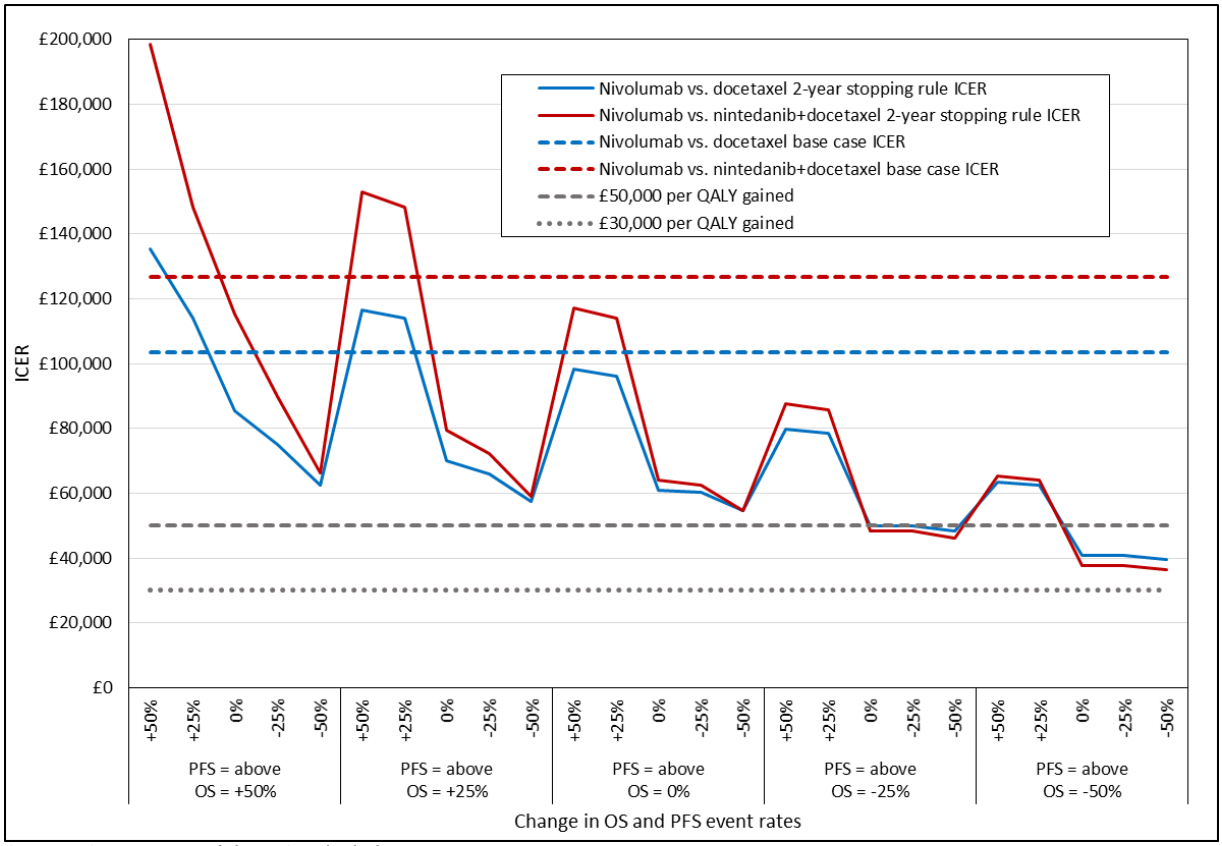
10.8 Sensitivity analysis of 1- and 2- year stopping rules

The following charts show the potential effects of varying the progression rates for PFS and mortality rates for OS by -50%, -25%, 0%, +25% and +50% after stopping treatment with nivolumab at 1 year (Figure 42) and 2 years (Figure 43).



Source: Company model, ERG calculations

Figure 42 ICERs for 1-year stopping rule with varying PFS and OS event rates



Source: Company model, ERG calculations

Figure 43 ICERs for 2-year stopping rule with varying PFS and OS event rates

10.9 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.
All scenarios are activated by a logic switch with 0 = unchanged, 1 = apply first ERG scenario option, 2 (or other number >1) = apply second ERG scenario option.
Logic switches are indicated by range variables Mod_*letter* where letter = A - J.
A menu of revisions, scenarios and Mod names appears below and on the 'Results' worksheet together with summary results as used to transfer to the ERG report.

Revision	Name	Description
R1	Mod_A	ERG OS
R2	Mod_B	ERG PFS
R3	Mod_C	Nivolumab vs. docetaxel: ERG TTD
R4	Mod_D	Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs
R5	Mod_E	Nivolumab vs. nintedanib+docetaxel: ERG TTD for nivolumab, ERG PFS for nintedanib+docetaxel
R6	Mod_F	Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel
R7	Mod_G	Nivolumab dosing calculations
R8	Mod_H	Calculate treatment administration costs at start cycle
R9	Mod_I	Use ERG utility values (Van den Hout + CheckMate 057)
R10	Mod_J	Use Nafees et al. utility values

Scenario	Name	Description
S1	Mod_Z	Sensitivity analysis PFS 1 year stopping rule: increased progression rates 0 = no change in mortality after 52 weeks, 1 = +25% mortality after 52 weeks, 2= +50% mortality after 52 weeks
S2	Mod_Y	Sensitivity analysis OS 1 year stopping rule: increased mortality rates 0 = no change in mortality after 52 weeks, 1 = +25% mortality after 52 weeks, 2= +50% mortality after 52 weeks
S3	Mod_V	Sensitivity analysis PFS 1 year stopping rule: decreased progression rates 0 = no change in mortality after 52 weeks, 1 = -25% mortality after 52 weeks, 2= -50% mortality after 52 weeks
S4	Mod_U	Sensitivity analysis OS 1 year stopping rule: decreased mortality rates 0 = no change in mortality after 52 weeks, 1 = +25% mortality after 52 weeks, 2= -50% mortality after 52 weeks
S5	Mod_X	Sensitivity analysis PFS 2 year stopping rule: increased progression rates 0 = no change in mortality after 104 weeks, 1 = +25% mortality after 104 weeks, 2= +50% mortality after 104 weeks
S6	Mod_W	Sensitivity analysis OS 2 year stopping rule: increased mortality rates 0 = no change in mortality after 104 weeks, 1 = +25% mortality after 104 weeks, 2= +50% mortality after 104 weeks
S7	Mod_T	Sensitivity analysis PFS 2 year stopping rule: decreased progression rates 0 = no change in mortality after 104 weeks, 1 = -25% mortality after 104 weeks, 2= -50% mortality after 104 weeks
S8	Mod_S	Sensitivity analysis OS 2 year stopping rule: decreased mortality rates 0 = no change in mortality after 104 weeks, 1 = -25% mortality after 104 weeks, 2= -50% mortality after 104 weeks

Instructions for modifying the company model

- Move all sheets from ID900_ERG survival estimates.xlsx into end of company model
- For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'modification' column in the table below
    - paste into the cells referred to in the 'Cell' column in the table below

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Response and Survival	H39:H1079	R1) ERG OS	Mod_A	=(IF(INT_OS="Spline",mSpline(INT_OSsplineform,INT_OSnoknots,INT_OSsplineparams,INT_OSknots,INT_OSsplinecoef,E39:E1079),mSurvival_func(INT_OS,INT_OS_Scale,INT_OS_Shape,E39:E1079,INT_OS_Q))*IF(AND(Mod_A=0,Mod_Y=0,Mod_W=0,Mod_U=0,Mod_S=0),1,0))+('ERG OS'!C12:'ERG OS'!C1052*IF(Mod_A=1,1,0))+('ERG stopping rule'!D11:'ERG stopping rule'!D1052*IF(Mod_Y=1,1,0))+('ERG stopping rule'!E11:'ERG stopping rule'!E1052*IF(Mod_Y=2,1,0))+('ERG stopping rule'!J11:'ERG stopping rule'!J1052*IF(Mod_W=1,1,0))+('ERG stopping rule'!K11:'ERG stopping rule'!K1052*IF(Mod_W=2,1,0))+('ERG stopping rule'!P11:P1052*IF(Mod_U=1,1,0))+('ERG stopping rule'!Q11:Q1052*IF(Mod_U=2,1,0))+('ERG stopping rule'!V11:V1052*IF(Mod_S=1,1,0))+('ERG stopping rule'!W11:W1052*IF(Mod_S=2,1,0))
		S2) Sensitivity analysis OS 1 year stopping rule: increased mortality rates	Mod_Y	
		S4) Sensitivity analysis OS 2 year stopping rule: dcreased mortality rates	Mod_W	
		S6) Sensitivity analysis OS 1 year stopping rule: decreased mortality rates	Mod_U	
		S8) Sensitivity analysis OS 2 year stopping rule: decreased mortality rates	Mod_S	

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Response and Survival	G39:G1079	S1) Sensitivity analysis PFS 1 year stopping rule: increased progression rates S3) Sensitivity analysis PFS 2 year stopping rule: increased progression rates S5) Sensitivity analysis PFS 1 year stopping rule: decreased progression rates S7) Sensitivity analysis PFS 2 year stopping rule: decreased progression rates	Mod_Z Mod_X Mod_V Mod_T	=(IF(INT_PFS="Spline", mSpline(INT_PFSsplineform, INT_PFSnoknots, INT_PFSsplineparams, INT_PFSknots, INT_PFSsplinecoef, E39:E1079), mSurvival_func(INT_PFS, INT_PFS_Scale, INT_PFS_Shape, E39:E1079, INT_PFS_Q)))*IF(AND(Mod_Z=0,Mod_X=0,Mod_V=0,Mod_T=0),1,0)+('ERG stopping rule'!B11:'ERG stopping rule'!B1052*IF(Mod_Z=1,1,0))+('ERG stopping rule'!C11:'ERG stopping rule'!C1052*IF(Mod_Z=2,1,0))+('ERG stopping rule'!H11:'ERG stopping rule'!H1052*IF(Mod_X=1,1,0))+('ERG stopping rule'!I11:'ERG stopping rule'!I1052*IF(Mod_X=2,1,0))+('ERG stopping rule'!N11:N1052*IF(Mod_V=1,1,0))+('ERG stopping rule'!O11:O1052*IF(Mod_V=2,1,0))+('ERG stopping rule'!T11:T1052*IF(Mod_T=1,1,0))+('ERG stopping rule'!U11:U1052*IF(Mod_T=2,1,0))
	J39:J1079	R1) ERG OS	Mod_A	=(IF(TRT1_OS="Spline",mSpline(TRT1_OSsplineform,TRT1_OSnosplines,TRT1_OSsplineparams,TRT1_OSknots,TRT1_OSsplinecoef,E39:E1079),mSurvival_func(TRT1_OS,TRT1_OS_scale,TRT1_OS_shape,E39:E1079,TRT1_OS_Q))*IF(Mod_A=0,1,0))+ ('ERG OS'!D12:'ERG OS'!D1052*IF(Mod_A=1,1,0))
	W38:W64	R1) ERG OS	Mod_A	=(MAX($J38,V38)*IF(Mod_A=0,1,0))+('ERG OS'!E11*IF(Mod_A=1,1,0))
	W65:W1079	R1) ERG OS	Mod_A	=(MAX($J65^TRT2_HR_OS_user,V65)*IF(Mod_A=0,1,0))+('ERG OS'!E38*IF(Mod_A=1,1,0))
	R38:R1079	R3) Nivolumab vs. docetaxel: ERG TTD R5) Nivolumab vs. nintedanib+docetaxel: ERG TTD for nivolumab, ERG PFS for nintedanib+docetaxel	Mod_C Mod_E	=(O38*IF(AND(Mod_C=0,Mod_E=0),1,0))+('ERG TTD'!C11*IF(OR(Mod_C=1,Mod_E=1),1,0))
	T38:T1079	R3) Nivolumab vs. docetaxel: ERG TTD	Mod_C	=(I38*IF(Mod_C=0,1,0))+('ERG TTD'!O11*IF(Mod_C=1,1,0))

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Response and Survival	V38:V46	R2) ERG PFS R5) Nivolumab vs. nintedanib+docetaxel: ERG TTD for nivolumab, ERG PFS for nintedanib+docetaxel R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_B Mod_E Mod_F	=($I38*IF(AND(Mod_B=0,Mod_E=0,Mod_F=0),1,0))+('ERG PFS'!E11*IF(OR(Mod_B=1,Mod_E=1,Mod_F=1),1,0))
	V47:V1079	R2) ERG PFS R5) Nivolumab vs. nintedanib+docetaxel: ERG TTD for nivolumab, ERG PFS for nintedanib+docetaxel R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_B Mod_E Mod_F	=(($I47^TRT2_HR_PFS_user)*IF(AND(Mod_B=0,Mod_E=0,Mod_F=0),1,0))+('ERG PFS'!E20*IF(OR(Mod_B=1,Mod_E=1,Mod_F=1),1,0))

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Cost	E10	R1) ERG OS	Mod_A	=((PF_cost/4)*((('Patient flow - 1'!$P14)*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!E11*IF(OR(Mod_B=1,Mod_D=1,Mod_F=1),1,0))))*$C10
		R2) ERG PFS	Mod_B	+ ((PD_cost/4)*((('Patient flow - 1'!$Q14)*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))+((('ERG health states'!I11)*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0)))+('ERG health
		R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_D	states'!M11*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0))))*$C10
		R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_F	+ ((terminal_cost)*('Patient flow - 1'!J14))*C10
Cost	E11:E1049	R1) ERG OS	Mod_A	=((PF_cost/4)*((('Patient flow - 1'!$P15)*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!E12*IF(OR(Mod_B=1,Mod_D=1,Mod_F=1),1,0))))*$C11
		R2) ERG PFS	Mod_B	+ ((PD_cost/4)*((('Patient flow - 1'!$Q15)*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))+((('ERG health states'!I12)*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0)))+('ERG health
		R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_D	states'!M12*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0))))*$C11
		R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_F	+ ((terminal_cost)*('Patient flow - 1'!J15-'Patient flow - 1'!J14))*C11+E10
	N10	R1) ERG OS	Mod_A	=((PF_cost/4)*((('Patient flow - 1'!$AH14)*IF(AND(Mod_B=0,Mod_D=0),1,0))+('ERG health states'!Y11*IF(OR(Mod_B=1,Mod_D=1),1,0))))*$C10
		R2) ERG PFS	Mod_B	+ ((PD_cost/4)*((('Patient flow - 1'!$AI14)*IF(AND(Mod_B=0,Mod_D=0),1,0))+((('ERG health states'!AC11)*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1)),1,0)))+('ERG health
		R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_D	states'!AG11*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1)),1,0))))*$C10 +(terminal_cost)*('Patient flow - 1'!AB14)*C10

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Cost	N11:N1049	R1) ERG OS R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_A Mod_B Mod_D	=((PF_cost/4)*((('Patient flow - 1'!$AH15)*IF(AND(Mod_B=0,Mod_D=0),1,0))+('ERG health states'!Y12*IF(OR(Mod_B=1,Mod_D=1),1,0))))*$C11 + ((PD_cost/4)*((('Patient flow - 1'!$AI15)*IF(AND(Mod_B=0,Mod_D=0),1,0))+((('ERG health states'!AC12)*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1)),1,0)))+('ERG health states'!AG12*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1)),1,0))))*$C11 + ((terminal_cost)*MAX(0, ('Patient flow - 1'!AB15-'Patient flow - 1'!X15))*$C11) + N10
	F10	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_B Mod_D Mod_F	=IF(econ_dose_cap_on, IF(B10 <= econ_dose_cap, 1, 0), 1)*IF(dose_cap_on, IF(B10 <= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B10 <= trt_cap, 1,0), 1) *((INT_acq*(('Patient flow - 1'!D14*IF(AND(Mod_D=0,Mod_F=0),1,0))+('ERG health states'!C11*IF(Mod_B=1,1,0))+('ERG TTD'!C11*IF(OR(Mod_D=1,Mod_F=1),1,0))))*1 + (INT_PD_Trt*INT_PD_doses*INT_acq*('Patient flow - 1'!E14))) + (0*('Patient flow - 1'!E14))*$C10
	F11:F1049	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R6) Nivolumab vs. .nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_B Mod_D Mod_F	=IF(MOD($A11, INT_periodicity) = 0, 1, 0)*IF(econ_dose_cap_on, IF(B11 <= econ_dose_cap, 1, 0), 1)*IF(dose_cap_on, IF(B11 <= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B11 <= trt_cap, 1,0), 1) *((INT_acq*(('Patient flow - 1'!D15*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!C12*IF(Mod_B=1,1,0))+('ERG TTD'!C12*IF(OR(Mod_D=1,Mod_F=1),1,0))))*$C11 + (INT_PD_Trt*INT_PD_doses*INT_acq*MAX(0,(('Response and survival'!BC38 - 'Response and survival'!BC39)*$C11))) + (0*('Patient flow - 1'!E15))*$C11) + F10

