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 (CDF review TA484) [ID1572]

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 (CDF review TA484) [ID1572]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Bristol Myers-Squibb Pharmaceuticals

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Royal College of Pathologists
   b. Roy Castle Lung Cancer Foundation
   c. Public Health England – SACT data report

4. **Expert personal perspectives** from:
   a. Clinical expert, nominated by Bristol Myers-Squibb Pharmaceuticals
   b. Professor Peter Clark – CDF clinical lead

5. **Evidence Review Group report** prepared by Liverpool Reviews & Implementation Group
   a. ERG report
   b. Erratum
   c. Continued treatment effect after stopping analyses

6. **Technical Report sent out for consultation**

7. **Technical engagement response** from Bristol Myers-Squibb Pharmaceuticals

   Technical engagement responses from experts:
   None

8. **Technical engagement response from consultees and commentators:**
   a. Royal College of Physicians

9. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews & Implementation Group

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

Cancer Drugs Fund Review of TA484

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

Document D

Company evidence submission for committee

Final

14 August 2019

File name	Version	Contains confidential information	Date
TA484 Nivolumab in 2L SQ NSCLC Document D_14 August 2019_CICAIC	1	Yes	14 August 2019

Contents

Tables and figures

Abbreviations

Term	Definition
AC	Appraisal Committee
ACD	Appraisal Consultation Document
ACM	Appraisal Committee Meeting
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BMS	Bristol-Myers Squibb
BSC	best supportive care
CDF	Cancer Drugs Fund
CE	cost-effective
CI	confidence interval
CR	complete response
CrI	credible interval
DBL	database lock
DSU	Decision Support Unit
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOL	end of life
ERG	Evidence Review Group
FAD	Final Appraisal Determination
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IO	immuno-oncology
K1	1 knot
K2	2 knots
KM	Kaplan-Meier
LYG	life-year gained
NA	not available
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	non-small-cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	patient access scheme
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QALY	quality-adjusted life-year
RCC	renal cell carcinoma
RCT	randomised controlled trial
SACT	systemic anticancer therapy
SD	stable disease
SmPC	summary of product characteristics
TTD	time to treatment discontinuation
UK	United Kingdom
VAT	value-added tax

D.1. Background

Nivolumab has a marketing authorisation as a monotherapy for the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) after prior chemotherapy in adults.

As described in the terms of engagement document[1]:

- Nivolumab is recommended by NICE for use within the Cancer Drugs Fund (CDF) as an option for treating locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy, only if:
  - Their tumours are programmed death-ligand 1 (PD-L1) positive, and
  - Nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and
  - The conditions in the managed access agreement are followed.

This recommendation was made after a lengthy appraisal process that included five appraisal committee meetings as summarised in Table 1. From the start of the process, there was disagreement between Bristol-Myers Squibb (BMS) and the Evidence Review Group (ERG) in terms of the potential appropriate survival extrapolation to use, particularly for overall survival (OS). BMS considered that a lognormal model based on 24-month data, including a long-term survival benefit for some patients treated with nivolumab, best fitted the clinical trial and other data. In contrast, the ERG considered that this was too optimistic and stated that, in advanced NSCLC, an exponential model was always appropriate, with no expectation of long-term survival, despite nivolumab having a very different mode of action from existing chemotherapies.

The committee concluded that the ERG's approach was appropriate and decision making was based on the hybrid exponential analysis for both OS and progression-free survival (PFS).

BMS presented clinical and cost-effectiveness data for the whole "all-comers" population in line with the marketing authorisation, however, the committee investigated subgroups defined by PD-L1 expression level. The committee concluded that, at that time, nivolumab had shown no convincing OS benefit compared with docetaxel for patients whose tumours were PD-L1 negative or in whom the PD-L1 level was unquantifiable, and so considered it reasonable to exclude those patients from the cost-effectiveness. Based on the clinical evidence presented at the fifth appraisal committee meeting in 2017, the committee decided the most plausible incremental cost-effectiveness ratio (ICER) for nivolumab compared with docetaxel in the full non-squamous NSCLC population (after the Decision Support Unit [DSU] corrections) was £49,160 per quality-adjusted life-year (QALY) gained. Therefore, the committee considered that nivolumab had shown plausible potential for cost-effectiveness for the subgroup of people with PD-L1–positive tumours and recommended it for use for those patients only within the CDF.

Below, BMS present the agreed updated longer-term clinical trial and real-world SACT data. This is presented by PD-L1 subgroup along with the all-comer population. The new long-term data demonstrate that nivolumab is cost-effective regardless of PD-L1 expression. BMS acknowledge the desire by NICE to review the recommendation as per the original CDF recommendation, therefore, analyses have been provided for all-comers and PD-L1 ≥ 1% to allow the committee to consider all the relevant evidence as required.

Table 1. Summary of initial NICE appraisal process for TA484

Step (date)	CheckMate 057 data presented / considered	Key assumptions	Committee decisions / recommendations	BMS commercial offer
ACM 1: 13 April 2016[2]			**ACD 1 issued May 2016[3]**	
BMS dossier submitted (December 2015)	12-month minimum follow-up All-comers	• OS: Non-proportional hazard – Generalised gamma based on 12 months data – Updated to lognormal based on 24-month data during first consultation • PFS: modelled by using TTD as a proxy fitted with generalised gamma • Stopping rule: Base case – treat to progression; scenario analysis for 1- and 2-year stop • Utility: based on EQ-5D in CheckMate 057 • No subgroups presented	• The committee did not recommend, concluding that: – Nivolumab is a clinically effective treatment option for previously treated non-squamous NSCLC – It could be plausible that nivolumab might have a different level of clinical effectiveness according to PD-L1 expression – ERG's approach to extrapolating OS vs. docetaxel was appropriate – ERG's modelling of OS vs. nintedanib + docetaxel was more appropriate for its decision making – The most appropriate [utility] values would be those calculated by the ERG for PFS and PD – CE results for comparing nivolumab with BSC were not presented, and concluded that this analysis should be done – EOL met – For the comparison with BSC, cost-effectiveness evidence was not presented • Base-case ICER with 1-year dose cap: £91,100 per QALY vs. docetaxel; £93,400 per QALY vs. nintedanib plus docetaxel (at list price); NA vs. BSC	All ICERs based on list price Submission included complex PAS with 1-year dose cap
ERG report (March 2016)	12-month minimum follow-up All-comers	• OS: Hybrid exponential fitted with mixed exponential model – Nivolumab; patients with postprogression treatment (12 months break point) and without postprogression treatment (8 months break point) – Docetaxel; break point of 8 months – Rationale for selection of break points not clear • PFS: Hybrid exponential with an 8-month break point • TTD: – Docetaxel; Kaplan-Meier data only as all patients had finished treatment – Nivolumab; not clearly stated but appears to be TTD Kaplan-Meier data for 3 months and		

Step (date)	CheckMate 057 data presented / considered	Key assumptions	Committee decisions / recommendations	BMS commercial offer
		the PFS exponential, as long-term predictions are very similar between TTD and PFS • Utility: Combination of EQ-5D values from CheckMate 057 with a Dutch lung cancer study by van den Hout et al. (2006)[4]		
ACM 2: 15June 2016[5]				
BMS response to ACD	24-month data All-comers	• OS extrapolation: lognormal curve • PFS/TTD: TTD to model PFS • Revised weighted utility, incorporating a disutility to account for EOL	• No document published • Following the committee meeting, BMS requested to make a further submission including a revised PAS • NICE agreed that the appraisal could be referred back to the appraisal committee	All ICERs based on list price Submission included complex PAS
ERG response	24-month data All-comers	• OS: – Mixed model – Exponential extrapolation – Used Kaplan-Meier data from CheckMate 057 up until 18 months and then extrapolates it until the end of the time horizon of the model • PFS/TTD – PFS and postprogression survival should be used to calculate QALYs • Utilities – Self-selection bias in EQ-5D completion rates in CheckMate 057 still true with new company proposed value Estimated new utility value for PD accounting for the 25% of patients who received treatment after progression		

Step (date)	CheckMate 057 data presented / considered	Key assumptions	Committee decisions / recommendations	BMS commercial offer
ACM 3: 10 August 2016[6]			**ACD 2 issued October 2016**	
BMS response to ACD 2		• Solutions to further support the case for the cost-effectiveness of nivolumab: – Revised PAS – 2-year stopping rule – Present scenarios in which a credit from melanoma and RCC is applied • PD-L1 subgrouping – BMS believes it is inappropriate for NICE to recommend subgroups • Intermediary curve presented between company base-case and ERG approach – BMS lognormal – Intermediary generalised gamma – ERG exponential	• The committee did not recommend, based on: – ERG preferred OS and PFS assumptions – Utility in between BMS and ERG for PD, and ERG utility for PFS – ERG amendment for dosing cost calculations – Most plausible ICER for nivolumab vs. docetaxel was above £80,000 per QALY gained; vs. nintedanib plus docetaxel was above £150,000 per QALY gained – Cost-effectiveness evidence comparing BSC was not presented • The committee invited BMS to submit a proposal for inclusion in the CDF	Complex PAS withdrawn; costs based on confidential simple discount PAS ([redacted]%)
NICE DSU comments		• Evidence not supportive of the use of a decreasing hazards function • OS extrapolation: Committee-preferred hybrid Kaplan-Meier/exponential approach		
ACM 4: 12 April 2017[7,8]				
BMS	3-year follow-up (plus 5-year from CheckMate 003)	• OS extrapolation – 3-year data presented from CheckMate 057 and 5-year data from CheckMate 003 alongside model estimates for nivolumab OS – Shows that trial data is outperforming even BMS-preferred Log-Logistic • Treatment waning – BMS argues against a treatment waning effect but presents 3 scenarios as requested	• Development of the FAD paused to allow BMS and NHS England to have commercial discussions	Based on new confidential simple discount PAS ([redacted]%)

Step (date)	CheckMate 057 data presented / considered	Key assumptions	Committee decisions / recommendations	BMS commercial offer
		– Treatment effect reduced at 3, 5, and 10 years • PFS – Long-term PFS uses an exponential curve in the base case, as requested by NICE – Alternate PFS analyses are submitted using Weibull and Gamma distributions		
NICE DSU Critique of new evidence		• OS extrapolation – Approach to hybrid exponential model differs to ERG approach – No sensitivity analysis around the choice of break points • PD-L1 subgroups – Estimation of constant hazard to patients following the break point is subject to considerable uncertainty due to low patient numbers		
ACM 5, August 2017[9]			**FAD issued September 2017 based on papers from ACM 4 and CDF proposal [6]**	
BMS CDF proposal	3-year follow-up (plus 5-year from CheckMate 003)	• BMS submitted CDF proposal for both squamous and non-squamous, highlighting that: – The PAS was designed to address uncertainty	• Nivolumab is recommended for use within the CDF as an option for treating locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy: – With a 2-year stopping rule – PD-L1 positive tumours • In the FAD, the following was noted: – OS extrapolations: ERG hybrid exponential most plausible – Declining hazard over time and crossing general population not plausible with the company predictions	Based on confidential simple PAS ([redacted])

Step (date)	CheckMate 057 data presented / considered	Key assumptions	Committee decisions / recommendations	BMS commercial offer
			• PFS: Hybrid exponential • TTD: preferred not mentioned in FAD • Utility values: Midway between ERG and company, thus utility values of 0.713 and 0.569 were used for PFS and PD, respectively • Continued treatment effect: Plausible that after stopping treatment at 2 years, nivolumab's treatment effect could last up to 3 years	

ACD = Appraisal Consultation Document; ACM = Appraisal Committee Meeting; BSC = best supportive care; CDF = Cancer Drugs Fund; CE = cost-effective; DSU = Decision Support Unit; EOL = end of life; ERG = Evidence Review Group; FAD = Final Appraisal Determination; ICER = incremental cost-effectiveness ratio; NA = not available; NICE = National Institute for Health and Care Excellence; NSCLC = non-small-cell lung cancer; OS = overall survival; PAS = patient access scheme; PD = progressive disease; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; QALY = quality-adjusted life-year; RCC = renal cell carcinoma; TTD = time to deterioration; VAT = value-added tax.

Note: All ICERs presented are cost per QALY for nivolumab vs. docetaxel.

In the 2 years since nivolumab for the second-line treatment of non-squamous NSCLC entered the CDF, additional database locks have occurred for both CheckMate 057 and CheckMate 003. In addition, it has become widely accepted that immuno-oncology (IO) treatments provide patients in this setting with the potential for long-term survival. Indeed, 5-year follow-up data from CheckMate 003 has been cited by other pharmaceutical companies with IO treatments to support their survival analyses and assumptions of long-term benefits and has been accepted by appraisal committees.[10,11]

D.2. Key committee assumptions

Table 2 presents the key committee assumptions as set out in the terms of engagement.[1] This submission adheres to these assumptions, except for the following:

- Population/subgroups: Although BMS acknowledge the desire by NICE to review the recommendation as per the original CDF recommendation, analyses have been provided for all-comers and PD-L1 ≥ 1% (and results for the subgroup of patients with PD-L1 < 1% are presented in Appendix A) in order to allow the committee to consider all the relevant evidence as required. Our submission is based on all patients in CheckMate 057; clinical data for the PD-L1 subgroups are presented following agreement that different PD-L1 expression levels be explored as part of the data collection arrangement, along with relevant economic scenario analyses.
- Comparators: Comparisons with docetaxel are presented because this was the standard of care in England before the introduction of immuno-oncology therapies. We understand that nintedanib plus docetaxel is not commonly used in this setting.
- Treatment costs: The labelled dose of nivolumab has changed since CDF entry.

In addition to the base case using the committee-preferred assumptions (except where noted above), we have explored relevant assumptions in light of the newly available data and will present scenario analyses incorporating these where appropriate.