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Cost	O10	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_B Mod_D	=(TRT1_acq*(('Patient flow - 1'!V14*IF(AND(Mod_B=0,Mod_D=0),1,0))+('ERG health states'!W11*IF(Mod_B=1,1,0))+('ERG TTD'!O11*IF(Mod_D=1,1,0)))*$C10) + (0*('Patient flow - 1'!W14)*$C10)
	O11:O1049	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_B Mod_D	=IF(MOD($A11, TRT1_periodicity) = 0, 1, 0) *(TRT1_acq*((('Patient flow - 1'!V15*IF(AND(Mod_B=0,Mod_D=0),1,0))+('ERG health states'!W12*IF(Mod_B=1,1,0))+('ERG TTD'!O12*IF(Mod_D=1,1,0)))*$C11 + 0*('Patient flow - 1'!W15*$C11))) + O10
	G10	R2) ERG PFS R4) Nivolumab vs docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel R8) Calculate treatment administration costs at start cycle	Mod_B Mod_D Mod_F Mod_H	=IF(dose_cap_on, IF(B10<= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B10 <= trt_cap, 1,0), 1)*(INT_admin*(('Patient flow - 1'!$P14*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0,Mod_H=0),1,0))+('Patient flow - 1'!$D14*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0,Mod_H=1),1,0))+('ERG health states'!E11*IF(AND(Mod_B=1,Mod_H=0),1,0))+('ERG health states'!C11*IF(AND(Mod_B=1,Mod_H=1),1,0))+('ERG TTD'!E11*IF(AND(Mod_H=0,OR(Mod_D=1,Mod_F=1)),1,0)) +('ERG TTD'!C11*IF(AND(Mod_H=1,OR(Mod_D=1,Mod_F=1)),1,0))*$C10+ (INT_PD_Trt*INT_PD_doses*INT_admin*('Patient flow - 1'!$Q14)*C10)+ (0*('Patient flow - 1'!$Q14))*$C10))

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Cost	G11:G1049	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel R8) Calculate treatment administration costs at start cycle	Mod_B Mod_D Mod_F Mod_H	=IF(MOD($A11, INT_periodicity) = 0, 1, 0)*IF(dose_cap_on, IF(B11 <= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B11 <= trt_cap, 1,0), 1) *(((INT_admin*(('Patient flow - 1'!$P15 *IF(AND(Mod_B=0,Mod_D=0,Mod_F=0,Mod_H=0),1,0))+('Patient flow - 1'!$D15*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0,Mod_H=1),1,0))+('ERG health states'!E12*IF(AND(Mod_B=1,Mod_H=0),1,0))+('ERG health states'!C12*IF(AND(Mod_B=1,Mod_H=1),1,0))+('ERG TTD'!E12*IF(AND(Mod_H=0,OR(Mod_D=1,Mod_F=1)),1,0)) +('ERG TTD'!C12*IF(AND(Mod_H=1,(OR(Mod_D=1,Mod_F=1))),1,0))))*$C11 + (INT_PD_Trt*INT_PD_doses*INT_admin*MAX(0,(('Response and survival'!BC38) - ('Response and survival'!BC39)))*C11)) + (0*('Patient flow - 1'!$Q15))*$C11) + G10
	P10	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R8) Calculate treatment administration costs at start cycle	Mod_B Mod_D Mod_H	=(TRT1_admin*(('Patient flow - 1'!$AH14*IF(AND(Mod_B=0,Mod_D=0,Mod_H=0),1,0))+('Patient flow - 1'!V14*IF(AND(Mod_H=1,Mod_B=0,Mod_D=0),1,0))+('ERG health states'!Y11*IF(AND(Mod_B=1, Mod_H=0),1,0))+('ERG health states'!W11*IF(AND(Mod_B=1, Mod_H=1),1,0))+('ERG TTD'!Q11*IF(AND(Mod_D=1, Mod_H=0),1,0))+('ERG TTD'!O11*IF(AND(Mod_D=1, Mod_H=1),1,0)))*$C10)+ (0*('Patient flow - 1'!$AI14))*$C10
	P11:P1049	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R8) Calculate treatment administration costs at start cycle	Mod_B Mod_D Mod_H	=IF(MOD($A11, TRT1_periodicity) = 0, 1, 0)*(TRT1_admin*(('Patient flow - 1'!$AH15*IF(Mod_D=0,1,0))+('Patient flow - 1'!V15*IF(AND(Mod_H=1,Mod_B=0,Mod_D=0),1,0))+('ERG health states'!Y12*IF(AND(Mod_B=1, Mod_H=0),1,0))+('ERG health states'!W12*IF(AND(Mod_B=1, Mod_H=1),1,0))+('ERG TTD'!Q12*IF(AND(Mod_D=1,Mod_H=0),1,0))+('ERG TTD'!O12*IF(AND(Mod_D=1,Mod_H=1),1,0))))*$C11+ 0*('Patient flow - 1'!W15)*$C11 + (0*('Patient flow - 1'!$AI15)*$C11) + P10

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Cost	Y10	R8) Calculate treatment administration costs at start cycle	Mod_H	=((TRT2_admin*(('Patient flow - 1'!$AZ14*IF(Mod_H=0,1,0))+'Patient flow - 1'!$AN14*IF(Mod_H=1,1,0)))*$C10 + (0*('Patient flow - 1'!$BA14))*$C10)
	Y11:Y1049	R8) Calculate treatment administration costs at start cycle	Mod_H	=IF(MOD($A11, TRT2_periodicity) = 0, 1, 0)*(TRT2_admin*(('Patient flow - 1'!$AZ15*IF(Mod_H=0,1,0))+('Patient flow - 1'!$AN15*IF(Mod_H=1,1,0)))*$C11 + (0*('Patient flow - 1'!$BA15))*$C11) + Y10
	H10	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_B Mod_D Mod_F	=(((INT_mon/4)*(('Patient flow - 1'!$P14*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!E11*IF(Mod_B=1,1,0))+('ERG TTD'!E11*IF(OR(Mod_D=1,Mod_F=1),1,0))))+(INT_PD_Trt*INT_PD_time*(INT_mon/4)*('Patient flow - 1'!$Q14)*C10))*IF(dose_cap_on, IF(B11 <= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B11 <= trt_cap, 1,0), 1)*$C10+(0*('Patient flow - 1'!$Q14))*$C10
	H11:H1049	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_B Mod_D Mod_F	=(((INT_mon/4)+ (INT_PD_Trt*INT_PD_time*(INT_mon/4)*MAX(0,(('Response and survival'!BC38) - ('Response and survival'!BC39)))*C11))*IF(dose_cap_on, IF(B11 <= dose_cap, 1, 0), 1)*IF(Cap_on, IF(B11 <= trt_cap, 1,0), 1)*(('Patient flow - 1'!$P15*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))++('ERG health states'!E12*IF(Mod_B=1,1,0))+('ERG TTD'!E12*IF(OR(Mod_D=1,Mod_F=1),1,0))))*$C11+(0*('Patient flow - 1'!$Q15))*$C11 + H10
	Q10	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_B Mod_D	=((TRT1_mon/4)*(('Patient flow - 1'!$AH14*IF(AND(Mod_B=0,Mod_D=0),1,0))+('ERG health states'!Y11*IF(Mod_B=1,1,0))+('ERG TTD'!Q11*IF(Mod_D=1,1,0))))*$C10 + (0*'Patient flow - 1'!$AI14*$C10)

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Cost	Q11:Q1049	R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_D	=((TRT1_mon/4)*(('Patient flow - 1'!$AH15*IF(AND(Mod_B=0,Mod_D=0),1,0))+('ERG health states'!Y12*IF(Mod_B=1,1,0))+('ERG TTD'!Q12*IF(Mod_D=1,1,0))))*$C11 + (0*('Patient flow - 1'!$AI15)*$C11) + Q10
	I10	R1) ERG OS R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_A Mod_B Mod_D Mod_F	=((INT_subtrt_cost*INT_subtrt_prop)+ (INT_subtrt_admin_cost*INT_subtrt_prop)+(INT_subtrt_mon_cost*INT_subtrt_prop))*('Patient flow - 1'!$Q14*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0)+MAX('ERG TTD'!G11,'ERG health states'!G11)*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0)+MAX('ERG TTD'!K11,'ERG health states'!K11)*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0))*C10
	I11:I1049	R1) ERG OS R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_A Mod_B Mod_D Mod_F	=((INT_subtrt_cost*INT_subtrt_prop)+ (INT_subtrt_admin_cost*INT_subtrt_prop)+ (INT_subtrt_mon_cost*INT_subtrt_prop)) *MAX(0,((('Response and survival'!BC38) - ('Response and survival'!BC39))*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))+(IF('ERG TTD'!G12>'ERG health states'!G12,'ERG TTD'!G12-'ERG TTD'!G11,'ERG health states'!G12-'ERG health states'!G11)*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0))+(IF('ERG TTD'!K12>'ERG health states'!K12,'ERG TTD'!K12-'ERG TTD'!K11,'ERG health states'!K12-'ERG health states'!K11)*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0)))*C11)+I10

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
	R10	R1) ERG OS R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_A Mod_B Mod_D	=((TRT1_subtrt_cost*TRT1_subtrt_prop) + (TRT1_subtrt_admin_cost*TRT1_subtrt_prop) + (TRT1_subtrt_mon_cost*TRT1_subtrt_prop)) *(('Patient flow - 1'!$AI14*IF(AND(Mod_B=0,Mod_D=0),1,0))+('ERG health states'!AA11*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1)),1,0))+('ERG health states'!AE11*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1)),1,0)))*C10
	R11:R1049	R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_B Mod_D	=((TRT1_subtrt_cost*TRT1_subtrt_prop) + (TRT1_subtrt_admin_cost*TRT1_subtrt_prop)+(TRT1_subtrt_mon_cost*TRT1_subtrt_prop))*MAX(0, ((('Response and survival'!BE38-'Response and survival'!BE39)*IF(AND(Mod_B=0,Mod_D=0),1,0))+(('ERG health states'!W11-'ERG health states'!W12)*IF(OR(Mod_B=1,Mod_D=1),1,0)))*C11) +R10
Nivolumab cost	I9	R7) Nivolumab dosing calculations	Mod_G	=((LN(D9)-I36^2/2)*IF(Mod_G=0,1,0))+((LN(D9)-I10^2/2)*IF(Mod_G=1,1,0))
	J9	R7) Nivolumab dosing calculations	Mod_G	=((LN(E9)-J36^2/2)*IF(Mod_G=0,1,0))+((LN(E9)-J10^2/2)*IF(Mod_G=1,1,0))
Outcomes	F12	R9) Use ERG utility values (Van den Hout + CheckMate 057) R10) Use Nafees et al. utility values	Mod_I Mod_J	=0.739*IF(AND(Mod_I=0,Mod_J=0),1,0)+0.713*IF(Mod_I=1,1,0)+0.65*IF(Mod_J=1,1,0)
	F13	R9) Use ERG utility values (Van den Hout + CheckMate 057) R10) Use Nafees et al. utility values	Mod_I Mod_J	=0.688*IF(AND(Mod_I=0,Mod_J=0),1,0)+0.476*IF(Mod_I=1,1,0)+0.43*IF(Mod_J=1,1,0)

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Outcome	F10	R1) ERG OS	Mod_A	=(utility_PFS*((('Patient flow - 1'!$P14*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!E11*IF(OR(Mod_B=1,Mod_D=1,Mod_F=1),1,0)))/52)*$C10) + (utility_PD*((('Patient flow - 1'!$Q14*IF(AND(Mod_A=0,Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!Q11*IF(AND(Mod_A=1,Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!M11*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0))+('ERG health states'!I11*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0)))/52)*$C10)
		R2) ERG PFS	Mod_B	
		R4) Nivolumab vs docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_D	
		R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_F	
Outcome	F11:F1049	R1) ERG OS	Mod_A	=(utility_PFS*((('Patient flow - 1'!$P15*IF(AND(Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!E12*IF(OR(Mod_B=1,Mod_D=1,Mod_F=1),1,0)))/52)*$C11) + (utility_PD*((('Patient flow - 1'!$Q15*IF(AND(Mod_A=0,Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!Q12*IF(AND(Mod_A=1,Mod_B=0,Mod_D=0,Mod_F=0),1,0))+('ERG health states'!M12*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0))+('ERG health states'!I12*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1,Mod_F=1)),1,0)))/52)*$C11) + F10
		R2) ERG PFS	Mod_B	
		R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_D	
		R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_F	
	L10	R1) ERG OS	Mod_A	=(utility_PFS*((('Patient flow - 1'!$AH14*IF(AND(Mod_B=0,Mod_D=0),1,0))+('ERG health states'!Y11*IF(OR(Mod_B=1,Mod_D=1),1,0)))/52)*$C10) + (utility_PD*((('Patient flow - 1'!$AI14*IF(AND(Mod_A=0,Mod_B=0,Mod_D=0),1,0))+('ERG health states'!AK11*IF(AND(Mod_A=1,Mod_B=0,Mod_D=0),1,0))+('ERG health states'!AG11*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1)),1,0)))+('ERG health states'!AC11*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1)),1,0)))/52)*$C10
		R2) ERG PFS	Mod_B	
		R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_D	

Sheet	Cell(s)	ERG revision/scenario number and row title	Modification name	Modification
Outcome	L11:L1049	R1) ERG OS R2) ERG PFS R4) Nivolumab vs. docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and AEs	Mod_A Mod_B Mod_D	=(utility_PFS*((('Patient flow - 1'!$AH15*IF(AND(Mod_B=0,Mod_D=0),1,0))+('ERG health states'!Y12*IF(OR(Mod_B=1,Mod_D=1),1,0)))/52)*$C11) + (utility_PD*((('Patient flow - 1'!$AI15*IF(AND(Mod_A=0,Mod_B=0,Mod_D=0),1,0))+('ERG health states'!AK12*IF(AND(Mod_A=1,Mod_B=0,Mod_D=0),1,0))+('ERG health states'!AG12*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_D=1)),1,0))+('ERG health states'!AC12*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_D=1)),1,0)))/52)*$C11) + L10
	R10	R1) ERG OS R2) ERG PFS R5) Nivolumab vs. nintedanib+docetaxel: ERG TTD for nivolumab, ERG PFS for nintedanib+docetaxel R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_A Mod_B Mod_E Mod_F	=(utility_PFS*((('Patient flow - 1'!$AZ14*IF(AND(Mod_B=0,Mod_E=0,Mod_F=0),1,0)))+('ERG health states'!AS11*IF(OR(Mod_B=1,Mod_E=1,Mod_F=1),1,0)))/52)*$C10+(utility_PD*((('Patient flow - 1'!$BA14*IF(AND(Mod_A=0,Mod_B=0,Mod_E=0,Mod_F=0),1,0))+('ERG health states'!BE11*IF(AND(Mod_A=1,Mod_B=0,Mod_D=0,Mod_E=0,Mod_F=0),1,0))+('ERG health states'!BA11*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_E=1,Mod_F=1)),1,0))+('ERG health states'!AW11*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_E=1,Mod_F=1)),1,0)))/52)*$C10)
	R11:R1049	R1) ERG OS R2) ERG PFS R5) Nivolumab vs. nintedanib+docetaxel: ERG TTD for nivolumab, ERG PFS for nintedanib+docetaxel R6) Nivolumab vs. nintedanib+docetaxel: ERG PFS for disease costs and QALYS, ERG TTD for treatment costs and Aes for nivolumab; ERG PFS for nintedanib+docetaxel	Mod_A Mod_B Mod_E Mod_F	=(utility_PFS*((('Patient flow - 1'!$AZ15*IF(AND(Mod_B=0,Mod_E=0,Mod_F=0),1,0)))+('ERG health states'!AS12*IF(OR(Mod_B=1,Mod_E=1,Mod_F=1),1,0)))/52)*$C11+(utility_PD*((('Patient flow - 1'!$BA15*IF(AND(Mod_A=0,Mod_B=0,Mod_E=0,Mod_F=0),1,0))+('ERG health states'!BE12*IF(AND(Mod_A=1,Mod_B=0,Mod_D=0,Mod_E=0,Mod_F=0),1,0))+('ERG health states'!BA12*IF(AND(Mod_A=0,OR(Mod_B=1,Mod_E=1,Mod_F=1)),1,0))+('ERG health states'!AW12*IF(AND(Mod_A=1,OR(Mod_B=1,Mod_E=1,Mod_F=1)),1,0)))/52)*$C11)+R10