Table 2. Key committee assumptions set out in the terms of engagement

Area	Committee-preferred assumptions
Population	People with PD-L1–positive previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer after prior chemotherapy. **Note: This dossier includes analyses for all-comers and PD-L1 ≥ 1% patients.**
Comparators	The most appropriate comparators for this appraisal are docetaxel monotherapy, nintedanib plus docetaxel (for people with adenocarcinoma only), and best supportive care. **Note: This dossier compares nivolumab with docetaxel only as the most appropriate comparator.**
Generalisability	The results of CheckMate 057 are generalisable to clinical practice in England.
Model structure	The company's model structure was accepted. **It is anticipated that the model structure will not change.**
Subgroups	The committee considered that it is plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression. The committee reviewed cost-effectiveness evidence by PD-L1 expression. **The company are expected to submit evidence by PD-L1 expression level in the CDF review.**
Extrapolation of OS	The observed Kaplan-Meier followed by the exponential model is an appropriate method for extrapolating OS. **It is anticipated that the committee's preferred approach to extrapolation**

Area	Committee-preferred assumptions
	of OS will remain, unless the company can demonstrate that additional data from the trial and SACT justify departure from this approach.
Extrapolation of PFS	Using the observed data followed by an exponential extrapolation is the most appropriate method to estimate PFS.
Utilities	A utility value of 0.569 should be used for the progressed-disease health state. A utility value of 0.713 should be used for the progression-free health state.
Stopping rule	A 2-year stopping rule was not included in the SmPC. A stopping rule was considered acceptable and implementable to both patients and clinicians. **A 2-year stopping rule was included in the recommendations, given current available evidence, but should be reviewed in light of any new evidence.**
Continued treatment effect	After stopping treatment at 2 years, nivolumab's treatment effect could last up to 3 years.
Dose intensity reduction	It is reasonable to adjust the dose intensity for both the intervention and the comparator.
Treatment costs	The committee accept the ERG's cost corrections to the dose of nivolumab, and the calculation of administration costs. **Note: As the dose of nivolumab specified in the SmPC is now 240 mg every 2 weeks, this will be used in the base-case model.**
End of life	Nivolumab met the criteria to be considered a life-extending, end-of-life treatment.

CDF = Cancer Drugs Fund; ERG = Evidence Review Group; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; SACT = systemic anticancer therapy; SmPC = summary of product characteristics.

Note: Where data collection addresses the committee's key uncertainties, alternative assumptions are explored and justified. All other committee-preferred assumptions remain unchanged.

Sources: NICE (2019)[1]; Bristol-Myers Squibb data on file (2019)[12]

D.3. Other agreed changes

The company have not altered the decision problem, submitted additional evidence, or made further alterations to the model during the CDF review period except those agreed by NICE in advance.

D.4. The technology

Table 3 presents an overview of nivolumab. The only change to the summary of product characteristics of relevance to this indication is the change in label dose, as described in Table 3.

Table 3. Technology being reviewed

UK-approved name and brand name	Nivolumab (Opdivo®)
Mechanism of action	Programmed death-1 (PD-1) inhibitor
Marketing authorisation/CE mark status	Marketing authorisation in this indication was granted in July 2015.
Indications and	Nivolumab as monotherapy is indicated for the treatment of locally advanced

any restriction(s) as described in the summary of product characteristics	or metastatic non-small cell lung cancer after prior chemotherapy in adults.[13] This indication includes both squamous and non-squamous histologies.
Method of administration and dosage	Intravenous infusion. At the time of the original submission, dosing was weight-based (3 mg/kg every 2 weeks). In 2018, dosing was changed to a flat dose of 240 mg every 2 weeks. [redacted]
	None
List price and average cost of a course of treatment	Nivolumab 100 mg: £1,097.00 Nivolumab 40 mg: £439.00 Average cost of treatment: £[redacted] based on label dose of 240 mg Q2W
Commercial arrangement (if applicable)	A simple discount PAS is currently in place that would apply to nivolumab in this indication.
Date technology was recommended for use in the CDF	September 2017
Data collection end date	June 2019

CDF = Cancer Drugs Fund; CE = cost-effectiveness; CR = complete response; NSCLC = non-small-cell lung cancer; PAS = patient access scheme; PR = partial response; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = stable disease.

Sources: EMA (2019)[13]; NICE (2017)[9]

D.5. Clinical effectiveness evidence

CheckMate 057 was the key study that provided evidence in support of nivolumab in non-squamous NSCLC (Table 4). Overall survival was the primary outcome in CheckMate 057; however, at the time of the original submission, data were immature. Additional follow-up data have now been collected, and 5-year follow-up data are included in this submission.

Table 4. Primary source of clinical effectiveness evidence

Study title	**CheckMate 057**
Study design	Phase 3, randomised, open-label study
Population	Adults (≥ 18 years) with advanced or metastatic non-squamous NSCLC after failure of prior platinum doublet-based chemotherapy
Intervention(s)	Nivolumab 3 mg/kg Q2W (n = 292)
Comparator(s)	Docetaxel 75 mg/m^2 Q3W (n = 290)
Outcomes collected that	**Overall survival** **Time to treatment discontinuation**

address committee's key uncertainties	**Subgroup data by PD-L1 expression**
Reference to section in appendix	Section 5.1 in the Data Collection Agreement (page 4)

NSCLC = non-small-cell lung cancer; PD-L1 = programmed death-ligand 1; Q2W = every 2 weeks; Q3W = every 3 weeks.

Source: Borghaei et al. (2015)[15]; NICE (2017)[16]

In addition, although not included in the terms of engagement, the data collection agreement stated that additional follow-up from CheckMate 003 would provide additional data on the long-term benefits of nivolumab in NSCLC.[16] Observational data have been collected during the period of managed access via the systemic anticancer therapy (SACT) data set to support the data collected in the clinical trial. This includes data on OS, duration of therapy, and PD-L1 expression. Public Health England have provided a summary of the observational data collected (Table 5).[17]

Table 5. Secondary source of clinical effectiveness evidence

Study title	**CheckMate 003**	**SACT data cohort study**
Study design	Single-arm, phase 1, dose-escalation non-RCT	SACT data cohort study
Population	Adults with advanced or recurrent malignancies, including a subset of patients with squamous NSCLC, who had received at least 1 prior and up to 5 previous therapies and had experienced progression through at least 1 platinum- or taxane-based regimen	Patients who applied for CDF funding for nivolumab for previously treated non-squamous NSCLC from 20 September 2017 to 19 December 2018 in NHS England's Blueteq database
Intervention(s)	Nivolumab 1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W for up to 96 weeks	Nivolumab
Comparator(s)	Not applicable	Not applicable
Outcomes collected that address committee's key uncertainties	Overall survival	Overall survival Duration of treatment Data on PD-L1 subgroups
Reference to section in appendix	Section 5.1 in the Data Collection Agreement (page 4)	Section 5.2 and 5.3 in the Data Collection Agreement (page 4)

CDF = Cancer Drugs Fund; NSCLC = non-small-cell lung cancer; PD-L1 = programmed death-ligand 1; Q2W = every 2 weeks; RCT = randomised controlled trial; SACT = systemic anticancer therapy.

Sources: Antonia et al. (2019)[18] NICE (2017)[16], Public Health England (2019)[17]

Evidence from CheckMate 003 was not used to update the economic model. The results of this study were used in validation of survival extrapolations. This study was not included in the economic model because it does not provide a comparison of nivolumab with docetaxel.

Evidence from SACT was not used to update the economic model. The results of this study were used in validation of survival extrapolations and to assess duration of treatment in routine clinical practice.

D.6. Key results of the data collection

As described in Sections D.1 and D.2, one of the main areas of uncertainty during the original appraisal process was the selection of appropriate extrapolations for OS. As shown in (Table 6), up to 2 years follow-up, there was little to differentiate the CheckMate 057 data from the preferred survival extrapolations. However, BMS argued that by the time 3-year data from CheckMate 057 and 5-year data from CheckMate 003 were available (with some patients followed for up to 4 and 5 years, respectively), it was clear that the Evidence Review Group's (ERG) preferred extrapolation severely underestimated OS, and that even the survival rates in the company base case could be conservative. This underestimation was confirmed during the CDF period, during which additional follow-up data from CheckMate 057 and CheckMate 003 were collected. Five-year OS in CheckMate 057 ([redacted]%) is [redacted] than that estimated by BMS (10.35%), [redacted] that estimated by the intermediary curve (8.70%), and [redacted] that estimated by the ERG (3.66%) at the time of the CDF recommendation.[19]

Table 6. Comparison of overall survival data versus modelled survival for nivolumab-treated patients at time of CDF entry

Data source	Curve	Proportion alive at each year (%)							
		1	2	3	4	5	6	10	15
CheckMate 057	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
CheckMate 003 (any histology)	Kaplan-Meier	41.8	24.8	18.4	15.6	15.6	14.7		
Model estimate for nivolumab overall survival	BMS-preferred Lognormal	46.78	27.78	18.75	13.61	10.35	7.11	3.83	1.93
	Intermediary Generalised gamma	47.64	27.35	17.58	12.08	8.70	5.09	2.47	0.98
	ERG exponential (AC preferred)	51.61	26.63	13.74	7.09	3.66	1.89	0.13	0.00

AC = appraisal committee; CDF = Cancer Drugs Fund; ERG = Evidence Review Group.

Sources: Bristol-Myers Squibb data on file (2019)[19]; NICE (2017)[8],Antonia et al. (2019)[18]

Figure 1 and Figure 2 depict the OS and PFS Kaplan-Meier data in CheckMate 057, respectively, versus that of the committee-preferred extrapolations based on the ERG analyses, and BMS-preferred extrapolation at the time of CDF entry. As can be seen from these figures, for both OS and PFS, the committee-preferred extrapolations significantly underestimated the 5-year data from CheckMate 057. As a result, updated survival analyses have been conducted as part of this submission to more accurately represent the long-term survival outcomes.

Figure 1. Overall survival committee-preferred extrapolation versus 5-year data in CheckMate 057

ERG = Evidence Review Group; KM = Kaplan-Meier.
Sources: Bristol-Myers Squibb data on file (2019)[20]; NICE (2017)[8]

Figure 2. Progression-free survival committee-preferred extrapolation versus 5-year data

ERG = Evidence Review Group; KM = Kaplan-Meier.
Sources: Bristol-Myers Squibb data on file (2019)[20]; NICE (2016)[2]

Sections D.6.1 to D.6.4 present results for key outcomes at the time of the original submission

and at the 5-year database lock of CheckMate 057. This is followed by OS results from the 6-year database lock of CheckMate 003 in Section D.6.5, and the SACT data from the analysis in Section D.6.6.

D.6.1. Overall survival: 5-year database lock, CheckMate 057

The initial database lock for CheckMate 057 took place in March 2015. The median OS was 12.2 months (95% confidence interval [CI], 9.7-15.0 months) for the 292 patients in the nivolumab group versus 9.4 months (95% CI, 8.1-10.7 months) for the 290 patients in the docetaxel group (hazard ratio [HR], 0.73; 95% CI, 0.59-0.89; *P* = 0.002). The 1-year OS rate was 51% (95% CI, 45%-56%) with nivolumab versus 39% (95% CI, 33%-45%) with docetaxel.[15] In May 2019, a targeted database lock occurred and had a minimum of 5 years of follow-up. The median OS was [redacted] months (95% CI, [redacted] months) for the nivolumab group versus [redacted] months (95% CI, [redacted] months) for the docetaxel group (HR, [redacted]; 95% CI, [redacted] *P* < [redacted] (Figure 3).[19] The 5-year OS rate for the nivolumab group ([redacted]%; 95% CI, [redacted]%-[redacted]%) was almost [redacted] times that for the docetaxel group ([redacted]%; 95% CI, [redacted] (Table 7).[19] Thus, a continued benefit of nivolumab therapy was still seen at 5 years of follow-up, even though docetaxel patients were likely also receiving the benefit of IO therapy after switching to nivolumab at 2 years or receiving IO as a subsequent therapy. The benefit of therapy in the nivolumab arm was likely to be underestimated because of this.

Figure 3. Kaplan-Meier of overall survival in CheckMate 057 (all randomised patients): 5--year update

CI = confidence interval.

Source: Bristol-Myers Squibb data on file (2019)[19]

Table 7. Overall survival rates by 6-month intervals up to 5 years in CheckMate 057 (all randomised patients)

Survival rate (95% CI)	Nivolumab 3 mg/kg	Docetaxel
6-Month	[redacted]	[redacted]
12-Month	[redacted]	[redacted]
18-Month	[redacted]	[redacted]
24-Month	[redacted]	[redacted]
36-Month	[redacted]	[redacted]
48-Month	[redacted]	[redacted]
60-Month	[redacted]	[redacted]

CI = confidence interval.

Source: Bristol-Myers Squibb data on file (2019)[19]

D.6.2. Progression-free survival: 5-year database lock, CheckMate 057

At the time of submission to NICE, results from the initial 12-month database lock in March 2015 were presented. 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 months] for nivolumab vs. 4.2 months [95% CI, 3.5-4.9 months] for docetaxel), the nivolumab and docetaxel Kaplan-Meier curves showed markedly different profiles and crossed between 7 and 8 months. The overall HR for disease progression or death also favoured nivolumab (HR, 0.92; 95% CI, 0.77-1.11; *P* = 0.39).[15] The 5-year PFS rate for the nivolumab group was [redacted]% (95% CI, [redacted]) compared with [redacted]% for the docetaxel group (Table 8, Figure 4).[19]

Figure 4. Kaplan-Meier of progression-free survival in CheckMate 057 (all randomised patients): 5-year update

[redacted]

Source: Bristol-Myers Squibb data on file (2019)[19]

Table 8. Progression-free survival rates by 6-month intervals up to 5 years in CheckMate 057 (all randomised subjects)

Survival rate (95% CI)	Nivolumab 3 mg/kg	Docetaxel
6-Month	[redacted]	[redacted]
12-Month	[redacted]	[redacted]
18-Month	[redacted]	[redacted]
24-Month	[redacted]	[redacted]
36-Month	[redacted]	[redacted]
48-Month	[redacted]	[redacted]
60-Month	[redacted]	[redacted]

Source: Bristol-Myers Squibb data on file (2019)[19]

D.6.3. Time to treatment discontinuation: 5-year database lock, CheckMate 057

Time to treatment discontinuation (TTD) was only included in the original non-squamous submission to NICE as part of the model development, and results are not included in the main Borghaei et al. (2015)[15] publication. However, at the time of the 5-year database lock, the median TTD was [redacted] months (95% CI, [redacted]) for patients receiving nivolumab compared with [redacted] months (95% CI, [redacted]) for patients receiving docetaxel. The 5-year TTD rate for the nivolumab group was [redacted]% (95% CI, [redacted]).(Figure 5)(Table 9).[19]

Figure 5. Kaplan-Meier of time to treatment discontinuation in CheckMate 057 (all randomised patients) 5-year update

Source: Bristol-Myers Squibb data on file (2019)[19]

Table 9. Time to treatment discontinuation rates by 6-month intervals up to 5 years in CheckMate 057 (all randomised subjects)

Survival rate (95% CI)	Nivolumab 3 mg/kg	Docetaxel
6-Month		
12-Month		
18-Month		
24-Month		
36-Month		
48-Month		
60-Month		

Source: Bristol-Myers Squibb data on file (2019)[19]

D.6.4. Efficacy in PD-L1 subgroups: 5-year database lock, CheckMate 057

At the time of the original submission, nivolumab was associated with longer OS and PFS and higher objective response rate than docetaxel at the prespecified PD-L1 expression levels of ≥ 1%, ≥ 5%, and ≥ 10% (Figure 6).[15]

Figure 6. Forest plot of overall survival and progression-free survival in CheckMate 057 by PD-L1 subgroup: 1-year analysis

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)	

CI = confidence interval; HR = hazard ratio; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival.