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small cell lung cancer [ID900]

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, 16th March 2016** 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 Inaccurate reporting of OS results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 9 of the ERG report it states "CheckMate 057 provides evidence of median overall survival (OS) benefit of nivolumab over docetaxel at both 12 and 18 months (12.2 versus 9.4 and 39 versus 23 months respectively." The 12 month data reported is the median OS, which remained unchanged in the 18 month analysis (as the median had been reached by the 12 month data cut). However the 18-month data reported is the OS rate (39% and 23% of patients alive at the 18 month data cut).	CheckMate 057 provides evidence of median overall survival (OS) benefit of nivolumab over docetaxel (12.2 versus 9.4 months respectively). The one-year OS rate was 51% for nivolumab versus 39% for docetaxel at 12 months, and 39% for nivolumab vs 23% for docetaxel at 18 months.	The existing wording is misleading as the OS rate at 18 months is described as the median OS.	Amended

Issue 2 Ruling out of CheckMate 003 for validation of survival analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On Pages 96-97 of the ERG, the use of CheckMate 003 data to validate the survival extrapolation is ruled out based on Figure 17 stating "It is clear from this plot that the survival profiles differ markedly between the two trials from around 7 months. The ERG therefore considers CheckMate 003 trial data to be unsuitable for validating projections based on data from CheckMate 057". In fact, after 7 months, the 057 curve remains above the 003 curve until 20 or	The description of the Checkmate 003 K-M should include the number at risk and ensure the interpretation of the data is in line with that presented. 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 (generalised gamma); the sensitivity analysis parametric model for OS; and	It is inappropriate to rule out use of the CheckMate 003 study based on data from the tail end of the K-M curve, to which few patients contributed, and is important that the extrapolations are validated against the data available.	The ERG considers CheckMate 003 to be inappropriate for validating the nivolumab OS curve because : a) the survival profiles – that is, the shape of the KM curves - from the two trials are different. This remains the case regardless of the final few data points (Figure 17). The KM OS curves

so months, at which time the curve is severely limited by the amount of follow up and the data are sparse. So while there are differences in the curves, the 003 curve may be appropriate as a lower bound for curve selection of parametric function for survival in 057.	the ERG model for OS in comparison to the long-term nivolumab trial data and real-word studies it appears that the ERG OS extrapolation approach consistently under predicts survival. Based on the evidence provided, we recommend the institute apply the most clinically plausible OS extrapolations (i.e. BMS base-case analyses) to inform the base case analyses. This includes validation against clinical trial data (CheckMate 003) and real-world conditional survival data from the NLCA.		from the CheckMate 057 and CheckMate 003 trials are similar in the first 6 months and then separate, which means that they must have different shapes and are not comparable. b) The CheckMate 003 trial is not an appropriate lower bound for nivolumab projections from CheckMate 057. There is no requirement that OS in CheckMate 057 must remain at or above OS in CheckMate 003 at 4 years just because it was above OS in the CheckMate 003 trial at 1 or 2 years. We can only estimate what happens to OS by analysing the data that we have, which indicates that OS in the nivolumab arm of the CheckMate 057 trial falls more sharply than it does in CheckMate 003. In any case, the ERG's projections remain above OS from the CheckMate 003 trial to 3 years (20% vs. 18%).

			c) The data from the CheckMate 003 trial did not represent patients with the same histology and dose as in the Checkmate 057 trial. It appears that the OS values given in Table 47 of the CS for OS from the CheckMate 003 trial come from BMS 2015h, which is the only source provided by the company to give 4 year OS data from CheckMate 003. BMS 2015h is a KM plot of OS for all NSCLC subjects (squamous and non squamous) treated at all doses (1 mg/kg, 3mg/kg and 10mg/kg) in the CheckMate 003 trial (n=129). Of these, only 19 patients with non-squamous histology received a 3mg/kg dose. We do not know whether any of these patients were still at risk by 4 years. The company states that there was little difference in OS rates between squamous and non-squamous patients in the

			CheckMate 003 trial at 1-, 2- and 3-years, which justifies using the pooled data. However, by 3 years, there were only six patients left in each subgroup[1] rendering OS comparisons between the subgroups very uncertain. The ERG was unable to validate the conditional survival values given in Table 48 of the CS for Stage IV patients from year 3 to year 5 from the NLCA database as, as the reference given (Health and Social Care Information Centre 2014) only contains survival data to 500 days (18 months). The ERG was unable to find appropriate survival data against which to validate its OS projections. The ERG based its nivolumab OS projections solely on data from the primary CheckMate 057 trial in order to avoid making inappropriate comparisons.

Issue 3 Error in reporting of EQ-5D completion rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 113, the EQ-5D completion rates are inaccurate. "At week 12, the respective completion rates at this time point were 40.8% and 38.9% for nivolumab and docetaxel patients. The corresponding completion rates for nivolumab and docetaxel arms at 24 weeks were 26.9% and 14.8%." Only patients on treatment at week 12 were eligible for the week 12 on-treatment assessment. However, in the denominator for this question, the ERG have included all randomised patients. Therefore, this is inappropriate as a description of the "completion" rate.	"At week 12, the respective completion rates at this time point were 77.2% and 75.8% for nivolumab and docetaxel patients. The corresponding completion rates for nivolumab and docetaxel arms at 24 weeks were 75.0% and 80.0%."	The values provided are taken from Table 19 of the CS, and include in the denominator only those patients who were eligible to complete the EQ-5D at each timepoint.	See amended text in Section 5.5.12.

Issue 4 Inaccurate statement on the treatment population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 9 it is stated that the population "changed from people with previously treated disease to those who have received prior chemotherapy (thus excluding epidermal growth factor receptor (EGFR) positive patients who have previously had a TKI)". The statement in parenthesis is inaccurate, as patients who are EGFR positive would still be eligible for nivolumab in	Remove statement in brackets.	Patients who are EGFR positive and receive a TKI first line, would be eligible for chemotherapy 2nd line and nivolumab 3rd line	Added the word "only" to the statement in brackets. The change in population excludes those who have not previously received chemotherapy but have received some prior treatment

the 3rd line setting.			

Issue 5 Unclear reporting of PFS results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9-10 "Patients receiving nivolumab show less benefit at 12 month (4.2 versus 2.3 months). However, 12 month data show a reversal with PFS rates for nivolumab versus docetaxel at 18.5 versus 8.1%." Wording around the median PFS and PFS rates and different time points is unclear.	Patients receiving nivolumab show less benefit than those receiving docetaxel in terms of median PFS (4.2 versus 2.3 months). However, PFS rates for nivolumab are higher than those for docetaxel (18.5% versus 8.1% at 12 months.	The median PFS was reached by 12 months, so the wording "12 month data show a reversal" is inaccurate. Due to the crossover in the PFS curves / pseudo-progression, the median PFS and PFS rates are conflicting.	Amended

Issue 6 Unclear reporting of ITC results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10. "The ITC provides evidence using restricted mean survival time (RMST) analysis demonstrating no benefit of nivolumab versus nintedanib+docetaxel in relation to OS, PFS, overall response rate (ORR) or AEs" In the ITC, only the OS and PFS analyses used the RMST approach.	"The ITC demonstrating no benefit of nivolumab versus nintedanib+docetaxel in relation to OS or PFS (using restricted mean survival time [RMST] analysis), overall response rate (ORR) or AEs.	To make sure it is clear that the RMST applies only to OS and PFS	Amended

Issue 7 Error in reporting of ORR OR

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 37. Error in the reporting of the 95%CI around the ORR OR.	Change from: (OR 1.7, 95% CI: 1.1 to 1.6; p=0.02) to (OR 1.7, 95% CI: 1.1 to 2.6; p=0.02)	There is an error in the values stated in the ERG report	Amended

Issue 8 Unclear reporting of TTD extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 88. Unclear reporting of discrepancy with TTD extrapolation. "Firstly, the projection of TTD data as a proxy for PFS data is implausibly long and results in 85% of patients being still alive at 20 years, remaining progression-free and being on treatment"	"Firstly, the projection of TTD data as a proxy for PFS data is implausibly long and means that, of those patients still alive at 20 years, 85% remain progression-free and on treatment"	The wording currently reads that 85% of patients are still alive at 20 years, and this is not what was intended. The proposed amendment ensures the meaning is clear.	See amended text in Section 5.5.1.

Issue 9 Misnaming of generalised gamma extrapolations

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In a number of places in Section 5 the generalised gamma model used in the CS as the basecase for modelling OS and PFS is misnamed as a gamma	Ensure the term generalised gamma is used where appropriate.	Generalised gamma is the model used in the base case for both OS and PFS.	See amended text in section 5.

model.			

Issue 10 Figure 11 misrepresents the data on OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 90-91, the ERG compares the OS curves from the model using Figure 11. This is inaccurately reported in 2 ways: 1) 18-month K-M data are compared with OS curves based on the 12-month data from the CS model. 2) The differences seen are only approximately 0.002-0.003 at weeks 2 and 3, and the “zoomed in” nature of the figure exaggerates this effect which is not considered clinically signficiant.	The extrapolations from the model based on the 12 month data from CheckMate 057 should be plotted against the 12 month K-M data (or 18 month data should be used for both). Figure 11 should be redrawn to ensure the scale of the issue is clear.	The reader may misinterpret this information based on the way the data are currently presented, which is inaccurate.	1) See amended figure 11 2) The differences between the OS and PFS curves may not be clinically significant, but the fact that a parametric curve that uses a fixed set of parameters to describe a whole curve needs to be manually amended in order to fit a logical requirement (OS>= PFS) means that either the OS or PFS (or both) parametric curve is mis-specified. The chart is drawn to highlight the fact that there is a difference between the specified generalised gamma curve for OS and the curve used in the model, not the magnitude of that difference.

Issue 11 Inaccurate representation of the post-progression survival data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 93, the ERG states "Examination of the PPS data at the time of the 18-month data lock shows that there is little difference in survival rates for all patients in the nivolumab and docetaxel arms immediately after progression, the curves then separate around 5 months and then converge again at around 20 months (**Error! Reference source not found.**~~Figure 14~~). *This implies that, compared to docetaxel, nivolumab has only a small incremental effect on PPS*". The data provided by BMS included the number of patients at risk and details of censoring, these show that there is significant uncertainty at the tail end of the curve in Figure 14, meaning that the conclusions stated cannot be made with confidence.	Add details of the number at risk to the figure so that the reader is able to interpret the figure in the context of all of the evidence. The full K-M with this data was included in our response to clarification questions (Question B1, Figure 3).	Including the number at risk data ensure the curves are interpreted in the appropriate context.	See amended text in section 5.5.4

Issue 12 Survival extrapolations are misrepresented.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In Section 5.5.5 (p 95), the ERG criticises the approach to survival extrapolation in the CS and states that	Wording around the assessment of the CS extrapolations should be reworded to ensure it reflects the data, and is in	Currently wording in the ERG report misrepresents the information available.	See 1) amended text in section 5.5.5 and 2) amended figure 16.

they are a poor fit. There are two inaccuracies involved in this: 1) According to the methods outlined in the DSU, the generalised gamma curves utilised were in the top 3 best fitting curves in terms of AIC/BIC goodness of fit statistics and would not therefore be considered a poor fit to the data. 2) In Figure 16, used to justify these statements, the OS extrapolation from the CS, based on the 12 month data from Checkmate 057 is plotted against the 18 month Kaplan-Meier plot, which is inaccurate and misrepresents the data.	line with the DSU guidance, which suggests that the survival curves do have a good fit. Figure 16 should be replaced with one that plots 18 month vs 18 month or 12 month vs 12 month data.		The ERG considers the generalised gamma curve to be an inadequate fit to the nivolumab OS KM data for the reasons set out in section 5.5.5. AIC/BIC values are relative indicators of fit when models are compared to one another and should not be interpreted in isolation - the best fitting model according to AIC/BIC does not necessarily mean the model is a good fit in an absolute sense. Models should also be examined for face validity to assess the absolute quality of fit.

Issue 13 Indirect comparison with nintedanib is not adjusted

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 108 of the ERG report it is stated "The ERG is of the opinion that baseline characteristics are fairly similar between the docetaxel arms of the CheckMate 057[2] and LUME-Lung 1[3] (adenocarcinoma population) trials. This means that, if there is sufficient evidence to suggest that the (comparator) docetaxel arms of the CheckMate 057 and LUME-	In LUME-Lung 1, 61.9 % of patients in the docetaxel arm had Stage IV disease at the time of diagnosis (Reck et al, 2014). This compares with 92% of patients in the docetaxel arm of Checkmate 057 (Borghaei et al 2015). As stage of disease is a key characterstic that is anticipated to affect clinical outcomes, adjusted comparisons should be used to compare nintedanib+docetaxel with nivolumab using docetaxel as a common comparator, in line with the analyses in the CS.	The assumption that the docetaxel arms of the CheckMate 057 and LUME-Lung trials are equivalent and that the intervention arms of both trials (nivolumab and nintedanib+docetaxel) may be compared without adjustment is not supported by the available evidence.	The 61.9% figure for docetaxel patients in the LUME-Lung 1 trial with Stage IV disease relates to the whole study population, whereas the data used by the company and the ERG to model nintedanib+docetaxel was for the adenocarcinoma subgroup of study participants. The proportion of adenocarcinoma patients in the LUME-Lung 1

Lung trials are equivalent, the intervention arms of both trials (nivolumab and nintedanib+docetaxel) may be compared without adjustment. However, it is important to note that the ERG did not have access to data summarising the disease stage of patients in the adenocarcinoma population of the LUME-Lung 1 trial,[3] d so it is not possible to compare the two trials in this respect". This is used to justify comparing nivolumab and nintednaib without adjustment. However, evidence suggests that there are differences between the docetaxel-treated patients in the two studies.			trial was 51% in the docetaxel arm (49.2% in the nivolumab arm). The proportion of the patients with adenocarcinoma who had stage IV disease was unknown at the time of analysis and the ERG highlighted the absence of this information in its report (section 5.5.7). Without access to the individual patient data (IPD) from the LUME-Lung 1 trial, it is not simple to derive the effect of disease stage or any other baseline characteristic on the survival of patients with adenocarcinoma. Although disease stage might differ between the two trials, there are other characteristics that could counteract the effect of disparities in the proportion of patients with Stage IV disease. For instance, 34.2% of participants in the docetaxel arm of the adenocarcinoma population in the LUME-Lung 1 trial had never smoked compared to 19.9% in the docetaxel arm of the CheckMate 057 trial (20.7% in the nivolumab arm). It is not possible to estimate how having Stage IV disease might interact with never having

			smoked without examining the IPD. The ERG provided its best possible alternative to the company's method for modelling survival for nintedanib+docetaxel given the time and resource constraints. The ERG's approach is necessarily based on the assumption that differences in baseline characteristics between the two trials do not produce different survival probabilities beyond the scope of the KM data. However, it would be misleading to single out potential differences in one characteristic (disease stage) and conclude that this disparity invalidates the approach.

Issue 14 ERG substitution and preference of utility values based on the study by Nafees et al 2008 (page 117)

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 057 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 057 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	The ERG's preferred utility values are based on responses from European patients in the CheckMate 057 trial plus terminal disutility calculations from van den Hout,[4] as stated at the end of section 5.5.12.

		definition of a pre-progression vs. post-progression patient to be captured. Moreover, CheckMate 057 study provides data collected from actual patients where Nafees et al derives values based on information from the general public.	

1. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA*, et al.* 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. 2015.
2. Bristol-Meyers Squib. Final Clinical Study Report for Study CA209057: An open-label randomized phase iii trial of bms-936558 (nivolumab) versus docetaxel in previously treated metastatic nonsquamous non-small cell lung cancer (NSCLC). Bristol-Meyers Squib confidential support document for STA [ID900] 2015.
3. Reck M, Kaiser R, Mellemgaard A, Douillard J, Orlov S, Krzakowski M*, et al.* Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): A phase 3, double-blind, randomised controlled trial. Lancet Oncol. 2014; 15:143-55.
4. van den Hout W. Cost–utility analysis of short- versus long-course palliative radiotherapy in patients with non-small-cell lung cancer. JNCI. 2006; 98:1786-94.

STA REPORT Erratum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small cell lung cancer [ID900]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/12

Completed 30th March 2016

CONTAINS CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

This document contains erratum in respect of the ERG report following the factual accuracy check by Bristol Myers Squibb.

Changes made to the original text in the ERG report are underlined.

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 Bristol-Myers Squibb Pharmaceuticals Ltd in support of the use of nivolumab (Opdivo®) for patients who have received prior chemotherapy for locally advanced or metastatic non-squamous, non-small cell lung cancer (NSCLC). A European licence for nivolumab in this specific patient population has not been received but the company expects a decision to be made in the first quarter of 2016.

1.1 Critique of the decision problem in the company's submission

The company submission (CS) indicates a slight change in wording in the included population – changed from people with previously treated disease to those who have received prior chemotherapy (thus excluding epidermal growth factor receptor (EGFR) positive patients who have previously **only** had a TKI). Although the company submission (CS) acknowledges the validity of all of the comparators in the scope they limit their analysis to available data which therefore provides comparison of nivolumab with docetaxel, nintedanib+docetaxel and best supportive care (BSC).

1.2 Summary of submitted clinical effectiveness evidence

Clinical evidence includes direct evidence of nivolumab compared with docetaxel from CheckMate 057. The trial was stopped early due to the pre-specified stopping rules related the superiority of nivolumab in relation to overall survival (OS). An indirect treatment comparison (ITC) comparing nivolumab with nintedanib+docetaxel as well as best supportive care (BSC) is provided. The company admits that the analysis of the original trial data and the ITC are limited by the fact that the proportional hazards assumption has been violated and therefore **none** of the hazard ratios (HRs) can be considered a reliable estimate of treatment effect.

CheckMate 057 provides evidence of median overall survival (OS) benefit of nivolumab over docetaxel **(12.2 versus 9.4 months respectively). The one-year OS rate was 51% for nivolumab versus 39% for docetaxel at 12 months, and 39% for nivolumab versus 23% for docetaxel at 18 months.** Due to issues of pseudo progression (tumours that initially increase as a result of the treatment action before shrinking/stabilising) with nivolumab, the results for progression free survival (PFS) are less clear. Patients receiving nivolumab show less benefit **than those receiving docetaxel in terms of median PFS** (4.2 versus 2.3

months). However, **PFS rates for nivolumab are higher than those for docetaxel** (18.5 versus 8.1%) **at 12 months**.

Subgroup analysis by EGFR status ('all comer'[1] population versus EGFR mutation-negative/unknown) show similar results.

The adverse event (AE) data presented indicate that nivolumab, although having a slightly different AE profile to standard cytotoxic chemotherapy, has fewer Grade 3-4 AEs than docetaxel. Data from additional non-randomised studies and studies of the use of nivolumab in patients with a variety of other cancers are provided to support this assertion. The CS makes the case that the uniqueness of the AE profile can be managed by established guidelines and that overall treatment with nivolumab is better tolerated than treatment with docetaxel alone and by association is also superior to nintedanib+docetaxel.

The ITC **demonstrates** no benefit of nivolumab versus nintedanib+docetaxel in relation to OS **or** PFS **(using restricted mean survival time [RMST] analysis),** overall response rate (ORR) or AEs in either the 'all comer' or EGFR mutation negative/unknown population. The comparison with BSC provides somewhat mixed results demonstrating the possible lack of homogeneity of the studies used in the comparison. No data are available for the EGFR positive population of patients.

1.3 Summary of the ERG's critique of clinical effectiveness evidence

The primary data provided in the CS comes from CheckMate 057 and an ITC that is limited by a lack of data to allow for comparison with all of relative comparators listed in the scope. The comparison of nivolumab is therefore limited to data related to docetaxel, nintedanib+docetaxel and BSC.

CheckMate 057 is a well conducted trial however the use of HRs in the analysis of the data cannot be considered a reliable estimate of treatment effectiveness as the CS points out that the proportional hazards assumption is violated for both OS and PFS. This limitation is also true of the ITC where only RMST analysis should be considered. The ITC is also limited by the fact differences in the patient populations included in the analysis (e.g. inclusion of patients with squamous disease, Asian population, length of follow-up etc.) The comparison with BSC provides mixed results demonstrating the effectiveness of nivolumab versus BSC in the all-comers group but not the EGFR mutation-negative/unknown patients supporting concerns that there were differences in the patient populations in the trials used in the ITC.

[1] all comers- the term used in the CS to denote the entire population of CheckMate 057

At the 18-month updated analysis, the HR for PFS with nivolumab versus docetaxel was 0.91 (95% CI: 0.76 to 1.09). Once again, the ERG does not believe that the use of HR is an appropriate way to summarise the PFS data. The ERG also notes that the company states that only OS results from the 18-month updated analysis are available, but then proceeds to present PFS results from this same time point.

Response

The ORR results are provided in Table 10. Nivolumab was found to statistically significantly improve ORR in comparison to docetaxel (OR 1.7, 95% CI: 1.1 to **2**.6; p=0.02). Four patients in the nivolumab group (1.4%) achieved a complete response (CR) compared with one patient (0.3%) in the docetaxel group. Median time to treatment response (TTR) was slightly shorter in the nivolumab arm than in the docetaxel arm (2.1 versus 2.6 months), and median duration of response (DoR) was found to be much longer in the nivolumab arm than in the docetaxel arm (17.2 versus 5.6 months). These findings are also demonstrated by the characteristics of responses provided by the company in Figure 14 of the CS. Patients achieving a response in either arm usually responded early on in the follow-up period, and often by the time of the first scan.

Table 10 CheckMate 057 summary of response analyses

	CheckMate 057	
	Nivolumab (n=292)	**Docetaxel (n=290)**
ORR		
n, responders	56	36
% of patients (95% CI)	19 (15 to 24)	12 (9 to 17)
Odds ratio estimate (95% CI)	1.7 (1.1 to 2.6)	
P value	0.02	
TTR		
Median, months	2.1	2.6
Min-Max (months)	1.2-8.6	1.4-6.3
DOR		
N, responders	56	36
Median, months (95% CI)	17.2	5.6
Min-Max (months)	1.8-22.6+	1.2+-15.2+

CI=confidence interval; DOR=duration of response; ORR=objective response rate; TTR=time to treatment response
The + symbol indicates a censored value. The value of 1.2 was censored because the patient discontinued treatment without disease progression, and the other values were censored because the response was ongoing at the time of the analysis.
Source: CS, Table 18

Treatment beyond progression

The CheckMate 057 protocol outlines how subjects treated with nivolumab were permitted to continue treatment beyond initial Response Evaluation Criteria in Solid Tumours (RECIST

1.1) defined progressive disease (PD), as long as they met specific criteria (trial protocol,[30] Section

monotherapy. The ERG's proposed amendments to the company model have a substantial impact on the size of each of the estimated ICERs per QALY gained.

The specific issues of concern identified by the ERG relate to the modelling of each health state and are compounded by the results of the ERG's examination of subgroups of patients within the group of patients treated with nivolumab; these subgroups have not been discussed in the CS. The ERG identified two distinct patient subgroups according to whether patients received treatment with nivolumab post-progression. Information describing the baseline characteristics of the patient subgroups was not available to the ERG at the time of analysis. Therefore, the ERG cannot ascertain whether there are fundamental differences between the groups other than that some patients received treatment with nivolumab after progression (PPTx) and other patients did not receive nivolumab after progression (no-PPTx).

The specific survival modelling issues identified by the ERG are as follows:

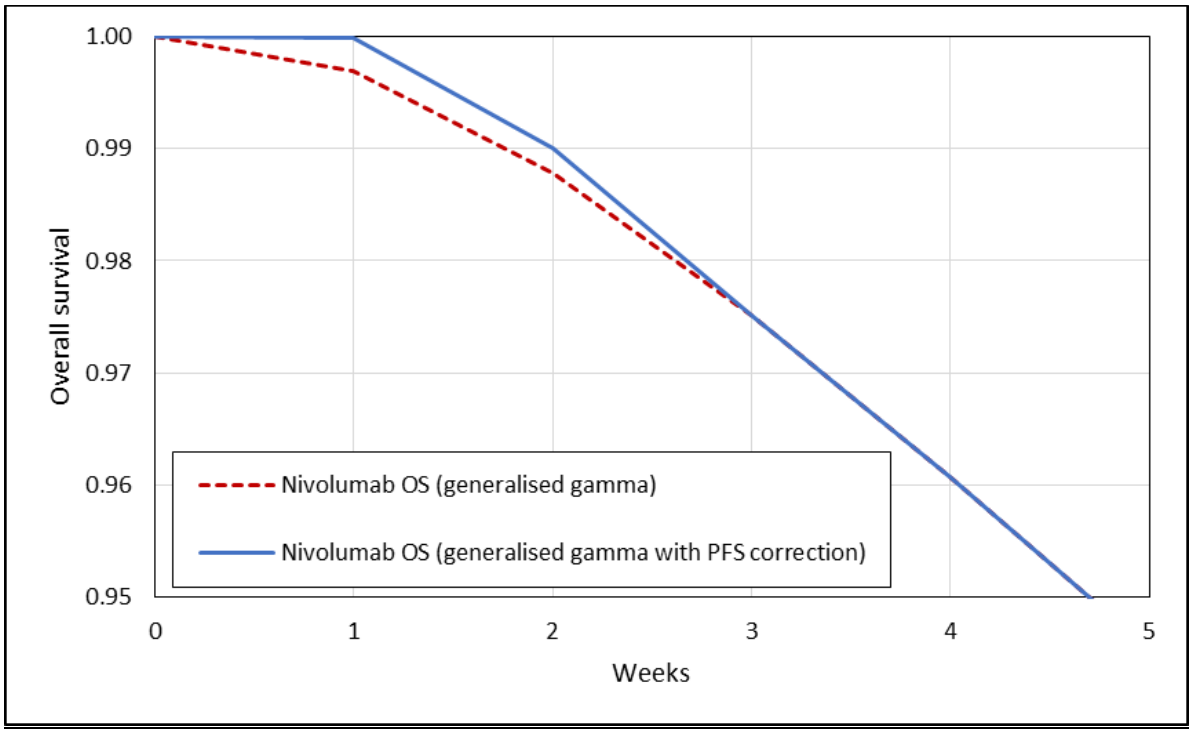
- the interdependence in the model between OS, PFS and all-cause mortality rates results in implausible projections for nivolumab PFS in particular, but also casts doubt on the reliability of the model used to estimate nivolumab OS

- survival gain is predominantly accrued in the PFS state for nivolumab in the company model, whereas the trial evidence suggests that nivolumab has a substantial post-progression benefit over docetaxel. This is particularly true for the PPTx patient subgroup

- the **generalised** gamma parametric model chosen to model OS for nivolumab is not a good fit to the K-M data from CheckMate 057. The CheckMate 00323 data used to validate the nivolumab OS model are inappropriate as the survival profiles are different

- TTD data have been used instead of PFS data in all parts of the company model. There are two key issues. **First, the projection of TTD data as a proxy for PFS data is implausibly long and means that, of those patients still alive at 20 years, 85% remain progression-free and on treatment** Second, the ERG considers that TTD data should only be used for estimating costs and not for estimating QALYs accruing in the different health states

values for OS in the first 2 weeks so that there are not more people in PFS than people who are alive. The choice of parametric distribution for either PFS or OS (or both) is therefore inappropriate, as their combination produces implausible values and cannot be used without adjustment. Figure 11 also emphasises the uncertainty in the fit of the generalised gamma curve to the K-M data during this early period.

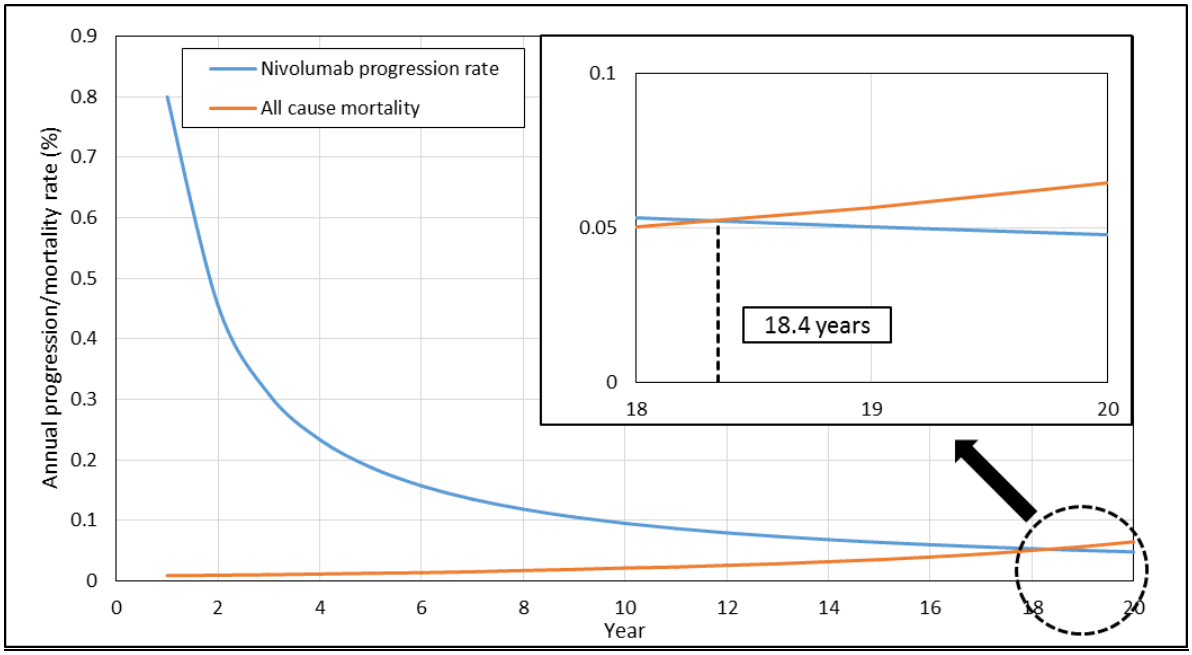


Source: Company model

Figure 11 Nivolumab OS with modelled generalised gamma curve, PFS correction and CheckMate 057 18-month K-M data

Second, the nivolumab arm is subject to a 'check and substitute' mechanism to ensure that disease specific mortality rates do not fall below all-cause mortality rates. Projections for both PFS and OS are compared to age- and sex- adjusted all-cause mortality rates and, should the latter be greater than the modelled rates, a substitution is made.

Figure 12 shows that the **generalised** gamma model used by the company to model PFS for patients treated with nivolumab projects annual mortality rates that fall below all-cause mortality rates 18.4 years after patients begin treatment. Hence, the model forecasts that any patient who remains in PFS for 18.4 years will never progress and is essentially cured of the disease. This is a very strong assumption for the company to make without providing supporting clinical evidence.