Source: Borghaei et al. (2015)[15]

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. However, the study was not stratified by PD-L1 or powered to show differences in PD-L1 subgroups within the study.[15]

The registration studies CheckMate-017 and -057 were powered to show superiority over docetaxel regardless of PD-L1 expression. The primary end point of superior OS was met with a clear positive, statistically significant, and clinically meaningful benefit regardless of PD-L1 expression.

The European Medicines Agency (EMA) assessed the risk-benefit profile of nivolumab to be favourable in all patients, regardless of PD-L1 status. Therefore, testing was not required by the EMA to select patients for eligibility to treatment.

During the process of marketing authorisation approval, posthoc analyses were requested by the Committee for Medicinal Products for Human Use. Therefore, the summary of product characteristics includes additional PD-L1 analyses at different intervals, and at the 50% threshold level for objective response rate (ORR) and OS in Section 5.1, and also a warning statement for early deaths in Section 4.4.[13]

However, as BMS noted to the committee, these posthoc analysis results should be interpreted with caution for several reasons: the analysis was retrospective, the subgroup sample sizes were small, and the PD-L1 test was not analytically validated at the 10% or 50% expression levels at the time of the analysis.

The information requested by the Committee for Medicinal Products for Human Use has been provided in the summary of product characteristics for information, but the licence remains for all patients regardless of PD-L1 expression level.

Programmed death-ligand 1 is an imperfect predictive biomarker. Testing methodologies are still being developed and there is no single standardised test routinely used by the NHS. The tests have a high positive predictive value but a low negative predictive value, i.e. if the patient is positive, they are more likely to have a good response, but if they are negative, they may still respond to nivolumab and may even achieve a complete response.

Not only has it been demonstrated that patients benefit from nivolumab regardless of PD-L1 expression, there are also numerous limitations to using PD-L1 expression as a biomarker in this population, and these include the following:

- Heterogeneity of PD-L1 expression throughout the tumour and therefore a biopsy may not be representative of PD-L1 expression within the whole tumour.
- In contrast to tumour driver mutations such as epidermal growth factor receptor (EGFR), protein expression such as PD-L1 may vary over time and after prior treatments including chemotherapy. Therefore, a biopsy at diagnosis may not be representative of PD-L1 expression level at the time of relapse and treatment decision making.

At the time of the 5-year database lock, OS results for all PD-L1 subgroups continue to be in favour of nivolumab (Figure 7).[20] Since a benefit was seen across all PD-L1 cohorts of patients with non-squamous NSCLC, and the study was not powered to detect differences by PD-L1 subgroup, BMS still considers that the "all-comers" population remains relevant and for completeness presents the cost-effectiveness below.

Figure 7. Forest plot of overall survival in CheckMate 057 by PD-L1 subgroup: 5-year update

CI = confidence interval; PD-L1 = programmed death-ligand 1.

Source: Bristol-Myers Squibb data on file (2019)[20]

The benefit to patients treated with nivolumab can be seen over the long-term inFigure 8, even though all docetaxel patients were likely receiving the benefit of IO therapy. The analysis is therefore likely to underestimate the benefit in the nivolumab arm. For patients with baseline PD-L1 ≥ 1%, the proportion of patients treated with nivolumab alive at 5 years was [redacted]%

compared with [redacted]% with docetaxel.[20] For patients with baseline PD-L1 < 1%, the proportion of patients treated with nivolumab alive at 5 years was [redacted]% compared with [redacted]% with docetaxel. For patients with unquantifiable PD-L1, the proportion of patients treated with nivolumab alive at 5 years was [redacted]% compared with [redacted]% with docetaxel. As such, at 5 years, nivolumab nearly [redacted] overall survival compared with docetaxel in patients who are PD-L1 negative.[20] A large number of patients with unquantifiable PD-L1 status also showed improved survival in the long-term, further supporting the appropriateness of using the all-comers population in the base case.

Additionally, a recent network meta-analysis by Almutairi et al. (2019)[21] includes a comparison of nivolumab and atezolizumab broken down by PD-L1 expression. No statistically significant differences in OS were seen between nivolumab and atezolizumab in the PD-L1 subgroups presented, with HRs of 0.98 (95% credible interval [CrI], 0.70-1.38) in patients with PD-L1 < 1%, 0.91 (95% CrI, 0.66-1.27) and in PD-L1 ≥ 1%. In an analysis of all enrolled patients, pairwise comparisons did not show statistically significant differences in OS between pembrolizumab, nivolumab and atezolizumab. However, some toxicity differences were seen favouring nivolumab over atezolizumab in terms of risk of anaemia, constipation, and nausea. The NICE recommendation for atezolizumab is for use after chemotherapy, regardless of PD-L1 status[11], since nivolumab has been shown to have similar efficacy to atezolizumab across all PD-L1 subgroups, nivolumab should also be recommended regardless of PD-L1 expression level.

Figure 8. Kaplan-Meier plots for overall survival in CheckMate 057 by PD-L1 subgroup: 5-year update

PD-L1 = programmed death-ligand 1.

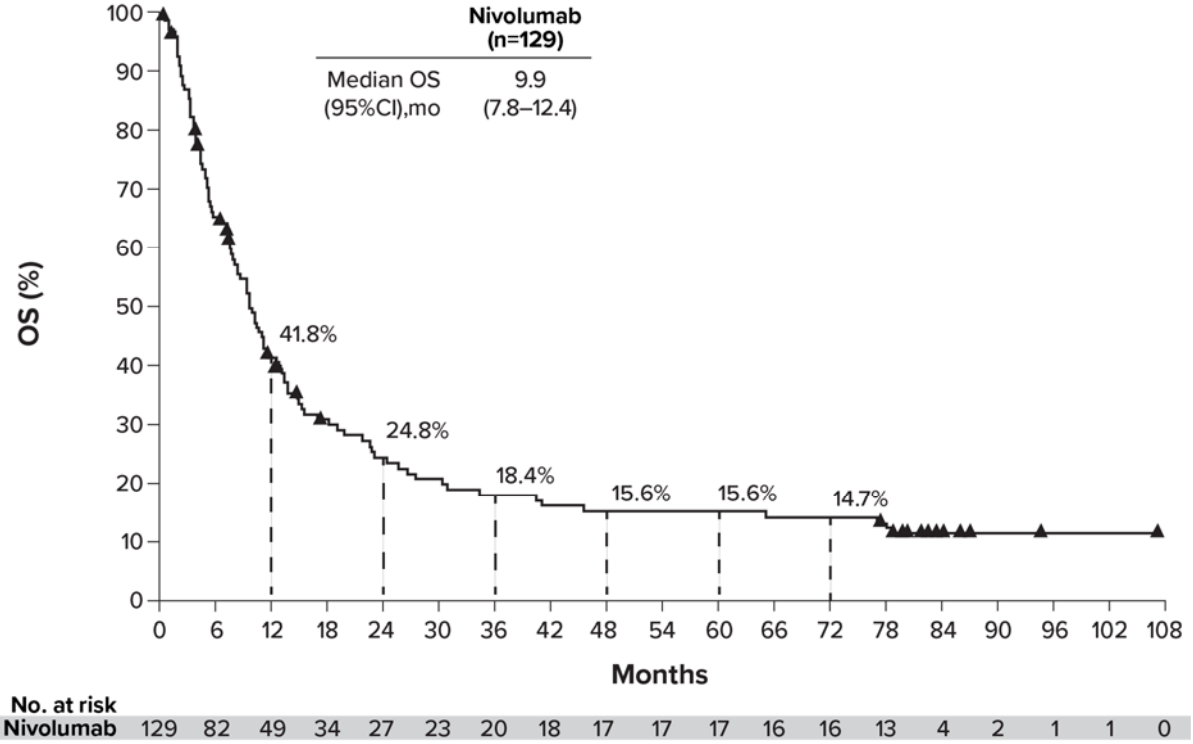
Source: Bristol-Myers Squibb data on file (2019)[20]

D.6.5. Overall survival: 6-year database lock, CheckMate 003

At the time of the original submission, the median OS in CheckMate 003 for the 37 patients with NSCLC who received nivolumab 3 mg/kg was 14.9 months (95% CI, 7.3-30.3 months).[22] 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 survival rates were similar in patients with squamous and non-squamous histologies (1-, 2-, and 3-year OS rate for non-squamous NSCLC at 3 mg/kg: 62%, 48%, and 24%, respectively).[22]

Data from the 6-year (May 2018) database lock are accepted for publication as part of a pooled analysis of nivolumab studies by Antonia et al. (2019)[18]. The estimated 6-year OS rate was 14.7% for all treated patients (n = 129) (Figure 9).[18]

Figure 9. Overall survival of all treated patients with NSCLC in CheckMate 003: 6-year database lock



CI = confidence interval; NSCLC = non-small-cell lung cancer; OS = overall survival.

Source: Antonia et al. (2019)[18]

In a previous analysis at 5 years, 12 patients (75%) received no subsequent therapy after nivolumab and were without evidence of progressive disease at last follow-up, demonstrating continued treatment effect up to 3 years after 2 years of nivolumab treatment. Therefore, it stands to reason that, at 6 years, and up to 4 years after 2 years of nivolumab treatment, most patients were still experiencing the treatment effect of nivolumab.

D.6.6. SACT database outcomes

The analysis of SACT data includes patients with a CDF application from 20 September 2017 to 19 December 2018, and patients were followed until 31 January 2019. In total, 59 new applicants for CDF funding for nivolumab in non-squamous NSCLC (in patients with PD-L1 ≥ 1%) were received: 10 had previously received nivolumab, 1 did not receive treatment, and 5 died before treatment started. Therefore, 43 patients were included in the analysis.[17] Due to

the limited number of patients and events, caution should be taken when interpreting these outcomes.

Overall, 67% of patients (n = 29) were male and 33% (n = 14) were female; the median age was 65 years, and most had a performance status of 0 (21%) or 1 (67%). PD-L1 expression was ≥ 1% in 98% of patients (n = 35) and not available in 2% of patients (n = 1).[17]

Of the included patients, 31 (72%) had completed treatment by 31 January, 2019. The median follow-up time in SACT was 125 days, the maximum follow-up was 486 days, and the median treatment duration was 124 days (4.1 months;95% CI, 3.0-8.3 months) (Figure 10). Overall, 38% of patients were still receiving treatment at 6 months (95% CI, 23%-53%), 21% of patients were receiving treatment at 12 months (95% CI, 9%-37%).[17] The median treatment duration in the SACT database is longer than that observed in CheckMate 057 (see overlay in Figure 10). However, the SACT data are not sufficiently mature to see the impact of the 2-year stopping rule.

Figure 10. Kaplan-Meier for treatment duration in the SACT database and CheckMate 057

SACT = systemic anticancer therapy.

Source: Public Health England (2019)[17], Bristol-Myers Squibb data on file (2019)[19]

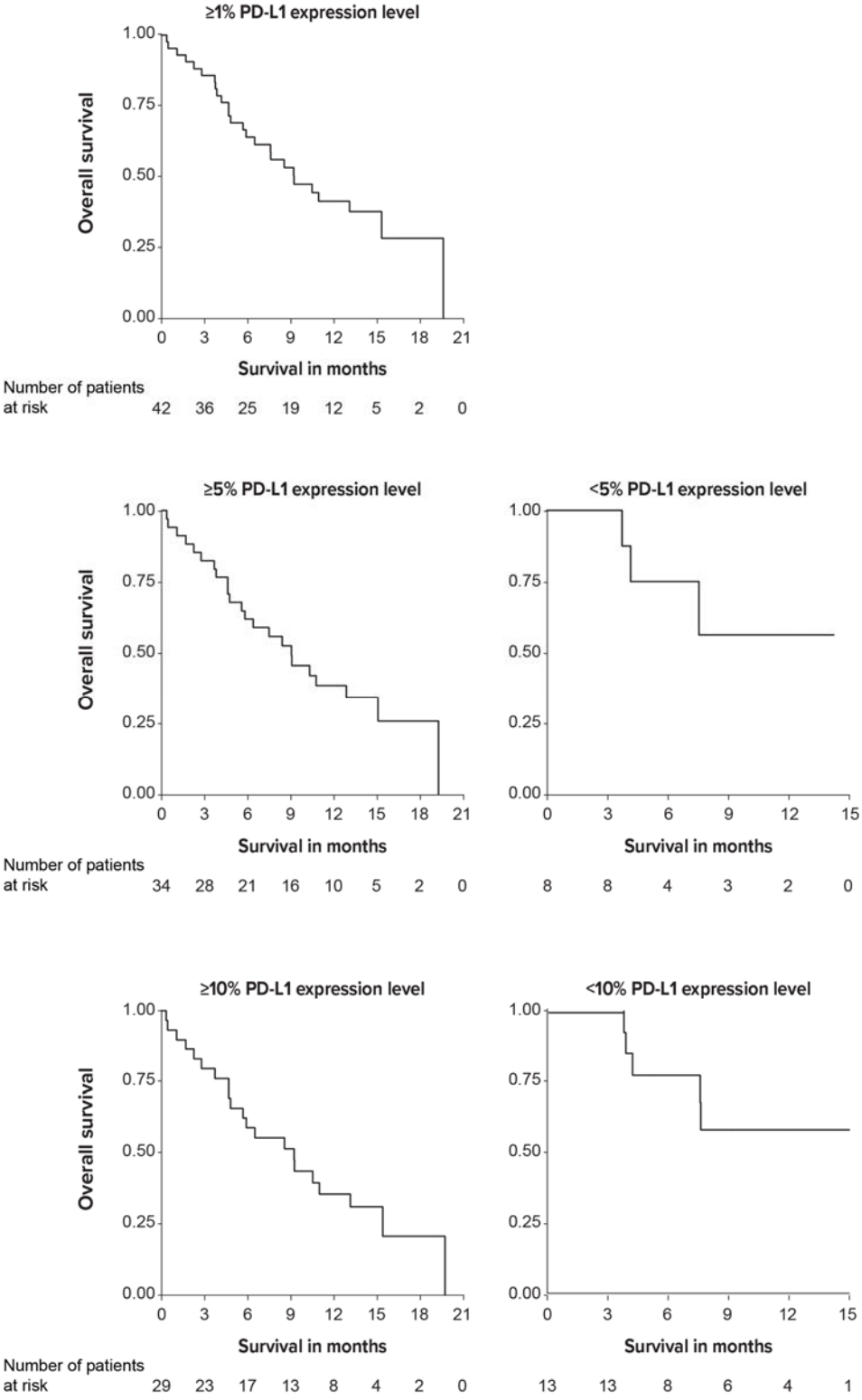
At the time of analysis, the median OS was 9.2 months (CIs could not be produced because there were insufficient events) (Figure 11), minimum follow-up in SACT was 5 months and the maximum follow-up period for survival was 20 months. Survival at 6 months was 62% (95% CI, 46%-75%), 12 months survival was 43% (95% CI, 28%-58%) For all patients who received treatment, 17 were still alive (censored) at the date of follow-up and 26 had died.[17] Of note, the two Kaplan Meier curves are similar (overlaid in Figure 11); suggesting the trial data are generalisable to the real world.[23]

Figure 11. Kaplan-Meier for overall survival in the SACT database and CheckMate 057

SACT = systemic anticancer therapy.
Source: Public Health England (2019)[17], Bristol-Myers Squibb data on file (2019)[19]

Figure 12 provides the Kaplan-Meier curves for OS by PD-L1 expression level, censored at 5 June 2019.

Figure 12. Kaplan-Meier for overall survival by PD-L1 expression in the SACT database



PD-L1 = programmed death-ligand 1.

A number of studies assessing the real-world efficacy of IO therapies in general and nivolumab in particular have been published. Similar to the SACT data, these demonstrate that the efficacy of nivolumab in a real-world setting is very similar to that seen in the pivotal trials, CheckMate 057 and 017.[24-26] Juergens et al. (2018)[25] evaluated the real-world benefit of

nivolumab in the treatment of lung cancer (regardless of PD-L1 status) in Canada, where it was the first IO agent available. Despite included patients having poorer prognosis than those in the randomised controlled trials, median OS among the 472 eligible patients was 12.0 months, comparable with the survival in CheckMate 017 and 057. Dixmier A et al. (2018)[26] reported similar findings from a French observational study and concluded that the survival and safety profile of nivolumab were consistent with those in the pivotal trials, confirming the favourable risk/benefit ratio of nivolumab in a real-world setting.

D.6.7. Overall interpretation of the clinical data

The updated 5-year follow-up data from CheckMate 057 clearly demonstrate that the ERG extrapolation substantially underestimated OS, and even the BMS base-case extrapolation was an underestimate at 5 years. Therefore, the approach used for OS extrapolation in the cost-effectiveness model needs to be reassessed.

In addition, it was demonstrated that the committee-preferred extrapolations for PFS deviate from the long-term data collected through the CDF, particularly for nivolumab. Thus, new extrapolations also are warranted for PFS based on the new data collected.

At the time of the 5-year database lock, nivolumab demonstrated OS benefits in all PD-L1 subgroups. Furthermore, with increasing length of survival data being collected, network meta-analyses looking at checkpoint inhibitors in the postprogression NSCLC indication have been published. In a recent network meta-analysis by Almutairi et al. (2019)[21], no statistically significant differences in OS were seen between nivolumab and atezolizumab in the PD-L1 subgroups presented. Considering nivolumab demonstrates a clear benefit to all patients and does not harbour the toxicity of docetaxel, nivolumab should be available to all patients regardless of PD-L1 status.

D.7. Incorporating collected data into the model

Overall survival, PFS and TTD from the original analyses were assessed in light of the new data collected during the CDF period. For outcomes for which it was apparent that the new evidence would result in new analyses being warranted, survival analyses were conducted.

The updated analyses followed the same approach taken for the original analyses and followed the Decision Support Unit guidelines with fitting both standard parametric functions and spline models. As for the original analysis, independent parametric survival models fitted separately to the docetaxel and nivolumab arms were considered. This was because no single survival model adjusted for shape and scale was likely to capture the treatment relationship owing to the crossover in survival curves for the two treatment arms. In addition to updating standard parametric and spline models, updated hybrid exponential functions were also fitted where this was the committee preferred extrapolation for OS and PFS in the original submission.

Selection of distributions was based on goodness-of-fit statistics assessed by Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) as well as visual fit to the CheckMate 057 Kaplan-Meier data. For AIC, it was considered that distributions with a difference of less than 4 to the distribution with the lowest AIC was appropriate based on the Burnham and Anderson rule of thumb.[27] Similarly, based on Raftery's rule of thumb,[28] it was considered that a difference in BIC larger than 10 to the distribution with the lowest BIC was inappropriate. Furthermore, as long as statistical and visual fit for both arms could be achieved by using the same distribution, using a common distribution was preferred over different distributions between arms.

The number of knots for the spline models fitted to the data was limited to 3. In the original

submission, more than 2 knots were not considered for inclusion into the model to avoid overfitting the data. However, given the clear plateau developing in the survival for nivolumab in the 5-year data it was recognized that more than 2 knots could be needed to adequately model the long-term survival. Thus, base-case curve selection was limited to 2 knots, but in instances where a good visual fit to the tail of the Kaplan-Meier data could not be achieved with curves other than 3-knot splines, these were included in scenario analyses.

D.7.1. Overall survival: all-comers

Figure 1 shows the committee-preferred hybrid exponential and BMS-preferred log-logistic extrapolations for OS overlaid with the 5-year Kaplan-Meier data from CheckMate 057. As clearly shown in Figure 1, the hybrid exponential model results in a poor visual fit to the CheckMate 057 data for both docetaxel and nivolumab. The fit is particularly poor for the long-term extrapolation of nivolumab for which the extrapolated survival significantly deviates from the Kaplan-Meier data from approximately 32 months onwards. Therefore, survival analyses have been run on the 5-year data to identify best-fitting survival extrapolations accounting for the additional CDF evidence collected.

Table 10 and Table 11 summarise the AIC and BIC values for the variety of independent parametric distributions explored for OS for docetaxel and nivolumab. Table 10 and Table 11 demonstrate that the three best-fitting parametric survival models (when not considering 3 knots spline models) are the lognormal, generalised gamma, and spline normal 1-knot distributions for the nivolumab arm. These distributions also provide a good statistical fit to the docetaxel arm.

Table 10. Summary of goodness-of-fit statistics for nivolumab extrapolations for overall survival

Distribution	AIC	BIC
Spline hazard 3 knots	2009.0	2027.4
Spline odds 3 knots	2010.7	2029.1
Spline normal 3 knots	2012.8	2031.2
Lognormal	2014.8	2022.2
Generalised gamma	2015.4	2026.4
Spline normal 1 knot	2016.1	2027.1
Spline odds 2 knots	2016.9	2031.6
Generalised F	2017.4	2032.1
Spline normal 2 knots	2017.8	2032.5
Gompertz	2017.8	2025.1
Spline odds 1 knot	2018.4	2029.4
Log-logistic	2018.6	2026.0
Spline hazard 1 knot	2020.3	2031.3
Spline hazard 2 knots	2021.2	2035.9
Weibull	2048.9	2056.3
Gamma	2058.7	2066.0
Exponential	2072.0	2075.7

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Table 11. Summary of goodness-of-fit statistics for docetaxel extrapolations for overall survival

Distribution	AIC	BIC
Spline normal 1 knot	2033.6	2044.6
Generalised gamma	2034.0	2045.0
Spline hazard 1 knot	2034.3	2045.3
Spline normal 2 knots	2035.3	2050.0
Lognormal	2035.7	2043.0
Spline hazard 2 knots	2035.7	2050.4
Generalised F	2035.9	2050.6
Log-logistic	2036.0	2043.3
Spline odds 1 knot	2036.5	2047.5
Spline normal 3 knots	2036.9	2055.3
Spline odds 2 knots	2037.6	2052.2
Spline hazard 3 knots	2037.6	2055.9
Spline odds 3 knots	2039.0	2057.4
Gamma	2047.8	2055.1
Exponential	2050.5	2054.2
Weibull	2051.0	2058.3
Gompertz	2051.2	2058.5

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Figure 13 shows the fit of lognormal, generalised gamma, and spline normal 1 knot to the CheckMate 057 OS data for docetaxel and nivolumab. Figure 14 shows the long-term extrapolation of the same distributions. As these figures show, all three distributions provide good visual fit to the docetaxel trial data and a reasonable fit to the nivolumab data. They also offer similar long-term extrapolations, although long-term survival for nivolumab is plausibly underestimated due to extrapolations not capturing the plateau observed in the latter section of the Kaplan Meier curve.

Figure 13. Overall survival in CheckMate 057: 5-year data and updated extrapolations

K1 = 1 knot.

Figure 14. Overall survival in CheckMate 057: long-term extrapolations based on 5-year data

KM = Kaplan-Meier; k1 = 1 knot.

To allow comparison of the predicted survival from the extrapolations with the long term trial data, Table 12 presents the survival estimates generated by the survival curves considered for the updated company base case alongside the observed survival from both CheckMate 057 and CheckMate 003.

Table 12. Overall survival estimates from nivolumab studies compared with extrapolations (based on updated extrapolations)

Data source	Curve	Proportion alive (%)						
		1 year	2 years	3 years	4 years	5 years	6 years	10 years
Model estimates for nivolumab OS	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline normal 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model estimates for docetaxel OS	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline normal 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 057	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA
CheckMate 003	Nivolumab OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA

NA = not available; OS = overall survival.

Sources: Bristol-Myers Squibb data on file (2019)[19]; Antonia et al. (2019)[18]

Based on statistical fit, visual inspection, and comparison with long-term data, the lognormal distribution was selected as the company-preferred distribution. As can be seen from Table 12, of the three models, lognormal is also the distribution producing the most optimistic survival for docetaxel and, thus, could be seen as a conservative selection.

As noted earlier, and as can be seen from the data presented above, the tail of the nivolumab arm is not fully captured by the selected common lognormal distribution, potentially leading to an underestimation of the long-term survival. Table 10 and Table 11 also show that 3 knots spline distributions provided the best statistical fit to the nivolumab arm, but would not be a candidate for docetaxel based on the criteria used for selection. As can be seen from Figure 15, spline hazard 3 knots (distribution providing the best statistical fit to the nivolumab data) provides an improved visual fit to the observed data compared to the common lognormal distribution selected for the base case. Thus, to investigate the impact of this improved fit to the data a scenario analysis is presented where the best-fitting distribution to each arm is used; spline hazard 3 knots for nivolumab and spline normal 1 knot for docetaxel.

Figure 15. Overall survival 5-year CheckMate 057 curve selection with spline 3 knots for nivolumab and spline normal 1 knot for docetaxel

KM = Kaplan-Meier; k1 = 1 knot; k3 = 3 knot.

D.7.2. Progression-free survival: all-comers

The committee-preferred assumption regarding PFS was a hybrid exponential for which the exponential distribution was fitted from an 8-month cut point. Similarly to the OS data, Figure 2 shows that the committee-preferred extrapolations for PFS deviate from the long-term data collected through CDF, particularly for nivolumab from approximately 32 months. Thus, survival analyses were performed on the 5-year PFS data to identify potential distributions that would provide a better fit to the long-term data than the hybrid exponential.

As with the OS analysis, independent parametric survival models fitted separately to the docetaxel and nivolumab arms were considered because of the crossover in PFS survival curves. Table 13 and Table 14 summarise the AIC and BIC values for the variety of distributions explored for PFS for nivolumab and docetaxel.

Table 13. Summary of goodness-of-fit statistics for nivolumab extrapolations for progression-free survival

Distribution	AIC	BIC
Spline odds 3 knots	1370.5	1388.8
Spline normal 3 knots	1371.6	1389.9
Spline hazard 3 knots	1371.6	1389.9
Generalised F	1375.2	1389.9
Spline odds 1 knot	1391.8	1402.9
Spline odds 2 knots	1394.3	1409.0
Spline hazard 2 knots	1395.6	1410.3
Spline hazard 1 knot	1399.0	1410.0
Spline normal 2 knots	1399.2	1413.9
Spline normal 1 knot	1403.0	1414.0
Generalised gamma	1416.2	1427.2
Log-logistic	1441.5	1448.9
Lognormal	1451.1	1458.4
Gompertz	1458.5	1465.8
Weibull	1544.7	1552.0
Gamma	1581.3	1588.6
Exponential	1627.7	1631.4

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Table 14. Summary of goodness-of-fit statistics for docetaxel extrapolations for progression-free survival

Distribution	AIC	BIC
Spline odds 2 knots	1323.9	1338.6
Spline hazard 3 knots	1325.8	1344.2
Spline odds 3 knots	1327.0	1345.3
Lognormal	1329.2	1336.6
Spline normal 2 knots	1329.9	1344.6
Spline hazard 2 knots	1330.2	1344.8
Generalised gamma	1331.2	1342.2
Spline normal 1 knot	1331.2	1342.2
Spline normal 3 knots	1332.4	1350.8
Generalised F	1333.3	1347.9
Spline hazard 1 knot	1334.7	1345.7
Log-logistic	1338.0	1345.3
Spline odds 1 knot	1340.0	1351.0
Gamma	1352.9	1360.2
Weibull	1363.3	1370.6
Exponential	1374.3	1378.0
Gompertz	1376.2	1383.5

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

The distribution that to provides the best common statistical fit is the spline odds 2 knots distribution and was chosen as the updated company-preferred base case. Figure 16 and Figure 17 show the spline odds 2 knots distribution, which also offers a good visual fit to the data.

Figure 16. Progression-free survival: 5-year data and updated extrapolations

KM = Kaplan-Meier, K2 = 2 knots.

Figure 17. Progression-free survival: 5-year data and updated extrapolations

KM = Kaplan-Meier, K2 = 2 knots.