Source: Company model, ERG calculations

Figure 12 Relationship between nivolumab PFS and all-cause annual mortality rates in the company model

5.5.4 Post-progression survival: nivolumab and docetaxel

When compared with docetaxel, the company model estimates that patients treated with nivolumab accrue 31% of mean survival gain during PPS; this 31% gain equates to a survival gain of 4.3 months.

On inspection of the cohort trace for nivolumab (Figure 13), it is clear that the proportion of survival gain attributable to PPS is influenced considerably by the implausibly long PFS tail in the nivolumab arm. In the company model, PFS is modelled with a tail so long that 85% of the nivolumab patients who are still alive at 20 years are in PFS and are still receiving treatment. In comparison, almost all of the patients treated with docetaxel (>99.9%) are estimated to have left the progression-free state by 1.8 years when only 17% of these patients are still alive.

Source: CS, Figure 40

•Figure 13 Cohort trace for nivolumab up to 20 years (company model base case analysis)

The ERG considers the PPS estimates from the model to be unreliable as a consequence of a flawed approach to modelling PFS. The ERG therefore requested PPS K-M data from CheckMate 057 to perform an independent analysis.

The amalgamated all-patient nivolumab PPS data conceal substantial differences between the PPTx and the no-PPTx subgroups. **Examination of the all-patient PPS data at the time of the 18-month data lock shows that there is little difference in survival rates between the nivolumab and docetaxel arms immediately after progression, the curves then separate around 5 months and then converge again at around 20 months (Figure 14). This implies that, compared to docetaxel, nivolumab has only a small incremental effect on PPS.**

However, PPS for patients treated with nivolumab until disease progression have PPS indistinguishable from patients treated with docetaxel (log-rank test, p=0.84), whereas patients treated with nivolumab beyond progression have a much better chance of survival post-progression than other patients treated with nivolumab or patients treated with docetaxel (Figure 15).

The effect of these differences in PPS between the PPTx and no-PPTx nivolumab subgroups versus docetaxel depends on the proportion of patients receiving each treatment who die in PFS and on the proportion of patients in each of the nivolumab subgroups.

5.5.5 Overall survival: nivolumab versus docetaxel

The company employed an independent-curve approach to modelling OS for nivolumab and docetaxel, as it noted that proportional hazards models and single survival models were not appropriate due to the crossing of the nivolumab and docetaxel OS curves of CheckMate 057 at around 7 months. The company explored the use of a number of OS models and concluded that separate generalised gamma models had the most appropriate fit to both the nivolumab and docetaxel arms of the trial.

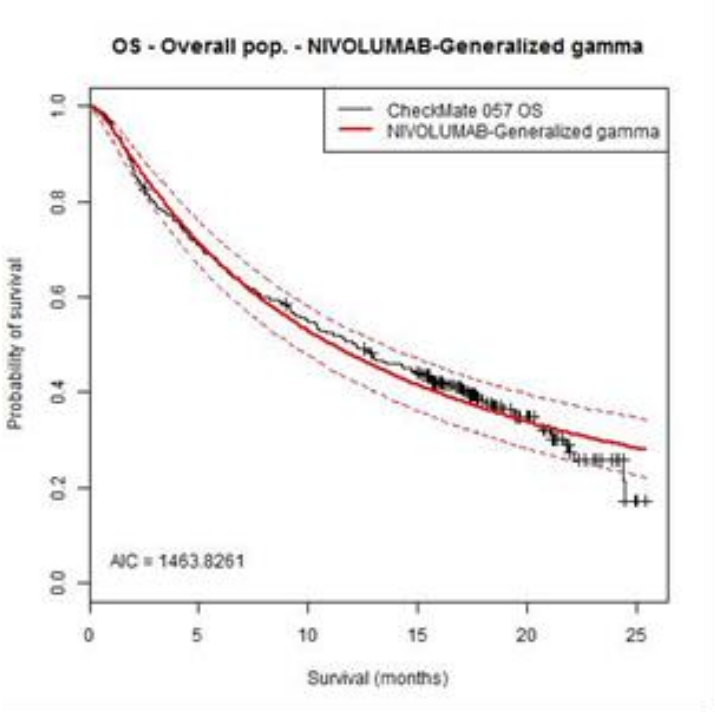
The ERG has identified three flaws in the company approach to modelling OS for patients in the nivolumab arm:

- the chosen **generalised** gamma curve systematically underestimates most of the K-M data and so **does not adequately** represent the nivolumab data from CheckMate 057

- the K-M data from CheckMate 003[23] Phase 1b clinical trial that were used to validate the projection exhibit a different survival profile to the data from CheckMate 057

- the modelled OS curve in the company model does not relate appropriately to the modelled PFS curve, as noted in Section 5.5.3 of this ERG report.

Inspection of the company model OS curve against the **12**-month K-M data for nivolumab shows that the fitted distribution systematically underestimates the trial data from 7 months to 20 months (Figure 16). This means that the fitted curve has not adequately incorporated all of the evidence on survival from CheckMate 057 for nivolumab patients who live beyond 7 months and relies too heavily on the pattern of survival during the first 7 months from randomisation. It is desirable to use all of the available clinical data when projecting survival. However, it is not always possible to fit a single parametric curve to the K-M data from time 0 without systematically misrepresenting that data to some extent. The principle objective of fitting a curve to K-M data is to be able to project a trend beyond the limits of available evidence, so it is preferable to closely model trends that are established later in the data and trends that might reasonably be expected to continue in the long-term rather than to seek a parametric distribution that fits well to earlier K-M data but does not adequately capture the later evidence.



Source: CS, Figure 30l

- Figure 16 Nivolumab OS: **12**-month K-M data vs. company model

At the time of writing the CS, the company had only 12 months of data with which to project 20 years of survival. However, the company was able to provide the ERG with 18 months of data during the clarification process. The company attempted to mitigate the uncertainty inherent in extrapolating immature data by comparing potential OS models to other clinical studies and to RWD, namely the single-arm, Phase 1b CheckMate 003[23] trial and the UK's NLCA database.[10]

Figure 17 compares the K-M OS data from the CheckMate 057[28] and CheckMate 003[23] trials. It is clear from this plot that the survival profiles differ markedly between the two trials from around 7 months. The ERG therefore considers CheckMate 003[23] trial data to be unsuitable for validating projections based on data from CheckMate 057.

lock provided by the company during the clarification process. It is clear that the company model is a poor fit to the TTD data and substantially overestimates time on treatment in the early part of the model for patients in both trial arms.

Source: Company model, clarification response-question B1d

- Figure 22 TTD K-M data and company model for nivolumab and docetaxel

The CS did not include any PFS projections based on PFS K-M data from CheckMate 057 as the number of patients in PFS was estimated from projections of TTD K-M data. When the company's TTD models are compared against the PFS K-M data for both nivolumab and docetaxel, it is clear that the **generalised** gamma curves are again inappropriate. Figure 23 shows that the TTD model used to estimate PFS for nivolumab overestimates almost all of the data and captures only a few of the final points. Conversely, the company TTD model serves to underestimate PFS for docetaxel.

5.5.12 Health state utilities

The ERG identified several limitations with regard to completion rates and the health state utility estimates associated with the EQ-5D data collected during CheckMate 057. **Table 19 of the CS gives compliance rates as the proportion of patients at risk at a given time point who completed the EQ-5D as well as having previously completed a baseline assessment. The EQ-5D compliance rates given by the company therefore relate only to a subset of patients at risk: those who initially completed a baseline assessment. For instance, the company quotes a compliance rate of 77.2% (n=112) from the 12-month data cut for patients receiving nivolumab who had completed a baseline assessment and who also completed an assessment at 12 weeks. However, Figure 28 in the CS indicates that there were 232 patients still alive in the nivolumab arm at 12 weeks, therefore only 48% of patients at risk completed the EQ-5D at 12 weeks. Similarly, 40.9% of patients at risk in the docetaxel arm at 12 weeks completed the EQ-5D compared to the compliance rate of 75.8% given in Table 19 of the CS. By 24 weeks, completion rates had declined to 35.6% and 20.6% of patients at risk who received nivolumab and docetaxel respectively.**

It is likely that patients' decisions to **complete a baseline assessment and to** continue completing the EQ-5D questionnaire throughout the trial period **were** subject to various influences. The ERG considers it is likely that patients who continue to complete HRQoL assessments are those with better health status and higher ECOG PS scores than non-respondents. An important implication of this finding is that self-selection is likely to cause health state utility values to be overestimated. Improvements in observed mean utility scores over time were observed (ERG report, Appendix 11.3). This phenomenon was previously observed in the NICE appraisal for nivolumab and squamous NSCLC patients.[49]

Health state utility values from CheckMate 057 indicate that patients in the PF health state have a mean utility score of 0.739 compared with patients in PD who have a mean utility score of 0.688. The ERG analysis of EQ-5D data by region provided utility estimates of 0.735 and 0.654 for the corresponding PF and PD states in European patients. Testing the effect of EQ-5D values obtained exclusively from European patients, as carried out by the ERG (Appendix 10.7), results in a slight increase in the overall ICERs per QALY gained when comparing nivolumab with both comparators.

The effects of using alternative utility values from (i) the study by Nafees et al[59] and (ii) a combination of EQ-5D values from CheckMate 057 with a Dutch lung cancer study by van den Hout et al[66] were investigated by the ERG.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient Access Scheme proposal template (full scheme)

5 January 2016

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Generic Name: Nivolumab

Brand Name: Opdivo

Disease area: Lung Cancer

Indication: Locally advanced or metastatic non-squamous non-small cell lung cancer (nsqNSCLC) after prior chemotherapy in adults

3.2 Please outline the rationale for developing the patient access scheme. Please describe the type of patient access scheme, as defined by the PPRS.

There are currently limited treatment options available for patients diagnosed with NSCLC, previously treated with chemotherapy. For nsqNSCLC patients, treatment of choice largely depends on the presence of specific mutations. Improvements have been seen with the use of newer targeted agents (directed at patients with EGFR and ALK gene mutations), but many of these newer agents are only effective for a small subset of patients and, in those patients, are used as a first-line treatment. Only about 10% of NSCLC patients have the defective EGFR gene; while the ALK mutation occurs in only 5% of NSCLC cases (Lung cancer profiles 2013). These patients then receive chemotherapy with platinum doublets second line.

Chemotherapy is still the main first-line systemic treatment for the majority of patients with advanced lung cancer. Less than one third of pre-treated patients with advanced NSCLC complete their first-line therapy as planned by their oncologist, due to toxicities, progression, treatment plan denial by health insurance, or death (Nadler 2011). This leads to the need for later-line therapies where it is more difficult to achieve a response.

There are still limited treatment options available for patients diagnosed with non-squamous NSCLC, previously treated with chemotherapy and there has been minimal improvement in overall survival despite recent advances. The current standard of care therapy after platinum doublets is docetaxel which has poor response rates and limited efficacy. Nintedanib combined with docetaxel has recently been approved by NICE for use in patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy. Erlotinib (an EGFR tyrosine kinase inhibitor) 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 for wild-type patients. There therefore remains an unmet need for effective treatments for pre-treated patients with advanced NSCLC.

Nivolumab provides a 27% reduction in death compared with standard of care, resulting in a median OS of 12.2 months compared with 9.4 months for docetaxel.

As the mode of treatment for nivolumab is to treat until progression, uncertainties exist around both the real life duration of response on Nivolumab therapy and the optimal length of real world treatment duration for a small number of patients. This can pose significant financial burden to the NHS.

BMS is proposing a dose cap PAS to mitigate this financial uncertainty and allow Nivolumab to meet NICE cost-effectiveness criteria for England and Wales. The scheme will cover the cost of nivolumab therapy after 26 administrations. The cost of therapy post cap will be covered by BMS until disease progression or cessation of nivolumab therapy.

3.3 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?

- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The proposed nivolumab patient access scheme (PAS) will apply to all patients covered by NICE guidance for nivolumab for locally advanced or metastatic non-squamous non-small cell lung cancer (nsqNSCLC) after prior chemotherapy in adults and those covered by NICE guidance for nivolumab for locally advanced or metastatic squamous non-small cell lung cancer (sqNSCLC) after prior chemotherapy in adults. Currently the scheme is not being considered for nivolumab as monotherapy in advanced (unresectable or metastatic) melanoma in adults or other future indications.

3.4 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

As noted above, BMS is proposing a dose cap PAS to mitigate this financial uncertainty and allow nivolumab to meet NICE cost-effectiveness criteria for England and Wales. The scheme will cover the cost of nivolumab therapy after 26 administrations. As nivolumab is administered once every two weeks, the cap will be placed at one year. The cost of therapy post cap will be covered by BMS until disease progression or cessation of nivolumab therapy.

3.5 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Population	Proportion of patients	Number of patients	Reference
Total NSCLC	N/A	27,300	(Health and Social Care Information Centre 2014)
Patients with stage IIIb/IV NSCLC	N/A	19,138	(Health and Social Care Information Centre 2014)
Non-squamous NSCLC	64.35%	12,315	(Powell 2013)
Patients who receive 1st line therapy	23%	2,832	(NICE 2010)
Patients who failed 1st line therapy	50%	1,413	(Sculier 2009)

Note: numbers do not calculate exactly due to rounding

3.6 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Please see below (section 3.8) a schematic of the fund flow for the proposed nivolumab PAS.

BMS will download a custom invoicing report from the PAS online portal (parameters for the report will be agreed between BMS and the NHS). This report is then used to calculate the value of BMS covered therapy. The report will highlight patients and doses received. Data extracts/reports used for calculations will be provided to the hospital/NHS Trust. The hospital/NHS Trust will also be able to access the PAS online portal to audit/verify calculations. Any errors around this process will be corrected immediately either by BMS (invoicing error) or Blueteq (data error) staff. Once agreement has been reached, post cap repayment will occur via their preferred

mechanism. BMS will offer three mechanisms of payback including free stock, rebate or credit note. Rebates or credit notes will be issued quarterly.

Consultation with the NHS suggested free stock was not a preferred payback option. However, some hospitals/Trusts may wish to utilise this payback mechanism for a variety of reasons. To allow NHS hospitals/Trusts flexibility, BMS will endeavour to support a free stock option for BMS covered therapy. Hospital/Trusts using free stock will be designated for specific BMS support. Manual data entry basis will be required to the PAS online portal or the paper based system, once a patient has passed 26 nivolumab administrations. BMS will monitor the online portal on a regular basis to pull off information for designated hospitals/Trusts to ensure timely provision of free stock. The free stock option will be provided as a line item with an attached zero value.

3.7 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

BMS has consulted with the NHS on the design, operation and administration of the nivolumab PAS. Stakeholders involved included pharmacists, commissioners, clinicians and finance staff. Their input has been implemented in the operational design of the nivolumab PAS. A summary of NHS feedback can be seen below:

BMS proposes to use a PAS online web portal, designed with Blueteq. A number of reasons have driven the decision to use Blueteq. The NHS already uses Blueteq systems for CDF funding and baseline commissioning within certain Trusts. Where Blueteq systems are used for commissioning of PbR excluded (PbRe) oncology drugs, patient registration for the nivolumab PAS can be automated by linking the Blueteq PbRe system and patient access scheme system. The Blueteq patient access scheme system is scalable, enabling multiple PAS schemes to be operated within a single system. It provides a common platform and way of working for hospital/Trust staff, making administration easier. The system is using technology and functionality from the existing Blueteq systems used by more than 150

hospitals/Trusts and over 100 CCGs, as well as NHS England. Blueteq is providing an online interface specifically for the nivolumab PAS allowing the portal to be accessed even in hospitals that do not use existing Blueteq systems for commissioning, for example, in Wales. All that the hospital will need is the nivolumab PAS url and their login credentials.

The PAS online portal will be able to interface for batch uploads with existing NHS pharmacy systems, thereby minimising administrative burden. The systems have proven resilience and are designed to be configured for users' requirements to make them as easy and light to touch as possible.

The online portal will drive various operational steps to administer the nivolumab PAS:

Participate in nivolumab PAS: BMS personnel will actively visit Trusts/hospitals to increase awareness of the nivolumab PAS amongst stakeholders (e.g. pharmacists, clinicians, commissioners, and where PAS administration is centralised – PAS administrators). Information on the nivolumab PAS will be made available in electronic, hard copy and online formats. Documentation will include a 'quick-start' high level guide to the nivolumab PAS, a detailed 'how-to' guide and frequently asked questions. Table of contents are embedded within this submission. Forms (online and paper based) will include a Trust/hospital registration form, a paper-based order form and claims/rebate form, with instructions for usage. Examples are provided within this PASLU submission. Relevant stakeholders within a Trust/hospital can review materials in their own time. NHS Trusts/hospitals will be able to join the PAS through registration via the PAS online portal, or alternatively using the paper-based registration form (described above) available within nivolumab PAS literature. This form must be completed and sent to BMS. Once nvolumab PAS registration is completed, BMS will check that all necessary details have been provided and then confirm registration with the relevant PAS administrator or pharmacy via email and/or the portal. To minimise administrative burden, BMS will support the NHS in form completion. BMS will also endeavour to provide training to relevant trust staff and stakeholders once registration is complete.

Initiating Patients: Patients must be registered with the nivolumab PAS. Registration can occur via one of three mechanisms. Option 1 is a batch upload/import to the PAS online portal from pharmacy systems on a monthly basis. This mechanism for data import can be used for new patient registrations and updating existing patient records when further treatments are received. If information is missing in the automatic upload, the system will prompt for the missing information to be entered. Option 2 is manual registration at the first prescription of a new patient. Registration can be performed by an oncologist pharmacist post physician consultation. This would be performed by manually filling out a patient registration form on the PAS online portal (estimated time for completion approx. 45 seconds). Alternatively if the trust/hospital uses the Blueteq PbRe system for cancer drug commissioning, patient registration details can be auto-populated from this system. BMS only recommends this mechanism for Trusts currently using the PbRe system. Once a patient registration is entered into the system, BMS will check the anonymised data to maintain data integrity and confirm registration either via an intra-portal message or an email.

Update of patient registration (adding nivolumab administrations to a patient record): Two options are provided. On a monthly basis a batch import of dispensing data submitted within the Trust for all patients receiving nivolumab therapy can be uploaded to the PAS online portal. The batch import data will be derived from either SLAM (service level agreement monitoring) data produced for NHS England or dispensing data produced for finance, utilising existing NHS data production processes. Should the pharmacy wish to record information in an alternative format to the pharmacy system, such as an Excel/Access database, then the PAS online portal will allow upload of these data formats.

Where required, data can also be added manually on a per patient basis, or corrected if a patient has not received a given administration mentioned above, to further streamline the process. The NHS will be the data owner for the PAS online portal, allowing creation of customised data reports regarding patients on therapy and those eligible for free treatment. Note that the PAS

online portal will also allow BMS to receive anonymised data reports to provide valuable information about patients receiving therapy and those eligible for BMS covered therapy.

Treatment post cap: The PAS online portal will flag patients who reach the predefined cap limit, based on number of therapies, and are eligible for free treatment. It will also detail numbers of patients and the amount of nivolumab administrations post cap to allow calculation of rebate/credit note or free stock to be provided by BMS to the Trust in its preferred format. A flag will notify NHS trust staff and BMS about these patients, but BMS will be responsible for ensuring that the NHS is aware of patients eligible for free treatment and that expense of therapy will be covered within quarterly invoicing. The portal will produce custom reports informing BMS of patient level administration numbers post cap, thereby allowing calculation of necessary rebate through invoicing. The PAS online portal will allow the NHS to query patient numbers and amount of administrations received post cap via customised reports, thereby allowing the NHS to audit and reconcile BMS rebates/credit notes/free stock provided.

Online access can be given to all stakeholders that the Trust deems necessary for administration of PAS. However, BMS recommend the Oncology Pharmacist remains the primary point of contact. As the portal is available via the internet, administration of the PAS should be possible for different pharmacy configurations in different Trusts. If dispensing or pharmacy function is outsourced or alternative arrangement exists, relevant stakeholders will be educated on the use of the PAS online portal. Note that the PAS online portal will allow manual correction of new/updated patient registrations if additional data fields are required, or should data errors occur or if a patient does not receive a nivolumab administration post dispensing.

Invoicing and Reimbursement: The PAS online portal will allow production of a custom rebate report which provides details of the patients receiving nivolumab therapy and patients who have passed the cap, and the number of therapies to be reimbursed per patient. This report will be available to the NHS, and in anonymised patient level format to BMS. BMS will calculate the

total cost of nivolumab therapy to be covered. Invoices will be prepared by BMS, on reimbursement of nivolumab administrations post cap due within a given quarter. Reimbursement will then be sent to the Trust/hospital in their preferred format (rebate/credit note). Note that, where agreed, commissioners can be given access to the PAS online portal to help reconcile budget and drug expenditure. It is proposed by BMS that rebates and credit notes are sent directly to the Trust/hospital.

Ordering of nivolumab: Administration of the nivolumab PAS is distinct from the ordering process. Ordering of nivolumab will be performed via the standard pharmacy ordering system within an NHS hospital. BMS will supply nivolumab to hospitals via existing channels. Administration of the nivolumab PAS occurs through the PAS online portal and normal inventory stock held by the pharmacy will be used to treat patients.

Consultation with the NHS suggested free stock was not a preferred payback option. However, some hospitals/Trusts may wish to utilise this payback mechanism for a variety of reasons. To allow NHS hospitals/Trusts flexibility, BMS will endeavour to support a free stock option for BMS covered therapy. Hospital/Trusts using free stock will be designated for specific BMS support. Manual data entry basis will be required to the PAS online portal or the paper based system once a patient has passed 26 nivolumab administrations. BMS will monitor the online portal on a regular basis to pull off information for designated hospitals/Trusts to ensure timely provision of free stock.

3.8 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Please see below a schematic of the fund flow for the proposed nivolumab PAS.

Nivolumab Fund
Flow requirements [

3.9 Please provide details of the duration of the scheme.

There are no plans or clauses or circumstances where BMS will withdraw the proposed nivolumab PAS nationally where the scheme is being operated with normal procurement practices and under standard terms and conditions. BMS will look to consult with stakeholders (including DH and PASLU) on any scheme changes and will participate in any required exit arrangement from the nivolumab PAS should these be required. In the event of negative NICE advice, PAS will not apply.

3.10 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

Not applicable

3.11 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

PAS agreement form (including terms and conditions): This is where BMS Standard Terms and Conditions will be used for supply of nivolumab

PAS registration form

PAS claim forms/rebate forms

Other relevant documents:

- BMS Pharmacy Confirmation Letter
- BMS How to guide

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

Not applicable

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

Incorporation of user friendly drop down menu ('pricing strategy for nivolumab') to calculate results based on a maximum of 26 nivolumab administrations. No other changes to the model or assumptions have been made.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The PAS has been implemented in the model in the form of an ‘economic dose cap’, which is only applied to patients receiving nivolumab. The economic dose cap is the maximum number of doses that the manufacturer can be reimbursed for per patient. Beyond the point at which the economic dose cap is implemented (e.g. 26 doses), the manufacturer will not be reimbursed for the drug, that is, no drug acquisition costs are included in the model calculations (however, administration and monitoring costs will continue to be accrued by patients who are still on treatment beyond the dose cap). In brief, for patients who continue to be treated beyond the dose cap, the drug will be provided free of cost by BMS.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

Table 1: Costs associated with the implementation and operation of the patient access scheme (PAS)

	Calculation of cost	**Reference source**
Stock management	Not applicable	Not applicable
Administration of claim forms	1 Band 7 Staff requiring 5 minutes per claim form at £68 per hour Total cost=£8	Primary Research and PSSRU Unit Health Costs and Social Care 2014
Staff training	2 Band 7 staff requiring 30 minutes time at £68 per hour Total cost=£68	Primary Research and PSSRU Unit Health Costs and Social Care 2014
Tracking of supplies	Not applicable	Not applicable
Other costs	Patient Registration – automated 1 Band 7 staff requiring 1 minutes time at £67 per hour Total cost =£1.12 Patient Registration – manual 1 Band 7 staff requiring 2 minutes time at £67 per hour Total cost =£2.25 per patient Patient Registration Update-automated 1 Band 7 staff requiring 2 minutes time at £67 per hour Total cost =£2.25	Primary Research and PSSRU Unit Health Costs and Social Care 2014

Other [add more rows as necessary]		
Total implementation and operation costs	Setup £68 per month Ongoing costs per month for administration= £9–£16 per patient per month	Primary Research and PSSRU Unit Health Costs and Social Care 2014

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (**Error! Reference source not found.**).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 2: Base-case cost-effectiveness results (without PAS)

	Nivolumab	Docetaxel	Nintedanib plus docetaxel
Intervention cost (£)	67,708.76	304.83	10,059.15
Treatment administration (£)	4,423.30	1,044.22	1,055.86
Treatment monitoring costs (£)	1,989.06	672.84	680.69
Subsequent treatment (£)	1,351.33	2,354.91	2,354.77
PF cost (£)	4,105.96	1,388.93	1,405.13
PD cost (£)	13,395.77	10,841.69	14,160.92
AE costs (£)	331.69	1,246.89	991.51
Total costs (£)	93,305.87	17,854.31	30,708.03
Difference in total costs (£; vs. nivolumab)		75,451.56	62,597.83
LYG	2.24	1.09	1.44
LYG difference (vs. nivolumab		1.15	0.80
QALYs	1.42	0.70	0.93
QALY difference (vs. nivolumab)		0.73	0.49
ICER (£; vs. nivolumab)		103,589.32	126,861.39

LYG: life-year gained; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

Table 3: Base-case cost-effectiveness results (with PAS)

	Nivolumab	Docetaxel	Nintedanib plus docetaxel
Intervention cost (£)	29,990.50	304.83	10,059.15
Treatment administration (£)	4,423.30	1,044.22	1,055.86
Treatment monitoring costs (£)	1,989.06	672.84	680.69
Subsequent treatment (£)	1,351.33	2,354.91	2,354.77
PF cost (£)	4,105.96	1,388.93	1,405.13
PD cost (£)	13,395.77	10,841.69	14,160.92
AE costs (£)	331.69	1,246.89	991.51
Total costs (£)	55,587.61	17,854.31	30,708.03
Difference in total costs (£; vs. nivolumab)		37,733.30	24,879.58
LYG	2.24	1.09	1.44
LYG difference (vs. nivolumab		1.15	0.80
QALYs	1.42	0.70	0.93
QALY difference (vs. nivolumab)		0.73	0.49
ICER (£; vs. nivolumab)		51,804.99	50,421.20

LYG: life-year gained; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in Table 4.

Table 4: Base-case incremental results (without PAS)

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremen cost per QALY (£)
Nivolumab	93,306	2.24	1.42				
Docetaxel	17,854	1.09	0.70	75,452	1.15	0.73	103,5
Nintedanib plus docetaxel	30,708	1.44	0.93	62,598	0.80	0.49	126,8

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 5: Base-case incremental results (with PAS)

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremen cost per QALY (£)
Nivolumab	55,588	2.24	1.42				
Docetaxel	17,854	1.09	0.70	37,733	1.15	0.73	51,8
Nintedanib plus docetaxel	30,708	1.44	0.93	24,880	0.80	0.49	50,4

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

The base-case comparators in the model are docetaxel and nintedanib in combination with docetaxel. These two comparators represent the current standard of care and likely future standard of care in pretreated patients with non-squamous NSCLC in the UK and are the treatments likely to be displaced by the introduction of nivolumab.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Deterministic sensitivity analysis was undertaken by varying cost, utility and efficacy parameters by their confidence intervals or ±20% based on data availability. The results are presented in Table 6 and in Figure 1 below.

Table 6: Results of deterministic sensitivity analysis versus docetaxel (with PAS)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		37,733	0.73	51,805
Discount rate - costs	Lower	40,007	0.73	54,926
	Higher	36,524	0.73	50,144
Discount rate - outcomes	Lower	37,733	0.88	42,885
	Higher	37,733	0.65	58,247
Average body weight	Lower	32,506	0.73	44,628
	Higher	43,082	0.73	59,149
BSA	Lower	37,781	0.73	51,871
	Higher	37,642	0.73	51,679
Costs				
Cost - PF state	Lower	37,190	0.73	51,059
	Higher	38,277	0.73	52,551
Cost - PD state	Lower	37,193	0.73	51,063
	Higher	38,274	0.73	52,547
Terminal cost	Lower	37,763	0.73	51,845
	Higher	37,704	0.73	51,765
Administration cost – nivolumab	Lower	36,849	0.73	50,590
	Higher	38,618	0.73	53,020
Administration cost – docetaxel	Lower	37,921	0.73	52,063
	Higher	37,545	0.73	51,547
Monitoring cost – nivolumab	Lower	37,335	0.73	51,259
	Higher	38,131	0.73	52,351
Monitoring cost - docetaxel	Lower	37,854	0.73	51,970
	Higher	37,613	0.73	51,640
Outcomes				
Utility weight, PFS	Lower	37,733	0.72	52,283
	Higher	37,733	0.73	51,382
Utility weight, PD	Lower	37,733	0.72	52,252
	Higher	37,733	0.73	51,346

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 1: Tornado diagram for nivolumab versus docetaxel (with PAS)

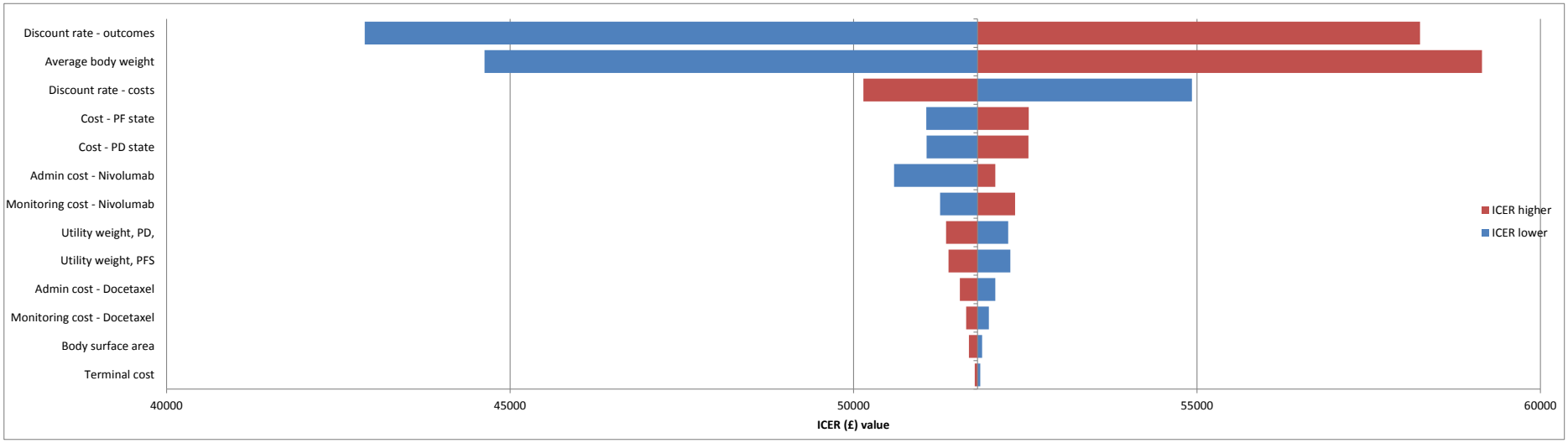
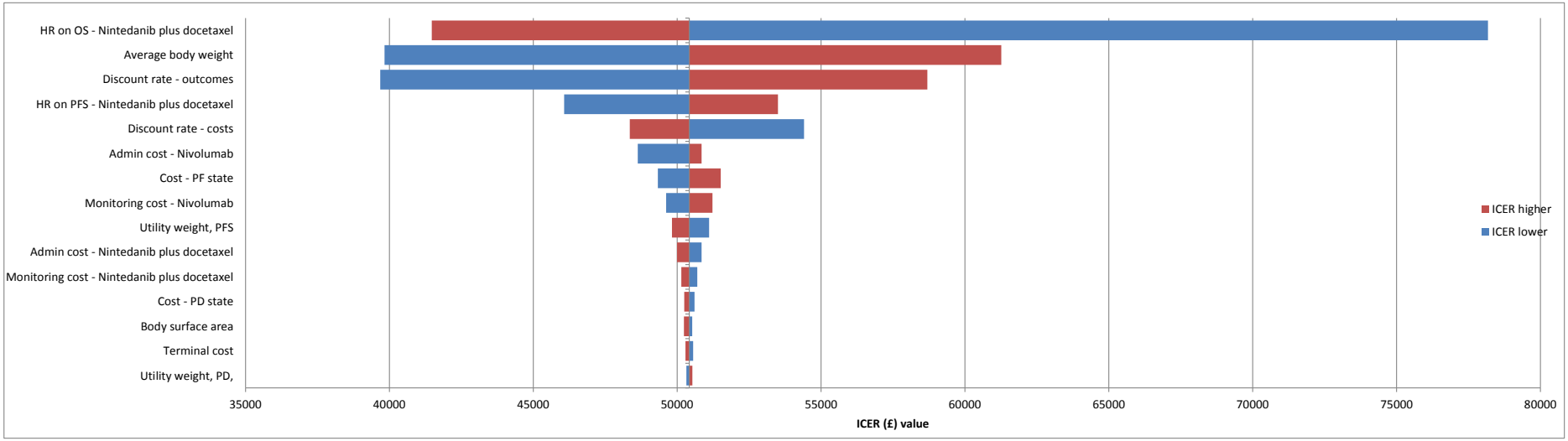