D.7.3. Duration of treatment effect and time to treatment discontinuation: all-comers

As can be seen from Figure 14, the 5-year follow-up confirms a long-term OS benefit for patients treated with nivolumab, even though patients in the docetaxel arm had switched over to nivolumab as subsequent treatment. This confirms the long-term durable response for nivolumab argued by the company during the original submission. The committee-preferred assumption during the original assessment regarding duration of treatment effect was that the treatment effect would last 3 years after treatment was stopped at 2 years. It was argued by the ERG and the committee that the sustained treatment effect extrapolated from CheckMate 057 would not be plausible beyond 3 years after the treatment was stopped. However, in CheckMate 003, nivolumab treatment was stopped after 96 weeks (1.8 years). As seen in Table 6, long-term survival of nivolumab in CheckMate 057 and CheckMate 003 is very similar despite differences in duration of therapy. As reported by Gettinger et al. (2018)[29], 12 of the 5-year survivors (75%) in CheckMate 003 received no subsequent therapy and were without evidence of progressive disease at the last follow-up. This confirms the long-term durable treatment effect of nivolumab with a similar stopping rule to that agreed for nivolumab for the UK.

The 5-year TTD data from CheckMate 057 (Figure 18) also show that, although treatment with nivolumab beyond 2 years was allowed in the study, only a minority of the long-term survivors in CheckMate 057 remained on treatment. After 5 years, approximately [redacted]% of the study population was still on treatment.

Figure 18. 5-year overall survival and time to treatment discontinuation: 5-year Kaplan-Meier data

KM = Kaplan-Meier; TTD = time to treatment discontinuation; OS = overall survival.

Based on this long-term evidence of sustained treatment effect, the updated company base case does not include a waning of treatment effect over time but uses the unadjusted survival extrapolations from CheckMate 057.

Given that complete follow-up data are available until the agreed 2-year stop of nivolumab treatment, the updated analyses use the Kaplan-Meier data directly without extrapolation. This follows a similar principle to that used by the ERG, and the curves do not require any extrapolations.

D.7.4. Survival analyses: PD-L1 ≥ 1% subgroup scenario

Overall survival

Table 15 and Table 16 show that several distributions could be considered a good common distribution. The lognormal and the spline normal 1 knot could be considered good common distributions according to the AIC statistic if considering one standard parametric and one spline distribution.

Table 15. Summary of goodness-of-fit statistics for nivolumab extrapolations for overall survival

Distribution	AIC	BIC
Spline hazard 3 knots	822.6	836.6
Spline odds 3 knots	824.7	838.7
Spline normal 3 knots	826.6	840.6
Lognormal	827.1	832.7
Gompertz	827.3	832.9
Generalised gamma	828.4	836.8
Spline normal 1 knot	828.8	837.2
Spline odds 2 knots	829.2	840.4
Log-logistic	829.3	834.9
Spline normal 2 knots	829.8	841
Spline odds 1 knot	830.2	838.6
Generalised F	830.4	841.6
Spline hazard 1 knot	831.1	839.5
Spline hazard 2 knots	831.9	843.1
Weibull	838.3	843.9
Gamma	842.5	848.1
Exponential	853.2	856

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Table 16. Summary of goodness-of-fit statistics for docetaxel extrapolations for overall survival

Distribution	AIC	BIC
Lognormal	861.3	866.9
Log-logistic	862.6	868.3
Spline normal 1 knot	863	871.5
Generalised gamma	863.1	871.5
Spline hazard 1 knot	863.4	871.9
Spline odds 1 knot	864.6	873.1
Spline normal 2 knots	864.8	876.1
Generalised F	865.1	876.3
Spline hazard 2 knots	865.4	876.6
Spline odds 2 knots	866.4	877.6
Spline normal 3 knots	866.9	881
Spline hazard 3 knots	867.4	881.5
Spline odds 3 knots	868.2	882.2
Exponential	871.6	874.4
Gamma	871.7	877.4
Gompertz	872.4	878
Weibull	873.2	878.8

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

The lognormal and the spline normal 1 knot had visually similar fits to the data over the trial time horizon (Figure 19) and had similar tails (Figure 20). From the visual inspection it is also clear that both distributions provide a good fit to the docetaxel data but do not fully capture the more complex shape of the nivolumab survival curve.

Figure 19. Overall survival PD-L1 ≥ 1%: 5-year CheckMate 057 curve selection

KM = Kaplan-Meier; PD-L1 = programmed death-ligand 1; K1 = 1 knot.

Figure 20. Overall survival PD-L1 ≥ 1%: 5-year CheckMate 057 curve selection

KM = Kaplan-Meier; PD-L1 = programmed death-ligand 1; K1 = 1 knot.

Based on slightly better AIC and BIC statistics, the lognormal distribution is used as the base-case OS extrapolation for the PD-L1 ≥ 1% subgroup.

As seen in Figure 19 and Figure 20 neither of the curves provide a really good fit to the middle section or the tail of the nivolumab arm, and therefore potentially leading to underestimation of long-term survival. To explore curves better capturing the complex shape of the nivolumab survival data, spline 3 knots curves were included in a scenario. As with previous analyses no spline 3-knot distribution provided a good statistical fit to the docetaxel arm and, thus, the lognormal was kept for extrapolating docetaxel. However, for nivolumab, spline hazard 3 knots provided the best statistical fit, as well as improved visual fit (Figure 21) to both the middle section and tail of the clinical data, compared with lognormal and was therefore used to model OS for nivolumab in the scenario.

Figure 21. Overall survival PD-L1 ≥ 1%: 5-year CheckMate 057 curve selection with spline 3 knots for nivolumab

KM = Kaplan-Meier; PD-L1 = programmed death-ligand 1.

Progression-free survival

On the basis of the AIC and BIC statistics presented in Table 17 and Table 18, the best-fitting common distributions across treatment arms appeared to be spline normal 1 knot and spline hazard 1 knot. The spline normal 1-knot distribution also had the third lowest BIC statistic in both treatment arms, while the spline hazard 1 knot had the fourth and sixth lowest BIC statistic in the docetaxel and nivolumab arms, respectively.

Table 17. Summary of goodness-of-fit statistics for nivolumab extrapolations for progression-free survival

Distribution	AIC	BIC
Generalised F	667.4	678.6
Spline odds 1 knot	669.7	678.1
Spline normal 3 knots	669.9	683.9
Spline odds 3 knots	670.4	684.4
Spline normal 1 knot	670.5	678.9
Spline hazard 1 knot	670.5	679.0
Spline hazard 3 knots	670.7	684.8
Spline hazard 2 knots	670.9	682.1
Spline odds 2 knots	671.3	682.6
Spline normal 2 knots	672.4	683.6
Generalised gamma	672.7	681.1
Lognormal	679.8	685.4
Log-logistic	681.2	686.8
Gompertz	688.0	693.6
Weibull	707.3	712.9
Gamma	720.2	725.8
Exponential	749.9	752.7

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Table 18. Summary of goodness-of-fit statistics for docetaxel extrapolations for progression-free survival

Distribution	AIC	BIC
Lognormal	580.0	585.7
Spline odds 2 knots	580.2	591.5
Spline normal 1 knot	581.9	590.3
Generalised gamma	581.9	590.4
Spline normal 2 knots	582.7	593.9
Spline odds 3 knots	582.9	597.0
Spline hazard 3 knots	583.2	597.2
Spline hazard 1 knot	583.5	591.9
Spline hazard 2 knots	583.5	594.8
Log-logistic	583.7	589.3
Generalised F	583.9	595.2
Spline normal 3 knots	585.0	599.1
Spline odds 1 knot	585.6	594.0
Gamma	589.4	595.0
Weibull	593.9	599.5
Exponential	597.3	600.1
Gompertz	599.3	604.9

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Both the spline normal 1 knot and spline hazard 1 knot had good visual fit to both arms of the data (Figure 22 and Figure 23). Therefore, based on a lower AIC and BIC statistic, the company-preferred base case for PD-L1 ≥ 1% extrapolation is the spline normal 1 knot distribution.

Figure 22. Progression-free survival PD-L1 ≥ 1%: 5-year CheckMate 057 curve selection

KM = Kaplan-Meier; PD-L1 = programmed death-ligand 1; K1 = 1 knot.

Figure 23. Progression-free survival PD-L1 ≥ 1%: 5-year CheckMate 057 curve selection

KM = Kaplan-Meier; PD-L1 = programmed death-ligand 1; K1 = 1 knot.

Time to treatment discontinuation

The reasoning discussed in Section D.7.3 for all-comers can also be applied to the PD-L1 ≥ 1% subgroup. Given that complete follow-up data are available until the agreed 2-year stop of nivolumab treatment, the updated analyses used the Kaplan-Meier data directly without extrapolation.

Figure 24. Time to treatment discontinuation PD-L1 ≥ 1%: 5-year Kaplan-Meier data

KM = Kaplan-Meier; OS = overall survival; PD-L1 = programmed death-ligand 1.

D.8. Key model assumptions and inputs

Committee- and company-preferred original model assumptions are presented in Table 19, and key model assumptions and inputs for this submission are presented in Table 20.

Table 19. Committee-preferred and company-preferred original model assumptions and inputs

Model input/ assumption	Committee-preferred parameter/assumption	Original company-preferred parameter/ assumption
Overall survival	Hybrid exponential fitted to the 36-month data cut (Feb 2017 DBL) for CheckMate 057. The hybrid exponential was fitted with a break point of 8 months from which the ERG argued that the hazard would be linear.	Log-logistic fitted to the 36-month data cut (Feb 2017 DBL) for CheckMate 057.
Progression-free survival	Hybrid exponential fitted to the 24-month data cut for CheckMate 057. The hybrid exponential was fitted with a break point of 8 months from which the ERG argued that the hazard would be linear.	Hybrid exponential fitted to the 24-month data cut for CheckMate 057 was used for the final submission to facilitate decision making, though alternate PFS analyses were thought to fit the data better and PFS using Weibull and Gamma distributions were also presented.
Duration of treatment	Treatment effect of nivolumab maintained 3 years after the	Maintained treatment effect represented by the extrapolation of CheckMate 057 data preferred

Model input/ assumption	Committee-preferred parameter/assumption	Original company-preferred parameter/ assumption
effect	2-year stopping rule for nivolumab.	though treatment waning over 3 years after treatment discontinuation agreed to facilitate decision making.

ERG = Evidence Review Group.

Table 20. Key model assumptions and inputs

Model input and cross-reference	Original parameter/ assumption	Updated parameter/ assumption	Source/Justification
Overall survival	Hybrid exponential fitted to the 36-month data cut (Feb 2017 DBL) for CheckMate 057. The hybrid exponential was fitted with a break point of 8 months from which the ERG argued that the hazard would be linear.	Lognormal fitted to the 5-year data cut (May 2019 DBL) for CheckMate 057.	This allows for the additional data provided from the 5-year follow-up of CheckMate 057 to be incorporated into the model. Further, the committee-preferred extrapolations did not provide a good visual fit to the 5-year data and underpredicted the observed survival for both nivolumab and docetaxel (Figure 25).
Progression-free survival	Hybrid exponential fitted to the 24-month data cut for CheckMate 057. The hybrid exponential was fitted with a break point of 8 months from which the ERG argued that the hazard would be linear.	Spline 2 knot odds fitted to the 5-year data cut (May 2019 DBL) for CheckMate 057.	Goodness-of-fit statistics and visual inspection demonstrate that the spline 2 knot odds provides the best-fitting extrapolation for the updated clinical data when assuming a common distribution for both the nivolumab and docetaxel arm (Figure 26).
Treatment duration	Hybrid exponential fitted to the 24-month data cut for CheckMate 057 and 2-year stopping rule	KM data 5-year data cut (May 2019 DBL) for CheckMate 057 and 2-year stopping rule	Treatment duration was updated with the most recent data and as follow-up was longer than the agreed 2-year stopping rule, extrapolation was no longer needed.
Duration of treatment effect	Treatment effect of nivolumab maintained 3 years after the 2-year stopping rule for nivolumab.	Maintained treatment effect represented by the extrapolation of CheckMate 057 data.	Long-term data from CheckMate 003 have confirmed long-term treatment benefit from nivolumab treatment after stopping treatment at 96 weeks.
Progressed disease health-state utility values	Post-progression utility value of 0.5686	Post-progression utility value of 0.688	Post-progression health state utility value from CheckMate 057

ERG = Evidence Review Group; KM = Kaplan-Meier.

Figure 25. Overall Survival All-Comers: ERG versus updated company base case

AC = appraisal committee; ERG = Evidence Review Group; KM = Kaplan-Meier.

Figure 26. Progression-free survival all-comers: ERG versus updated company base case

AC = appraisal committee; ERG = Evidence Review Group; KM = Kaplan-Meier; K2 = 2 knots.

D.9. Cost-effectiveness results (deterministic)

As clearly shown the data collected through the CDF agreement warrants updates to the data used in the economic model. As requested, Table 21 shows the initial cost-effectiveness results that demonstrated plausible cost-effectiveness at CDF entry for the all-comers

population (1a) with the CDF-agreed patient access scheme discount for nivolumab. Results in analyses (1b) and (1c) then show the results when incorporating the updated flat dosing of nivolumab and the standard patient access scheme discount for nivolumab. Unless noted, both of these changes have been included in all following results presented. Cost-effectiveness analyses 2 and 3 show the results with updates made to the original committee-preferred parameters for decision making using the 5-year CheckMate 057 data, and the updated company base case.

The analyses described above are replicated for the PD-L1 > 1% subgroup in Table 22.

To illustrate the impact of each individual change in model parameters, Table 23 shows the impact of changing each individual parameter on the ICER when compared with the updated company base case.

Table 21. Cost-effectiveness results: all-comers

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Cost-effectiveness analysis 1a: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF PAS ([redacted]%)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£16,032	0.44	0.32	£49,936[a]
Cost-effectiveness analysis 1b: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF PAS ([redacted]%)and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£18,025	0.44	0.32	£56,141
Cost-effectiveness analysis 1c: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with [redacted]% PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£26,552	0.44	0.32	£82,702
Cost-effectiveness analysis 2: analysis that demonstrated plausible potential for cost-effectiveness at CDF entry, with [redacted]% PAS and incorporating updated OS and PFS hybrid exponential fitted to CheckMate-057 5-year data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£26,073	0.51	0.37	£70,017
Cost-effectiveness analysis 3: new company base case with [redacted]% PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£28,360	1.23	0.73	£38,703

[a]; This ICER deviates slightly from the £49,122 ICER at CDF entry. This deviation is due to that ICER being derived through the ERG partially hardcoded health state occupancy sheet instead of through the overall model structure. Updated model has utilised the survival curve applied to the company health state model structure for consistency across all scenarios.