Table 7: Results of deterministic sensitivity analysis versus nintedanib in combination with docetaxel (with PAS)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		24,880	0.49	50,421
Discount rate - costs	Lower	26,847	0.49	54,409
	Higher	23,859	0.49	48,352
Discount rate - outcomes	Lower	24,880	0.63	39,678
	Higher	24,880	0.42	58,692
Average body weight	Lower	19,652	0.49	39,827
	Higher	30,228	0.49	61,261
BSA	Lower	24,928	0.49	50,519
	Higher	24,788	0.49	50,235
Costs				
Cost - PF state	Lower	24,339	0.49	49,326
	Higher	25,420	0.49	51,516
Cost - PD state	Lower	24,968	0.49	50,600
	Higher	24,792	0.49	50,243
Terminal cost	Lower	24,945	0.49	50,553
	Higher	24,815	0.49	50,289
Administration cost – nivolumab	Lower	23,995	0.49	48,628
	Higher	25,764	0.49	52,214
Administration cost – docetaxel	Lower	25,091	0.49	50,849
	Higher	24,668	0.49	49,993
Monitoring cost – nivolumab	Lower	24,482	0.49	49,615
	Higher	25,277	0.49	51,227
Monitoring cost - docetaxel	Lower	25,016	0.49	50,697
	Higher	24,743	0.49	50,145
Outcomes				
Utility weight, PFS	Lower	24,880	0.49	51,107
	Higher	24,880	0.50	49,819
Utility weight, PD	Lower	24,880	0.49	50,318
	Higher	24,880	0.49	50,530
Survival outcomes				
HR on PFS - Nintedanib plus docetaxel	Lower	22,527	0.49	46,071
	Higher	26,575	0.50	53,503
HR on OS - Nintedanib plus docetaxel	Lower	21,610	0.28	78,178
	Higher	27,498	0.66	41,470

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 2: Tornado diagram for nivolumab versus nintedanib in combination with docetaxel (with PAS)



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Results of the PSA are shown in Table 8, which also shows results from the deterministic analysis for comparison. The probabilistic ICER versus docetaxel is £49,787 per QALY gained compared with £51,805 per QALY gained in the deterministic analysis. The probabilistic ICER versus nintedanib plus docetaxel is £46,855 per QALY gained compared with £50,421 per QALY gained in the deterministic analysis.

The PSA was run for 1,000 iterations and the cost-effectiveness scatter plot and acceptability curve are shown in Figure 3 and Figure 5, respectively.

Table 8: Probabilistic results (with PAS)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Nivolumab	56,619	1.50			
Docetaxel	17,693	0.72	38,925	0.78	49,787
Nintedanib plus docetaxel	31,136	0.96	25,483	0.54	46,855
Deterministic values vs. docetaxel			37,733	0.73	51,805
Deterministic values vs. nintedanib plus docetaxel			24,880	0.49	50,421

ICER: Incremental cost-effectiveness ratio; QALYs: Quality adjusted life years

Figure 3: Cost-effectiveness plane for nivolumab vs. docetaxel (with PAS)

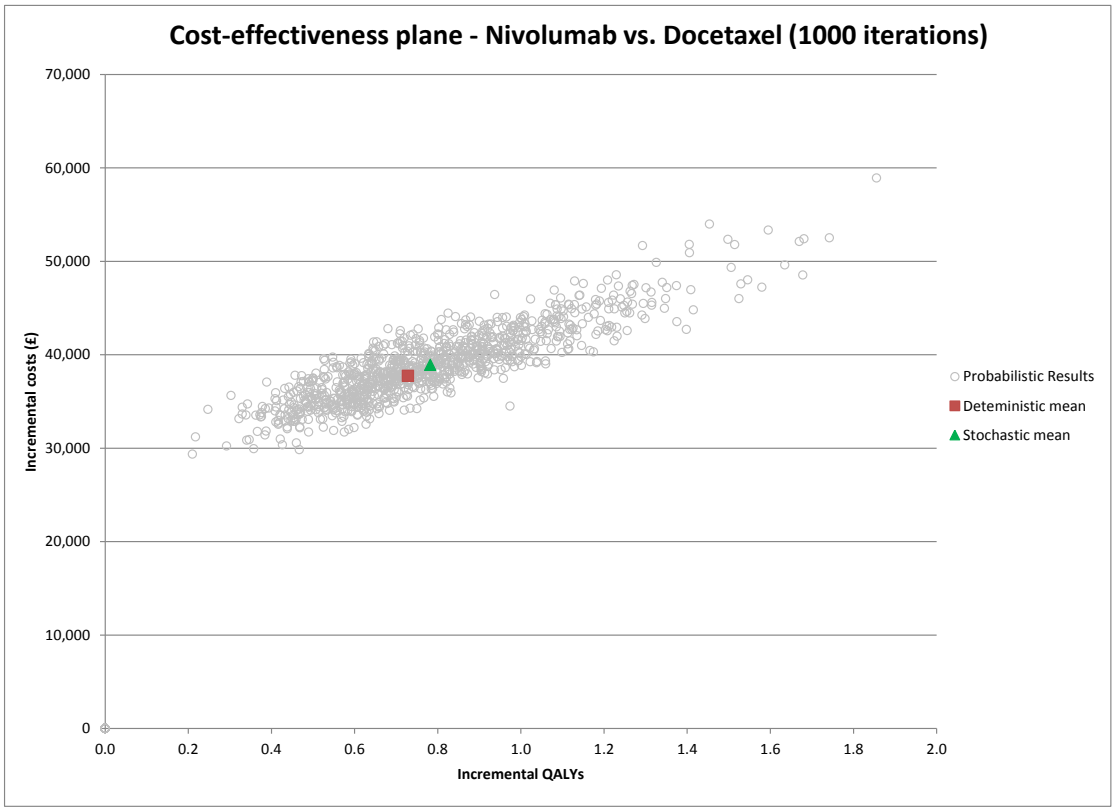


Figure 4: Cost-effectiveness plane for nivolumab vs. nintedanib in combination with docetaxel (with PAS)

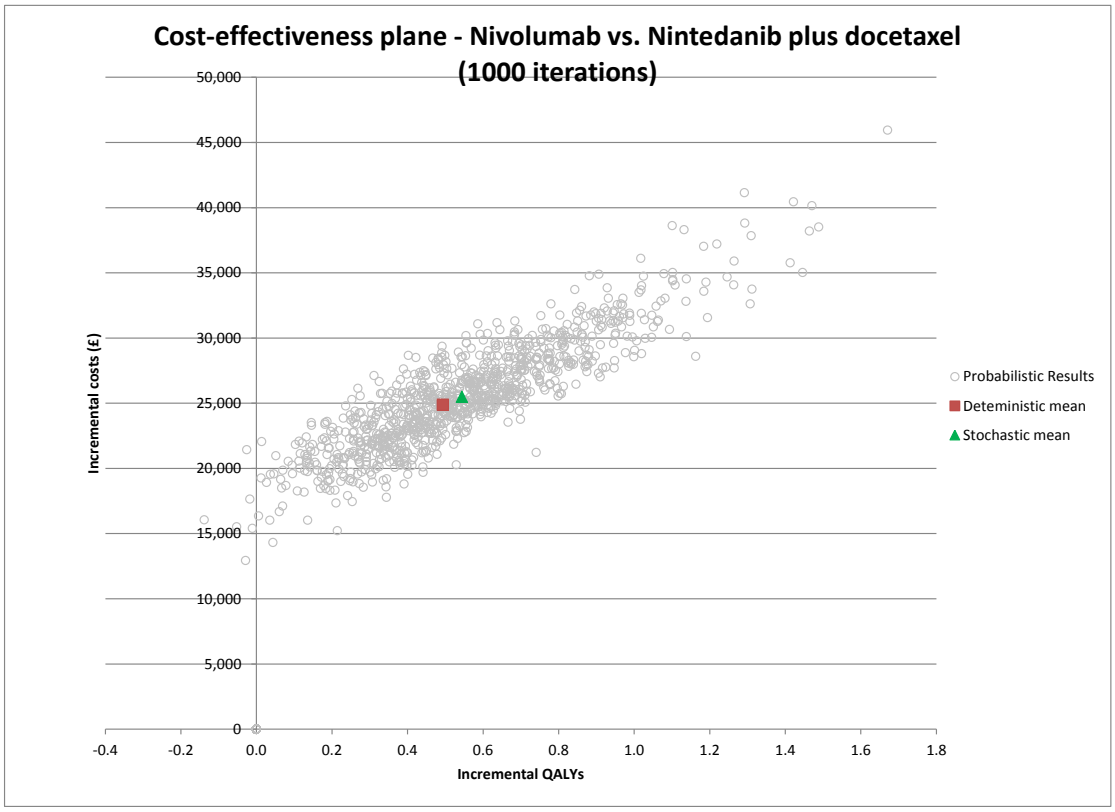
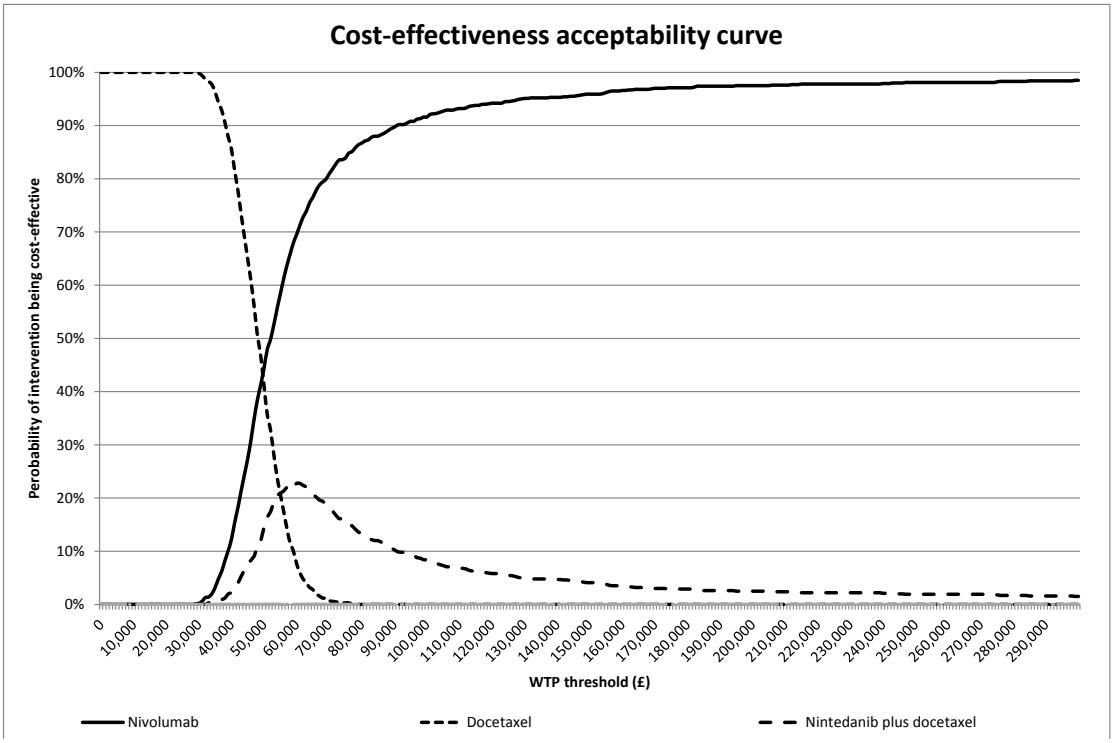


Figure 5: Cost-effectiveness acceptability curve of nivolumab vs. docetaxel (with PAS)



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Scenario 1: Gamma for docetaxel OS and 2-knot spline hazards model for nivolumab OS (with PAS)

Table 9: Scenario 1: summary of QALY gain by health state

	QALYs			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib + docetaxel**	**Incremental**	**% absolute incremental**	**Incremental**	**% absolute incremental**
PF	0.74	0.25	0.25	0.49	98.7%	0.49	159.6%
PD	0.43	0.47	0.64	-0.04	-8.6%	-0.22	-70.7%
AE disutility	-0.01	-0.06	-0.04	0.05	9.9%	0.03	11.1%
Total	1.16	0.66	0.85	0.50	100.0%	0.31	100.0%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year

Note: No utility is assigned to the death state

Table 10: Scenario 1: summary of costs

	Cost (£)			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib + docetaxel**	**Incremental**	**% absolute incremental**	**Incremental**	**% absolute incremental**
PF	4,105.96	1,388.93	1,405.13	2,717.02	7.9%	2,700.82	12.2%
PD*	9,642.55	10,364.20	13,066.36	-721.65	-2.1%	-3,423.81	-15.4%
Drug acquisition cost	29,990.50	304.83	10,059.15	29,685.67	86.1%	19,931.35	89.7%
Administration cost	4,423.30	1,044.22	1,055.86	3,379.08	9.8%	3,367.44	15.2%
Monitoring cost	1,989.06	672.84	680.69	1,316.21	3.8%	1,308.36	5.9%
Subsequent treatment	1,351.33	2,353.02	2,352.88	- ,001.69	-2.9%	- ,001.55	-4.5%
AEs	331.69	1,246.89	991.51	-915.20	-2.7%	-659.81	-3.0%
Total treatment cost	51,834.39	17,374.94	29,611.58	34,459.45	100.0%	22,222.80	100.0%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free

*PD includes the costs of managing patients who have progressed and end-of-life/terminal care. No costs are assigned to the death state.

Table 11: Scenario 1: cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	51,834	1.16			
Docetaxel	17,375	0.66	34,459	0.50	69,033
Nintedanib plus docetaxel	29,612	0.85	22,223	0.31	72,424

Abbreviations: QALY = Quality-Adjusted Life-Year

Scenario 2: Gamma for docetaxel TTD and 1-knot spline hazards model for nivolumab TTD (with PAS)

Table 12: Scenario 2: summary of QALY gain by health state

	QALYs			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib +docetaxel**	**Incremental**	**% absolute incremental**	**Incremental**	**% absolute incremental**
PF	0.95	0.25	0.25	0.70	89.3%	0.70	127.1%
PD	0.54	0.50	0.72	0.03	4.4%	-0.18	-33.4%
AE disutility	-0.01	-0.06	-0.04	0.05	6.3%	0.03	6.2%
Total	1.48	0.70	0.93	0.78	100.0%	0.55	100.0%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year

Note: No utility is assigned to the death state

Table 13: Scenario 2: summary of costs

	Cost (£)			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib + docetaxel**	**Incremental**	**% absolute incremental**	**Incremental**	**% absolute incremental**
PF	5,245.76	1,389.31	1,404.54	3,856.45	10.3%	3,841.22	15.6%
PD*	1,156.78	10,840.75	14,162.36	316.03	0.8%	-3,005.58	-12.2%
Drug acquisition cost	29,069.58	304.93	10,056.16	28,764.64	76.8%	19,013.42	77.3%
Administration cost	5,639.18	1,044.53	1,055.47	4,594.65	12.3%	4,583.71	18.6%
Monitoring cost	2,541.21	673.03	680.41	1,868.19	5.0%	1,860.81	7.6%
Subsequent treatment	1,326.49	2,358.97	2,358.86	-1,032.49	-2.8%	-1,032.37	-4.2%
AEs	331.69	1,246.89	991.51	-915.20	-2.4%	-659.81	-2.7%
Total treatment cost	55,310.70	17,858.42	30,709.31	37,452.28	100.0%	24,601.39	100.0%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free

*PD includes the costs of managing patients who have progressed and end-of-life/terminal care. No costs are assigned to the death state.