CDF = Cancer Drugs Fund; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

Table 22. Cost-effectiveness results: PD-L1 ≥ 1% subgroup scenario

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Cost-effectiveness analysis 1a: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF PAS ([redacted]%)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£22,645	1.11	0.72	£31,589
Cost-effectiveness analysis 1b: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF PAS ([redacted]%)and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£25,196	1.11	0.72	£35,147
Cost-effectiveness analysis 1c: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with [redacted]% PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£36,116	1.11	0.72	£50,381
Cost-effectiveness analysis 2: analysis that demonstrated plausible potential for cost-effectiveness at CDF entry, with [redacted]% PAS and incorporating updated OS and PFS hybrid exponential fitted to CheckMate-057 5-year data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£38,410	1.27	0.80	£47,793
Cost-effectiveness analysis 3: new company base case with [redacted]% PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£43,128	2.24	1.30	£33,191

CDF = Cancer Drugs Fund; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

Table 23. Impact on the ICER of individual parameter changes to the committee preferred assumptions: all-comers

Scenario and cross-reference	Scenario detail	Impact on ICER
Committee preferred assumptions: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with [redacted] PAS and nivolumab flat dose		**£82,702**
OS extrapolation	OS modelled with updated base case lognormal extrapolation (5-year May 2019 CheckMate 057 database lock).	-£20,329
PFS extrapolation	PFS modelled with updated base case spline odds 2 knots extrapolation (5-year May 2019 CheckMate 057 database lock).	-£40,543
Duration of effect	Duration of treatment effect modelled with no waning of effect.	-£4,569
Time to treatment discontinuation	Time to treatment discontinuation modelled with KM data (5-year May 2019 CheckMate 057 database lock)	-£1,730
Post-progression health state utility value	Scenario shows the impact of updating the post-progression utility value from original committee preferred 0.5686 to the company preferred 0.688	-£3,739

ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; Q2W = every 2 weeks; SmPC = summary of product characteristics.

D.10. Probabilistic sensitivity analysis

A second-order Monte Carlo simulation was run for 1,000 iterations. Results of the probabilistic sensitivity analysis are shown in Table 24. The probabilistic ICER for the new company base case for all-comers population was £38,762 per QALY gained compared with £38,703 per QALY gained in the deterministic analysis.

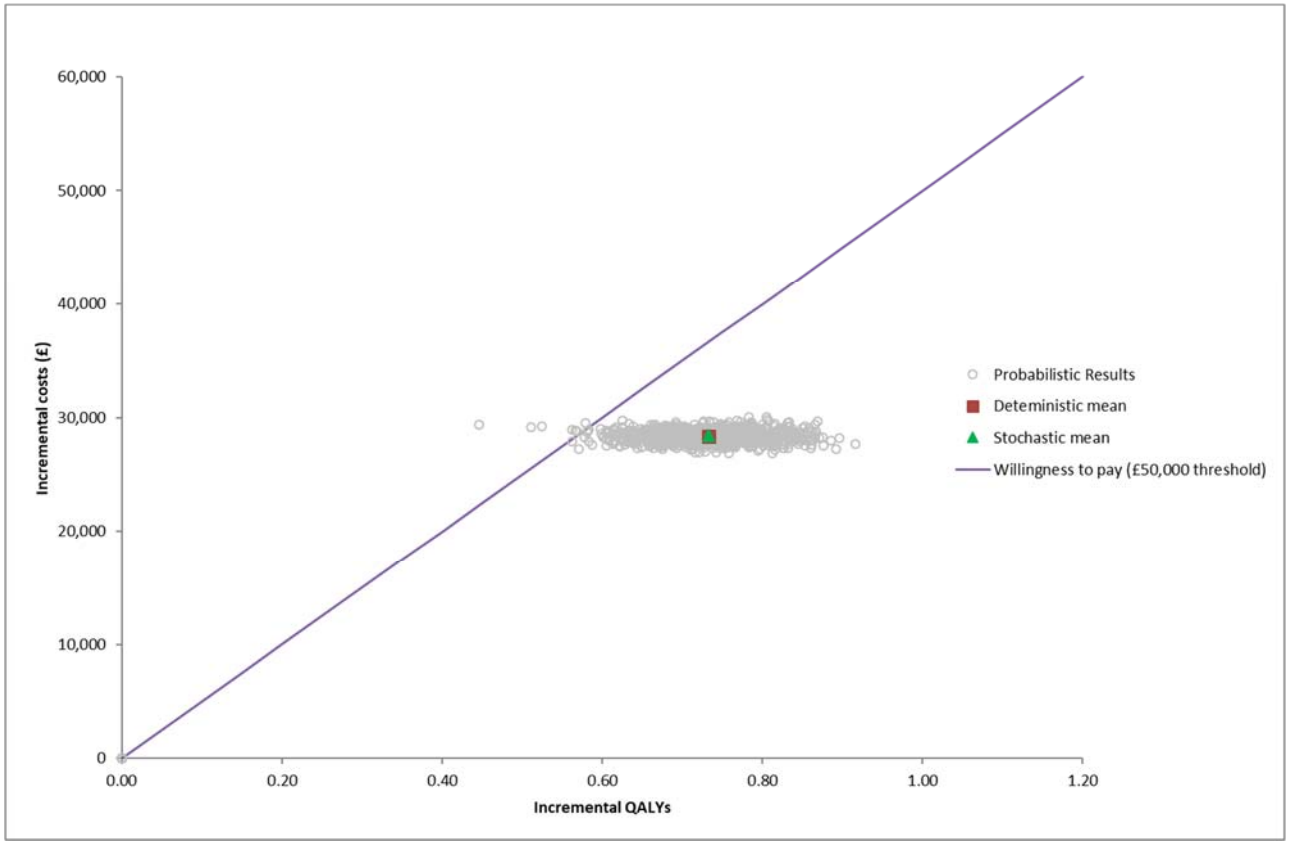
Figure 27 presents the cost-effectiveness plane, which shows that most of the 1,000 iterations fall below the willingness to pay threshold for an end-of-life therapy (£50,000 / QALY).

Table 24. Updated company base-case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Nivolumab	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	£28,388	0.73	£38,762

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Figure 27. Scatterplot of probabilistic results

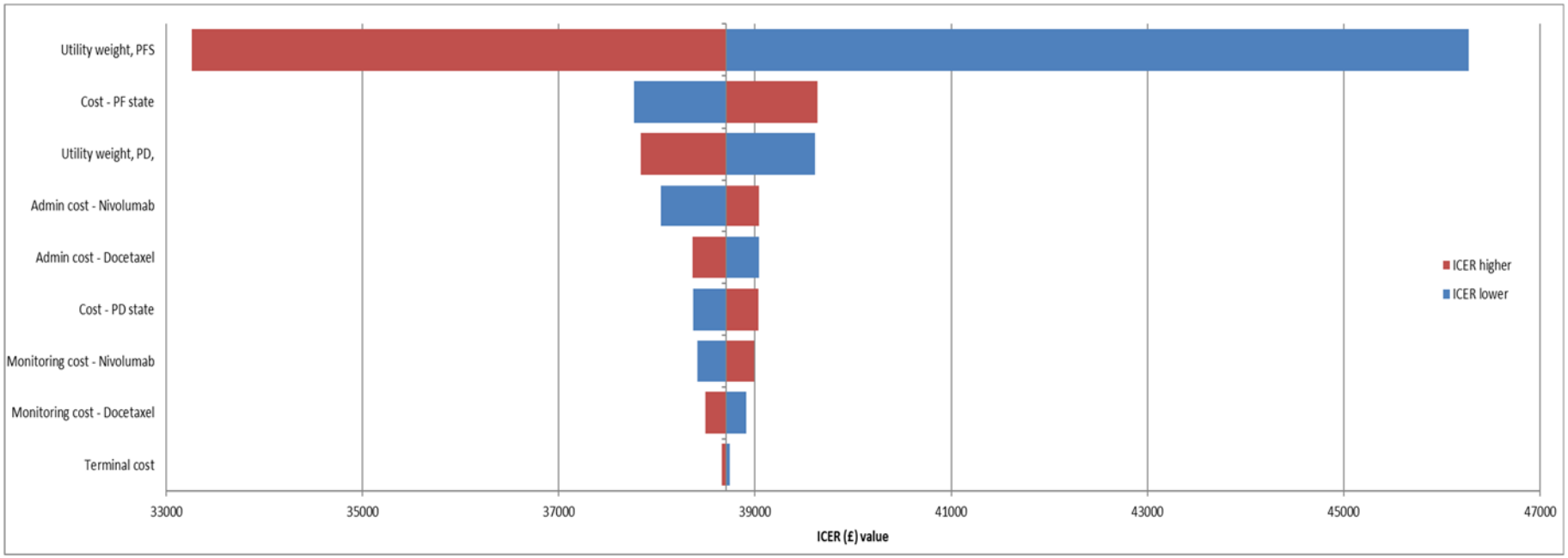


ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

D.11. Key sensitivity and scenario analyses

Figure 28 presents a tornado diagram showing the results of the deterministic sensitivity analyses.

Figure 28. Tornado diagram



ICER = incremental cost-effectiveness ratio; PD = progressed disease; PF = progression-free.

Scenario analyses were undertaken to investigate the effect of certain model inputs on the ICERs. All undertaken scenario analyses are presented in Table 25 for all-comers and Table 26 for PD-L1 ≥ 1%.

Table 25. Key scenario analyses: all-comers

Scenario and cross-reference	Scenario detail	Brief rationale	ICER (change from base case ICER)
Base case			**£38,703**
[redacted] dosing	Dosing of nivolumab at [redacted]	This dosing may be introduced into clinical practice in the future	[redacted]
Best-fitting OS curve to each treatment arm	3-knot spline for nivolumab	None of the standard parametric or up to 2 knot spline distributions provided a very good fit to the observed plateau in the tail of the OS extrapolation for the nivolumab arm. Therefore, a 3-knot spline hazard distribution was fitted to the nivolumab 5-year data, and spline normal 1 knot to docetaxel. These curves represent the lowest AIC of the distributions fitted for the individual treatment arms and relaxing of the restriction to only choose up to 2 knots for spline.	£33,832 (-£4,871)
Tumour agnostic analysis	Scenario shows the impact of assessing the cost-effectiveness of nivolumab regardless of tumour histology	To facilitate comparison to other interventions currently licensed across tumour histology in 2nd-line NSCLC and aligned with nivolumab license not being specific to squamous or non-squamous histology.	£37,442 (-£1,261)

ICER = incremental cost-effectiveness ratio; NSCLC = non-small-cell lung cancer; OS = overall survival; Q4W = every 4 weeks.

Table 26. Key scenario analyses: PD-L1 ≥ 1%

Scenario and cross-reference	Scenario detail	Brief rationale	ICER (change from base case ICER)
Base case			**£33,191**
[redacted] dosing	Dosing of nivolumab at [redacted]	This dosing may be introduced into clinical practice in the future	[redacted]
Best-fitting OS curve to each treatment arm	3-knot spline for nivolumab	None of the standard parametric or up to 2 knot spline distributions provided a very good fit to the observed plateau in the tail of the OS extrapolation for the nivolumab arm. Therefore, a 3-knot spline hazard distribution was fitted to the nivolumab 5-year data and lognormal to docetaxel. These curves represent the lowest AIC of the distributions fitted for the individual treatment arms and relaxing of the restriction to only choose up to 2 knots for spline	£29,289 (-£3,902)

ICER = incremental cost-effectiveness ratio; NSCLC = non-small-cell lung cancer; OS = overall survival; Q4W = every 4 weeks.

D.12. Key issues and conclusions based on the data collected during the CDF review period

The main area of uncertainty and concern to the original appraisal committee was the long-term survival benefit of nivolumab in this population. There was a large discrepancy between the BMS-proposed extrapolations for OS and PFS and those of the ERG. In the 2 years since nivolumab entered the CDF in this indication, additional database locks have occurred for both CheckMate 057 and CheckMate 003. These provide additional evidence that demonstrates that nivolumab treatment is leading to a plateau in survival, with [redacted]% of patients alive at 5 years and, thus, the potential for long-term survival Figure 1 and Figure 2).[19] The data clearly show that the original ERG-preferred extrapolations (which the appraisal committee agreed most valid) for nivolumab for both OS and PFS significantly underestimated the 5-year survival from CheckMate 057.

Further, the data show that the BMS base case was the most appropriate although still an underestimate of observed 5-year OS (Table 6). It should also be noted that docetaxel patients were also receiving the benefit of IO therapy after switching to nivolumab at 2 years or receiving IO as a subsequent therapy. The Kaplan-Meier curves show this benefit with a flattening of the OS curve after 2 years. Thus, the hazard ratios and extrapolations based on CheckMate 057 are likely to underestimate the true benefit of nivolumab in the active treatment arm compared with a situation with no nivolumab treatment.

An additional area of uncertainty in this appraisal was the benefit of nivolumab in PD-L1 negative patients. At the time of the 5-year database lock, OS results for all PD-L1 subgroups were in favour of nivolumab (Figure 7).[20] At 5 years, nivolumab nearly [redacted] OS compared with docetaxel in patients who are PD-L1 negative.[20] Unfortunately English real-world data are not available for the PD-L1 negative population of patients with non-squamous NSCLC, as they were excluded from the CDF. But observational studies from other countries suggest that nivolumab is effective in all patients, regardless of PD-L1 status.[24-26] In addition, a recent network meta-analysis shows that nivolumab is at least as effective as atezolizumab in terms of OS in all PD-L1 subgroups and NICE recommends atezolizumab regardless of PD-L1 status.[11,21]

As nivolumab is at least as effective as other IO therapies recommended by NICE, and that a benefit was seen across all PD-L1 cohorts of patients with non-squamous NSCLC in CheckMate 057. BMS considers that the “all-comers” population remains the most relevant to this appraisal.

In the light of the new data, the original committee-preferred survival extrapolations are clearly not valid, therefore, survival analyses have been run on the 5-year data to identify best-fitting survival extrapolations accounting for the additional CDF evidence collected in both the all-comers and PD-L1 subgroup populations. On the basis of the original cost-effectiveness model and assumptions, but with these new survival analyses, nivolumab is a cost-effective treatment option for all patients with non-squamous NSCLC and should be available to patients in England through routine commissioning without further PD-L1 restriction.