Table 14: Scenario 2: cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	55,311	1.48			
Docetaxel	17,858	0.70	37,452	0.78	47,854
Nintedanib plus docetaxel	30,709	0.93	24,601	0.55	44,917

Abbreviations: QALY = Quality-Adjusted Life-Year

Scenario 3: 1-year treatment stopping rule (with PAS)

Please note, this scenario is similar to the PAS, but rather than assuming an economic stop, all nivolumab treatment stops at 1 year. Therefore, in this scenario the administration and monitoring costs also stop at 1 year (whereas in the PAS, these continue, without the drug acquisition costs).

Table 15: Scenario 3: summary of QALY gain by health state

	QALYs			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib + docetaxel**	**Incremental**	**% absolute incremental**	**Incremental**	**% absolute incremental**
PF	0.74	0.25	0.25	0.49	67.6%	0.49	99.2%
PD	0.69	0.50	0.72	0.19	25.6%	-0.03	-6.2%
AE disutility	-0.01	-0.06	-0.04	0.05	6.8%	0.03	6.9%
Total	1.42	0.70	0.93	0.73	100.0%	0.49	100.0%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year

Note: No utility is assigned to the death state

Table 16: Scenario 3: summary of costs

	Cost (£)			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib + docetaxel**	**Incremental**	**% absolute incremental**	**Incremental**	**% absolute incremental**
PF	4,105.96	1,388.93	1,405.13	2,717.02	8.0%	2,700.82	12.7%
PD*	13,395.77	10,841.69	14,160.92	2,554.09	7.5%	-765.15	-3.6%
Drug acquisition cost	29,990.50	304.83	10,059.15	29,685.67	87.0%	19,931.35	93.7%
Administration cost	1,943.78	1,044.22	1,055.86	899.55	2.6%	887.92	4.2%
Monitoring cost	866.98	672.84	680.69	194.13	0.6%	186.29	0.9%
Subsequent treatment	1,351.33	2,354.9	2,354.77	-1,003.58	-2.9%	-1,003.44	-4.7%
AEs	331.69	1,246.89	991.51	-915.20	-2.7%	-659.81	-3.1%
Total treatment cost	51,986.01	17,854.31	30,708.03	34,131.70	100.0%	21,277.98	100.0%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free

*PD includes the costs of managing patients who have progressed and end-of-life/terminal care. No costs are assigned to the death state.

Table 17: Scenario 3: cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	51,986	1.42			
Docetaxel	17,854	0.70	34,132	0.73	46,860
Nintedanib plus docetaxel	30,708	0.93	21,278	0.49	43,122

Abbreviations: QALY = Quality-Adjusted Life-Year

Scenario 4: 2-Year treatment stopping rule

Table 18: Scenario 4: summary of QALY gain by health state

	QALYs			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib + docetaxel**	**Incremental**	**% absolute incremental**	**Incremental**	**% absolute incremental**
PF	0.74	0.25	0.25	0.49	67.6%	0.49	99.2%
PD	0.69	0.50	0.72	0.19	25.6%	-0.03	-6.2%
AE disutility	-0.01	-0.06	-0.04	0.05	6.8%	0.03	6.9%
Total	1.42	0.70	0.93	0.73	100.0%	0.49	100.0%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free; QALY = Quality-Adjusted Life-Year

Note: No utility is assigned to the death state

Table 19: Scenario 4: summary of costs

	Cost (£)			Docetaxel		Nintedanib plus docetaxel	
Health state	**Nivolumab**	**Docetaxel**	**Nintedanib + docetaxel**	**Incremental**	**% absolute incremental**	**Incremental**	**% absolute incremental**
PF	4,105.96	1,388.93	1,405.13	2,717.02	6.1%	2,700.82	8.6%
PD*	13,395.77	10,841.69	14,160.92	2,554.09	5.8%	-765.15	-2.4%
Drug acquisition cost	39,365.33	304.83	10,059.15	39,060.50	88.0%	29,306.17	92.9%
Administration cost	2,558.12	1,044.22	1,055.86	1,513.90	3.4%	1,502.26	4.8%
Monitoring cost	1,144.12	672.84	680.69	471.28	1.1%	463.43	1.5%
Subsequent treatment	1,351.33	2,354.91	2,354.77	-1,003.58	-2.3%	-1,003.44	-3.2%
AEs	331.69	1,246.89	991.51	-915.20	-2.1%	-659.81	-2.1%
Total treatment cost	62,252.32	17,854.31	30,708.03	44,398.02	100.0%	31,544.29	100.0%

Abbreviations: AE = Adverse Event; PD = Progressed Disease; PF = Progression-Free

*PD includes the costs of managing patients who have progressed and end-of-life/terminal care. No costs are assigned to the death state.

Table 20: Scenario 4: cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	62,252	1.42			
Docetaxel	17,854	0.70	44,398	0.73	60,955
Nintedanib plus docetaxel	30,708	0.93	31,544	0.49	63,928

Abbreviations: QALY = Quality-Adjusted Life-Year

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

The PAS is not dependent on any clinically variable parameters.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 21: Results showing the impact of patient access scheme on ICERs for scenarios

ICERs	Nivolumab vs. docetaxel		Nivolumab vs. nintedanib plus docetaxel	
	Without PAS	**With PAS**	**Without PAS**	**With PAS**
Base-case	103,589	51,805	126,861	50,421
Scenario 1: Gamma for docetaxel OS and 2-knot spline hazards model for nivolumab OS (with PAS)	144,594	69,033	195,348	72,424
Scenario 2: Gamma for docetaxel TTD and 1-knot spline hazards model for nivolumab TTD (with PAS)	120,773	47,854	149,112	44,917
Scenario 3: 1-Year treatment stopping rule	46,860	46,860	43,122	43,122
Scenario 4: 2-Year treatment stopping rule	60,955	60,955	63,928	63,928

PAS: patient access scheme.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

PAS agreement form (including terms and conditions): This is the BMS Standard Terms and Conditions which will be used for supplying nivolumab

5.2 Appendix B: Details of outcome-based schemes

Not applicable

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Addendum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small cell lung cancer [ID900]

Addendum including nivolumab discount:

nivolumab versus docetaxel

nivolumab versus nintendanib+docetaxel

This report was commissioned by the NIHR HTA Programme as project number 14/206/12

07 April 2016

CONTAINS noACIC DATA

1 INTRODUCTION

As part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process to consider the clinical and cost effectiveness of nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (ID900), Bristol-Myers Squibb (the company) developed an economic model using MS Excel.

In the company submission (CS), cost effectiveness results are presented for comparisons between nivolumab and docetaxel monotherapy, and nivolumab and nintedanib+docetaxel combination therapy using list prices only.

The PAS is conceptually simple, consisting of an undertaking to provide nivolumab free of charge to the NHS in respect of the treatment required by any patient beyond the first year. This is equivalent to capping the acquisition cost of nivolumab to the NHS to no more than 26 fortnightly doses. However, the cost of administering nivolumab beyond one year must still be borne by the NHS.

The Evidence Review Group (ERG) report for this appraisal summarises the cost effectiveness results presented in the CS. In addition, it includes results generated after applying a number of ERG amendments to the company model and two scenario analyses. Again, the results presented in the ERG report have been generated using list prices for all drugs.

The amendments made by the ERG to the company model are:

- use of ERG preferred overall survival (OS) estimates (R1)
- use of ERG preferred progression-free survival (PFS) estimates (R2)
- use of ERG preferred treatment duration estimates (based on time-to-treatment discontinuation [TTD]) for nivolumab and docetaxel (R3)
- application of ERG preferred PFS and TTD estimates to relevant cost and quality adjusted life year (QALY) categories for nivolumab and docetaxel (R4)
- ERG TTD for nivolumab and ERG PFS for nintedanib+docetaxel (R5)
- ERG PFS for nivolumab disease costs and QALYs, ERG TTD for nivolumab treatment costs and AEs; ERG PFS for nintedanib+docetaxel disease costs and QALYs (R6)
- nivolumab dosing calculations (R7)
- treatment administration costs at the start of each cycle (R8)
- use of preferred health state utility values (R9)
- use of health state utility values from study by Nafees[1] (R10).

This addendum includes the deterministic cost effectiveness results generated by the company model using PAS price for nivolumab.

2 DETERMINISTIC RESULTS

Cost effectiveness results (using PAS price for nivolumab) for the comparisons of nivolumab versus docetaxel and for nivolumab versus nintedanib+docetaxel are displayed in **Error! Reference source not found.** and Table 2 respectively.

The results show that, once the relevant PAS discounts are applied to nivolumab, nivolumab remains more expensive than docetaxel in the company base case and when all of the ERG's suggested amendments have been implemented.

The incremental cost effectiveness ratios (ICERs) for nivolumab versus docetaxel fall below £50,000 per QALY gained for two of the ERG's revisions: when the ERG's revised TTD projections are applied (£47,526 [R3]) and when the ERG's revised PFS is used for disease costs and QALYs, and the ERG's revised TTD for treatment costs and AEs (£49,110 [R4]). The ERG's revised base case ICER per QALY gained for nivolumab versus docetaxel, when all its preferred revisions are combined and using the PAS price for nivolumab, is £91,089.

Once the relevant PAS discounts are applied to nivolumab, nivolumab also remains more expensive than nintedanib+docetaxel in the company base case and when all of the ERG's suggested amendments have been implemented.

The incremental cost effectiveness ratios (ICERs) for nivolumab versus nintedanib+docetaxel fall below £50,000 per QALY gained for four of the ERG's revisions: using the ERG's revised PFS (£42,268 [R2]); using the ERG's revised TTD for all nivolumab costs, QALYs and AEs, and the ERG's PFS for all nintedanib+docetaxel costs and QALYs (£36,387 [R5]); using the ERG's revised PFS for nivolumab disease costs and QALYs, the ERG's revised TTD for nivolumab treatment costs and AEs, and the ERG's revised PFS for nintedanib+docetaxel disease costs and QALYs (£35,512 [R6]); and amending the dosing calculations for nivolumab (£49,208 [R7]).

The ERG's revised base case ICER per QALY gained for nivolumab versus nintedanib+docetaxel, when all its preferred revisions are combined and using the PAS price for nivolumab, is £93,355.

Table 1 Cost effectiveness results (nivolumab vs docetaxel) with PAS included for nivolumab (discount=economic dose cap after 1 year)

Model scenario ERG revision	**Nivolumab**			**Docetaxel**			**Incremental**			**ICER**
	Cost £	**QALYs**	**Life years**	**Cost £**	**QALYs**	**Life years**	**Cost £**	**QALYs**	**Life years**	**£/QALY[+]**
A. Company base case	***55,588***	***1.424***	***2.243***	***17,854***	***0.696***	***1.095***	***+37,733***	***+0.728***	***+1.149***	***51,805***
R1) ERG OS	52,155	1.184	1.806	17,666	0.683	1.072	+34,488	+0.501	+0.734	68,772*
R2) ERG PFS	54,881	1.410	2.243	18,715	0.702	1.095	+36,166	+0.708	+1.149	51,062
R3) ERG TTD	52,144	1.411	2.243	17,991	0.693	1.095	+34,153	+0.719	+1.149	47,526
R4) ERG PFS for disease costs and QALYs, ERG TTD for treatment costs and AEs	51,699	1.410	2.243	16,915	0.702	1.095	+34,784	+0.708	+1.149	49,110
R7) Nivolumab dosing calculations	54,989	1.424	2.243	17,854	0.696	1.095	+37,135	+0.728	+1.149	50,983
R8) Treatment administration costed at start of cycle	55,628	1.424	2.243	18,759	0.696	1.095	+36,869	+0.728	+1.149	50,618
R9) ERG utility values (Van den Hout[2] + CheckMate 057)	55,588	1.186	2.243	17,854	0.532	1.095	+37,733	+0.654	+1.149	57,733
R10) Utility values from study by Nafees[1]	55,588	1.076	2.243	17,854	0.477	1.095	+37,733	+0.599	+1.149	62,981
B. ERG revised base case A+R1, R4, R7:R9	***46,187***	***0.870***	***1.806***	***16,781***	***0.547***	***1.072***	***+29,407***	***+0.323***	***+0.734***	***91,089***

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; PAS=patient access scheme; ICER=incremental cost effectiveness ratio; TTD=time to treatment discontinuation
R2 and R3 (shaded) are superseded by R4
* Interpret with caution due to interdependence of nivolumab ERG OS and company PFS projection in the company model
[+] Rounding errors account for difference between ICERs calculated using the incremental cost and QALY values given in the table and ICERs in this column

Table 2 Cost effectiveness results (nivolumab vs nintedanib+docetaxel) with PAS included for nivolumab (discount=economic dose cap after 1 year)

Model scenario ERG revision	**Nivolumab**			**Nintedanib+docetaxel**			**Incremental**			**ICER**
	Cost £	**QALYs**	**Life years**	**Cost £**	**QALYs**	**Life years**	**Cost £**	**QALYs**	**Life years**	**£/QALY[+]**
A. Company base case	***55,588***	***1.424***	***2.243***	***30,708***	***0.931***	***1.440***	***+24,880***	***+0.493***	***+0.803***	***50,421***
R1) ERG OS	52,155	1.184	1.806	30,709	0.946	1.457	+21,446	+0.238	+0.349	90,200
R2) ERG PFS	54,881	1.410	2.243	34,974	0.939	1.440	+19,907	+0.471	+0.803	42,268
R5) ERG TTD for nivolumab costs, QALYs and AEs, ERG PFS for nintedanib+docetaxel disease costs and QALYs	52,144	1.411	2.243	34,974	0.939	1.440	+17,170	+0.472	+0.803	36,387
R6) ERG PFS for nivolumab disease costs and QALYs, ERG TTD for nivolumab treatment costs and AEs; ERG PFS for nintedanib+docetaxel disease costs and QALYs	51,699	1.410	2.243	34,974	0.939	1.440	+16,725	+0.471	+0.803	35,512
R7) Nivolumab dosing calculations	54,989	1.424	2.243	30,708	0.931	1.440	+24,281	+0.493	+0.803	49,208
R8) Treatment administration costed at start of cycle	55,628	1.424	2.243	30,736	0.931	1.440	+24,892	+0.493	+0.803	50,447
R9) ERG utility values (van den Hout[2] + CheckMate 057)	55,588	1.186	2.243	30,708	0.700	1.440	+24,880	+0.486	+0.803	51,238
R10) Utility values from Nafees[1]	55,588	1.076	2.243	30,708	0.630	1.440	+24,880	+0.446	+0.803	55,802
C. ERG revised base case A+R1, R6:R9	***46,187***	***0.870***	***1.806***	***35,007***	***0.750***	***1.457***	***+11,180***	***+0.120***	***+0.349***	***93,355***

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; PAS=patient access scheme; ICER=incremental cost effectiveness ratio; TTD=time to treatment discontinuation
R2 and R5 (shaded) are superseded by R6
* Interpret with caution due to interdependence of nivolumab ERG OS and company PFS projection in the company model
[+] Rounding errors account for difference between ICERs calculated using the incremental cost and QALY values given in the table and ICERs in this column

3 REFERENCES

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