D.13. References

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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 (CDF review TA484) [ID1572]

Clarification questions

December 2019

File name	Version	Contains confidential information	Date
ID1572 nivolumab (non-squ) company response to clarification questions [Redacted]	**1**	**No**	**31 Dec 2019**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Priority request. How many patients (proportion) randomised to the docetaxel arm of the CheckMate-057 trial crossed over to receive treatment with nivolumab?

Subsequent therapies

Rates of subsequent therapy received by patients in CheckMate 057 at the June 22, 2017 database lock (minimum follow-up 40.3 months) are presented in Table 1.[1] Overall, 11% of patients in the docetaxel arm received immunotherapy subsequent to study treatment compared with 3% in the nivolumab arm.

Crossover

At the five-year database lock on May 16, 2019 (minimum follow-up [redacted] months), [redacted] patients randomised to docetaxel had crossed over at any time to receive nivolumab treatment, [redacted] of whom were alive at the time of database lock.[2]

Table 1: Subsequent systemic therapy received in CheckMate 057

Subsequent therapy (all randomised patients), n (%)	Nivolumab (N = 292)	Docetaxel (N = 290)
Any subsequent systemic therapy[a]	141 (48)	156 (54)
Immunotherapy[b]	10 (3)	32 (11)[c]
Nivolumab	7 (2)[d]	24 (8)[e]
Other anti–PD-(L)1	0	4 (1)
Anti–CTLA-4	0	3 (1)
Investigational/unspecified	3 (1)	1 (<1)
ALK/EGFR inhibitor	40 (14)	68 (23)
VEGF/VEGFR inhibitor	13 (4)	8 (3)
Investigational agent/other	24 (8)	14 (5)
Chemotherapy	120 (41)	115 (40)

Source: Felip et al. (2017)[1]

Abbreviations: ALK = Anaplastic Lymphoma Kinase; CTLA-4 = cytotoxic T-lymphocyte antigen; EGFR = Epidermal Growth Factor Receptor; VEGF(R) = Vascular Endothelial Growth Factor (Receptor)
a Patients may have received ≥1 subsequent therapy; b 3 patients received subsequent immunotherapy as part of a combination therapy; c 20% (3/15 patients) received subsequent immunotherapy as the first therapy after discontinuing docetaxel; d Includes subsequent nivolumab post-study; e Includes crossover to nivolumab in the extension phase of the study or subsequent nivolumab post-study

A2. Priority request. Please provide Kaplan-Meier analysis to the following specifications:

Trial data set: CheckMate-057 trial

Data cut: 5-year May 2019 database lock

Population 'All comers'

Trial arms: (i) Nivolumab (n=292)

(ii) Docetaxel (n=290)

Analyses (i) Progression-free survival
(ii) Time to death from any cause (overall survival)
(iii) Time to treatment discontinuation

Format: Please present analysis outputs using the format used in the sample table provided at the end of this document.

The following analyses were conducted in CheckMate 057 at 5-year database lock for nivolumab and docetaxel, as follows:

- Progression-free survival (Table 2 and Table 3)

- Time to death from any cause (OS; Source: Bristol Myers-Squibb Data on File (2019)[4]

- *Table 4* and Table 5)

Time to treatment discontinuation (Table 6Source: Bristol Myers-Squibb Data on File (2019)[4]

- *Table 6* and Source: Bristol Myers-Squibb Data on File (2019)[3]

- *Table 7*)

Table 2: Progression-free Survival Kaplan-Meier analysis for all-comers – Nivolumab (n=292)

Time (weeks)	n.risk	n.event	Survival	Standard error	Lower	Upper
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Source: Bristol Myers-Squibb Data on File (2019)[3]

Table 3: Progression-free Survival Kaplan-Meier analysis for all-comers – Docetaxel (n=290)

Time (weeks)	n.risk	n.event	Survival	Standard error	Lower	Upper
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Source: Bristol Myers-Squibb Data on File (2019)[4]

Table 4: Time to Death from Any Cause (Overall Survival) Kaplan-Meier analysis for all-comers – Nivolumab (n=292)

Time (weeks)	n.risk	n.event	Survival	Standard error	Lower	Upper
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Source: Bristol Myers-Squibb Data on File (2019)[3]

Table 5: Time to Death from Any Cause (Overall Survival) Kaplan-Meier analysis for all-comers – Docetaxel (n=290)

Time (weeks)	n.risk	n.event	Survival	Standard error	Lower	Upper
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Source: Bristol Myers-Squibb Data on File (2019)[4]

Table 6: Time to treatment discontinuation Kaplan-Meier analysis for all-comers – Nivolumab (n=292)

Time (weeks)	n.risk	n.event	Survival	Standard error	Lower	Upper
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Source: Bristol Myers-Squibb Data on File (2019)[3]

Table 7: Time to treatment discontinuation Kaplan-Meier analysis for all-comers – Docetaxel (n=290)

Time (weeks)	n.risk	n.event	Survival	Standard error	Lower	Upper
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[redacted]						

Source: Bristol Myers-Squibb Data on File (2019)[4]

Section B: Clarification on cost-effectiveness data

B1. Priority request. We have been unable to generate the cost effectiveness ratios for the PD-L1 subgroups using the updated model provided as part of the CDF Review submission. Please provide a corrected version of the model that will allow us to generate these results.

In order to generate the results for the PD-L1≥1% subgroup, first ensure that the base-case settings required to generate the "All-Comers" ICER are correctly selected. These are detailed in Table 20 of the submission.

Select the subgroup "≥1% PD-L1 expression status" from the population dropdown menu in "Dashboard!C3".

Select the PFS for both docetaxel and nivolumab in dropdown menus "Dashboard!C30" and "Dashboard!C31" to be "Spline 1 knot normal - PFS". As discussed in Section D.7.4, this was found to be the most appropriate distribution for the progression-free survival in the ≥1% PD-L1 population.

The base case ICER for the PD-L1≥1% subgroup population should now be showing in "Dashboard!M8".

Information on the approach to use to generate results for the PD-L1 <1% subgroup is presented in the Appendix.

B2. Please re-create table 7 (overall survival by 6-month intervals up to 5 years) from the company submission for the PD-L1 positive subgroups

Overall survival (OS) rates up to 5 years from CheckMate-057 are presented by PD-L1 expression in all-comers (Table 8), patients with baseline PD-L1 expression ≥1% (Table 9) and <1% (Table 10), patients with baseline PD-L1 expression ≥5% (Table 11) and <5% (Table 12), and patients with baseline PD-L1 expression ≥10% (Table 13) and <10% (Table 14). A benefit of nivolumab was seen across all subgroups, but the study was not powered to detect differences by PD-L1 subgroup.

Table 8: OS rates up to 5 years by PD-L1 expression in CheckMate 057 – all-comers

Survival rate (95% CI)	Nivolumab 3mg/kg (n = 292)	Docetaxel (n = 290)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Bristol-Myers Squibb data on file (2019)[5]

Table 9: OS rates up to 5 years by PD-L1 expression in CheckMate 057 – patients with baseline PD-L1 expression ≥1%

Survival rate (95% CI)	Nivolumab 3mg/kg (n = 122)	Docetaxel (n = 123)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Bristol-Myers Squibb data on file (2019)[5]

Table 10: OS rates up to 5 years by PD-L1 expression in CheckMate 057 – patients with baseline PD-L1 expression <1%

Survival rate (95% CI)	Nivolumab 3mg/kg (n = 109)	Docetaxel (n = 101)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Bristol-Myers Squibb data on file (2019)[5]

Table 11: OS rates up to 5 years by PD-L1 expression in CheckMate 057 – patients with baseline PD-L1 expression ≥5%

Survival rate (95% CI)	Nivolumab 3mg/kg (n = 94)	Docetaxel (n = 86)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Bristol-Myers Squibb data on file (2019)[5]

Table 12: OS rates up to 5 years by PD-L1 expression in CheckMate 057 – patients with baseline PD-L1 expression <5%

Survival rate (95% CI)	Nivolumab 3mg/kg (n = 137)	Docetaxel (n = 138)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Bristol-Myers Squibb data on file (2019)[5]

Table 13: OS rates up to 5 years by PD-L1 expression in CheckMate 057 – patients with baseline PD-L1 expression ≥10%

Survival rate (95% CI)	Nivolumab 3mg/kg (n = 85)	Docetaxel (n = 79)
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Bristol-Myers Squibb data on file (2019)[5]

Table 14: OS rates up to 5 years by PD-L1 expression in CheckMate 057 – patients with baseline PD-L1 expression <10%

Survival rate (95% CI)	Nivolumab 3mg/kg (n = 146)	Docetaxel (n = 145)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Bristol-Myers Squibb data on file (2019)[5]

B4. Please provide cost-effectiveness results for the PD-L1 subgroups as defined in section 7.2 of the MAA for TA484 (1%, 5% and 10% expression levels)

As previously described in the original submission, the EMA assessed the risk benefit profile of nivolumab to be favourable in all patients, regardless of PD-L1 status and post-hoc analysis results should be interpreted with caution. It is important to note that PD-L1 is an imperfect predictive biomarker with limitations including heterogeneity of expression throughout a tumour, expression that varies over time and the fact that patients with low expression may still benefit from immuno-oncology therapy.

As described in Document D there were no clinically or statistically meaningful differences in OS between the PD-L1 positive patients at different cut-offs (≥1%, ≥5%, ≥10%) or in the PD-L1 negative patients at different cut-offs (<1%, <5%, <10%) in CheckMate-057 (see Figure 1 and Figure 2 below and OS rates in response to Question B2), and the study was not powered to detect differences between PD-L1 sub-groups. Therefore, there will be no substantial impact on the ICERs between these sub-groups. As such, undertaking modelling on additional subgroups will not help to inform decision making.

***Figure 1: Forest plot of overall survival in CheckMate 057 by PD-L1* subgroup: 5-*year* update**

CI = confidence interval; PD-L1 = programmed death-ligand 1.
Source: Bristol-Myers Squibb data on file (2019)[5]

Figure 2: Kaplan-Meier for overall survival in CheckMate 057 by PD-L1 subgroup: 5-year update

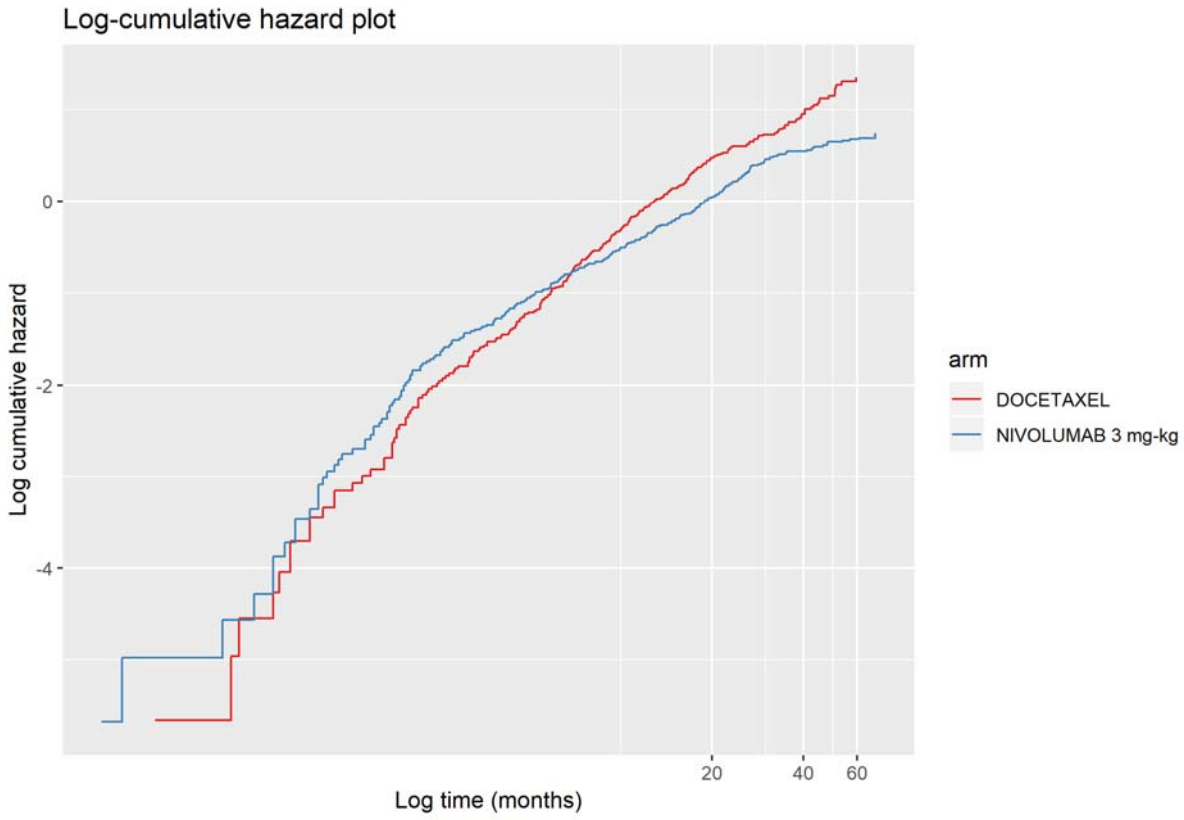
PD L1 = programmed death-ligand 1.
Source: Bristol-Myers Squibb data on file (2019)[5]

B5. The updated model includes an option using a hybrid exponential method (36- or 60-month KM data) to extrapolate overall survival. Please explore alternative hybrid models fitted to the mature Kaplan-Meier overall survival data and extrapolate the

tail. Please include these as scenario analyses and ensure these options are included in the model.

Updates have been included in a new version of the model to allow for alternative parametric distributions to be used for hybrid extrapolation of OS based on the 60-month data. The previously incorporated hybrid extrapolation was incorporated to reflect how the original hybrid exponential model preferred by the ERG would perform in light of the mature data. For the original hybrid exponential, the break point from when to fit the exponential model was set to 8-months with the exponential extrapolation applied from the end of the 36-month KM data. A breakpoint at 8 months were chosen by the ERG which argued that the hazards would be linear from this timepoint. However, particularly for nivolumab such linear non-declining hazards has not been confirmed in the mature data (Figure 3).

Figure 3:Log-cumulative hazards plot CheckMate 057 - all comers: 5-year update



Further, as shown in Document D, the hybrid exponential fitted from the 8-month break point, advocated by the ERG in the original submission, provided a poor fit to the 60 months OS data. As shown in Figure 4, even other parametric distributions

fitted from the 8 months break point provided a poor visual fit to the 60 months OS data.

Figure 4: Overall survival in CheckMate 057: 5-year data and hybrid extrapolations from an 8 months break point

From investigating the log cumulative hazard (Figure 3), additional potential breakpoints for all-comers can be observed for docetaxel around 22 months and nivolumab around 30-months. The updated analyses where therefore performed based on the 30 months breakpoint to allow for KM data to be utilised for an extended period and parametric distributions fitted from the latest clear break point. For the PD-L1 ≥1% there are clear break points at 21 months for the docetaxel arm and one at 30 months for the nivolumab arm (Figure 5). The 21 months break point were selected for the updated analysis.

Figure 5: Log-cumulative hazards plot CheckMate 057 – PD-L1 ≥1%: 5-year update

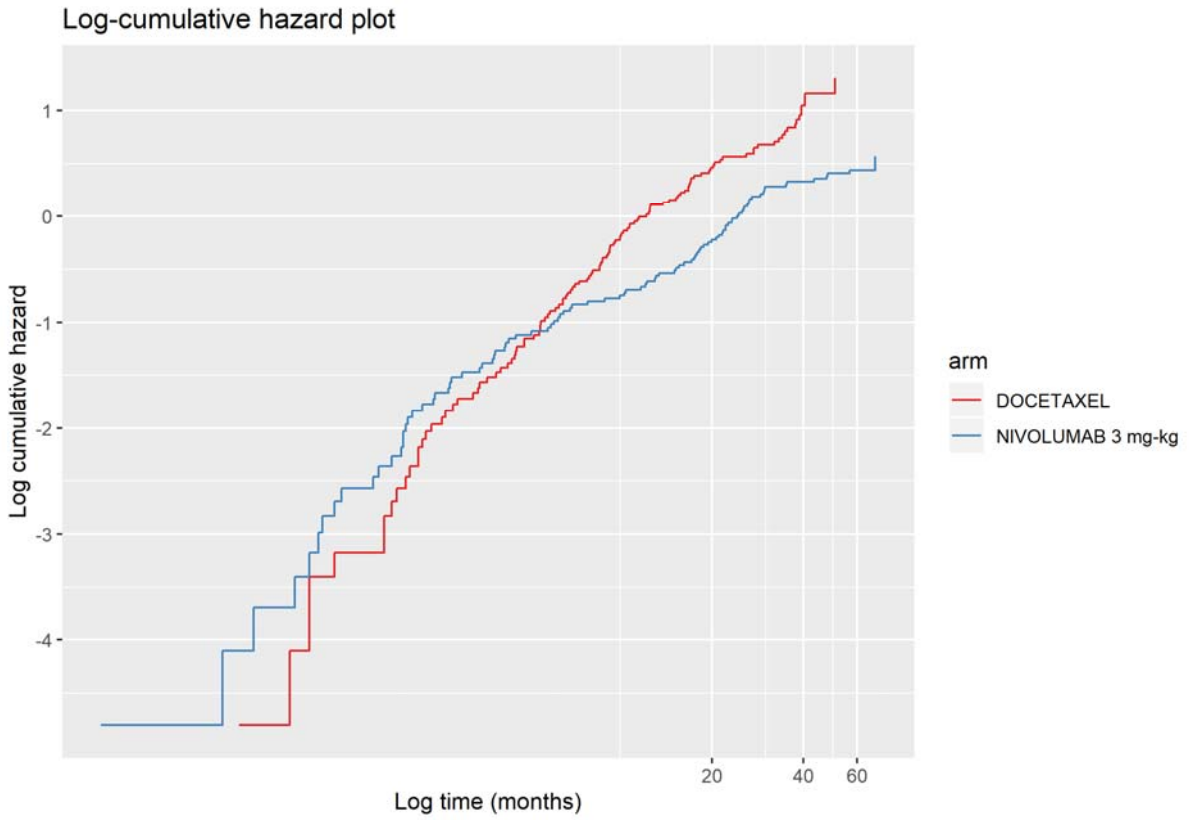


Table 15 and Table 16 summarise the AIC and BIC values for the independent parametric distributions explored for all-comers OS for docetaxel and nivolumab. The AIC and BIC demonstrate that lognormal and log-logistic provide good statistical fit to both the nivolumab and docetaxel arms for choosing a common distribution to both arms. Both distributions also provided a good visual fit to the KM data (Figure 6). Given that lognormal provided the best fit according to AIC and BIC for both arms it was chosen as the base case distribution for the updated analysis, with log-logistic tested in a scenario. The second-best fitting distribution per AIC and BIC for each treatment (Gompertz for nivolumab and log-logistic for docetaxel) was tested in a scenario analysis allowing for different distributions to be used per arm.

Table 15: Summary of goodness-of-fit statistics for nivolumab extrapolations for overall survival - all-comers

Distribution	AIC	BIC
Lognormal	215.5	219.6
Gompertz	216.1	220.2
Log-logistic	216.4	220.5
Exponential	216.6	218.6
Weibull	216.9	221.0

Gamma	217.1	221.2
Generalised gamma	217.1	223.3

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Table 16: Summary of goodness-of-fit statistics for docetaxel extrapolations for overall survival - all-comers

Distribution	AIC	BIC
Lognormal	225.5	228.6
Log-logistic	226.2	229.3
Generalised gamma	226.8	231.4
Gamma	229.1	232.2
Exponential	229.4	230.9
Weibull	230.0	233.1
Gompertz	231.4	234.5

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Figure 6: Overall survival in CheckMate 057 – all comers: 5-year data and hybrid extrapolations from a 30-month break point

Table 17 and Table 18 summarise the AIC and BIC values for the independent parametric distributions explored for OS for PD-L1 ≥1% patients for docetaxel and nivolumab. None of the distributions where among the best fitting for both arms but Gompertz, log-logistic and Weibull could be considered common candidates. However, Gompertz and log-logistic provide better visual fit, with Gompertz providing the best visual fit to the nivolumab KM data (Figure 7). Gompertz provide a low long-term hazard for nivolumab and crosses general population survival already after about 6 years. Thus, log-logistic was chosen as a common base case distribution with Gompertz tested in a scenario. In a second scenario the distribution with lowest AIC and BIC per treatment arm (Gompertz for nivolumab and exponential for docetaxel) were also tested to relax the assumption of equal distributions between arms.

Table 17: Summary of goodness-of-fit statistics for nivolumab extrapolations for overall survival – PD-L1 ≥1%

Distribution	AIC	BIC
Gompertz	257.8	261.8
Lognormal	258.1	262.0
Log-logistic	258.7	262.7
Generalised gamma	260.0	265.9
Weibull	260.8	264.8
Gamma	262.4	266.3
Exponential	274.8	276.8

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Table 18: Summary of goodness-of-fit statistics for docetaxel extrapolations for overall survival – PD-L1 ≥1%

Distribution	AIC	BIC
Exponential	162.4	163.5
Weibull	164.0	166.3
Gamma	164.1	166.4
Gompertz	164.3	166.6
Log-logistic	165.2	167.5
Generalised gamma	166.0	169.4
Lognormal	168.9	171.2

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Figure 7: Overall survival in CheckMate 057 – PD-L1 ≥1%: 5-year data and hybrid extrapolations from a 21 months break point

Results of the analyses with the updated hybrid parametric models are presented in Table 19 and Table 20 for all-comers and PD-L1 ≥1% respectively compared to the company base case ICERs presented in Document D. As can be seen all ICERs with the new hybrid parametric models result in lower ICERs compared with the company submitted ICERs.

Table 19: Cost effectiveness results: all comers, base case and updated hybrid models with [redacted] PAS and nivolumab flat dose

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Original analysis	£28,135	0.73	£38,703
Hybrid lognormal	£31,796	0.98	£32,454
Hybrid log-logistic	£31,269	0.94	£33,195
Hybrid Gompertz for nivolumab and log-logistic for docetaxel	£33,174	1.08	£30,766

Table 20: Cost effectiveness results: PD-L1 ≥1, base case and updated hybrid models with [redacted] PAS and nivolumab flat dose

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Original analysis	£43,128	1.30	£33,191
Hybrid log-logistic	£45,252	1.45	£31,147
Hybrid Gompertz	£49,911	1.78	£27,968
Hybrid Gompertz for nivolumab and exponential for docetaxel	£49,845	1.78	£28,003

Similar analyses for the PD-L1 <1% subgroup are presented in the Appendix.

Section C: Textual clarification and additional points

C1. Priority request. Please provide a copy of the model that was used to generate the cost effectiveness results quoted in the NICE FAD and instructions that will allow us to convert that model to the model that was provided as part of the CDF Review submission.

Updates to the model were only made as necessary to reflect the new data collected as part of the data collection agreement. Structural updates to the model were kept to a minimum. As a result of more mature data, some of the base case settings were updated as detailed in Table 19 and Table 20 of the CDF-exit submission. Finally, some elements of the model that were not relevant to the original decision-making ICER and that remained unused for the final analysis at CDF exit were removed.

Some small changes to the order and labelling of dropdown selections on the "Dashboard" sheet were made in order to make the selections clearer and more intuitive.

Instructions for the update of the initial model at CDF-entry to the CDF reappraisal model are detailed in sections below.

Update of 5-year OS and PFS data

The "Doc_OS" and "Nivo_OS" sheets were updated to include the survival analysis parameters from the 5-year overall survival output for both parametric and spline models. The survival parameters required to recreate the original analysis were retained in the model, along with other standard parametric curves from the 2-year and 3-year data cuts. The ranges "list_NivolumabOS_analysis" and "list_DocetaxelOS_analysis" in the "Survival Inputs" sheet were updated to ensure that all options for OS are linked to the updated "Nivo_OS" and "Doc_OS" sheets.

An option to use the 3-knot spline extrapolation for Nivolumab OS was added in "Dashboard!C16" and is available for all subgroups. As the model was not set up to handle 3-knot spline distributions, these survival curves are hard-coded in "Response and survival!GA12:GD1079" and are used in the model when this option is selected.

Similarly, the “Nivo_PFS” and “Doc_PFS” sheets were updated with the progression-free survival parameters from the updated analysis. Further, named ranges “list_NivolumabPFS_analysis” and “list_DocetaxelPFS_analysis” were updated to ensure that all options were linked to “Nivo_PFS” and “Doc_PFS” sheets. As the ERG hybrid exponential approach was used in the original model, this is updated and can be selected using “Dashboard!C21” and “Dashboard!C22”.

Update of 5-year TTD data

All of the 5-year Kaplan-Meier curves for OS, PFS, and TTD were added to “5-Year KMs” sheet. The TTD curves were linked to “Patient flow – 1!FF12:FG1054” such that the selection dropdown in “Dashboard!C27” could be used to toggle between the ERG 2-year hybrid exponential TTD, the updated 5-year KM data, and the parametric distributions described below.

Though unused in the final base case, the “Nivo_TTD” and “Doc_TTD” sheets were updated with the TTD parameters from the updated analysis. Further, named ranges “list_NivoTTDanalysis” and “list_DocetaxelTTDanalysis” were updated to ensure that all options were linked to “Nivo_TTD” and “Doc_TTD” sheets.

Update of dosing for scenarios:

The model base case was updated from a weight-based approach using hard-coded cost per dose in “Dashboard!C23”, to allow an update to the dosing to reflect changes[redacted].

A dropdown menu was added in “Dashboard!C49” allowing the user to toggle between weight-based dosing and fixed dosing approaches.[redacted]

Updated labelling and order of dropdown selections for OS, PFS, and TTD

The dropdown selections in the “Dashboard” sheet allowing the user to select alternative survival extrapolation options for OS, PFS, and TTD were updated to

make them more intuitive and clearer for the user. Dropdown selections were added in “Dashboard!C9” and “Dashboard!C21” in which the user can clearly select whether the hybrid exponential approach is being used. Further, the user can select in “Dashboard!C10” and “Dashboard!C22” which hybrid exponential analysis is being used for OS and PFS.

“Dashboard!C27” is updated and more clearly labelled for the approach to modelling TTD.

Removal of redundant elements of the model

The dropdown selection in “Dashboard!C3” was streamlined to only include PD-L1 subgroups of relevance to the CDF-exit appraisal. Furthermore, survival analysis parameters related to these unused subgroups were removed from the background sheets.

Options to select ERG hybrid exponential survival curves based on 18-month data were removed from the model. These options were removed for OS, PFS, and TTD as they were not used in the original committee preferred settings. These were removed from dropdown selections in “Dashboard!C10”, “Dashboard!C22”, and “Dashboard!C27”, respectively.

The option to include a “melanoma rebate” was removed from the Dashboard. All options in the “Dashboard” sheet from the original model relating to rebates were removed.

References

1. Felip E, Gettinger S, Burgio MA, Antonia S, Holgado E, Spigel D, et al. Three-year follow-up from CheckMate 017/057: nivolumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer. . Presented at the ESMO 42nd Congress; September 8-12, 2017 2017. Madrid, Spain.
2. Bristol Myers-Squibb Data on File. Addendum 02 to Final Clinical Study Report. CA209057. BMS936558. 2019.
3. Bristol Myers-Squibb Data on File. Progression-free Survival, Overall Survival and Time to Treatment Discontinuation Kaplan-Meier analyses for Nivolumab in CheckMate 057. 2019.
4. Bristol Myers-Squibb Data on File. Progression-free Survival, Overall Survival and Time to Treatment Discontinuation Kaplan-Meier analyses for Docetaxel in CheckMate 057. 2019.
5. Bristol-Myers Squibb data on file. 5-year overall survival update for nonsquamous (NSQ) advanced non-small cell lung cancer (NSCLC) patients in CheckMate 057 by tumor PD-L1 expression level (OR NIVO 179). 2019.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484) [ID1572]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**RCPath is the professional body tasked with training and maintaining professional standards in pathology in the UK**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Progression free survival, and improved overall survival. Quality of life for patients living with lung cancer.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Stable disease or any reduction in tumour burden. Progression free survival. Overall survival
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes metastatic NSCLC is an incurable disease and the biggest cause of cancer related deaths in men and women. There is an unmet need in therapies which provide effective response rates with good quality of life. Responses to current chemotherapy are variable and the treatment has significant co-morbidity. Many patients are ineligible for chemotherapy because of co-morbidity. There is a need for more effective treatment, curative therapy and a wider range of treatment options better suited to the patient population..
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Targeted therapies for EGFR, ALK ROS1 mutated tumours, followed by platinum chemotherapy. Platinum doublet chemotherapy or permetrexed, in high PD-L1 expressing tumours, for non mutated tumours. Docetaxel with or without Nintenamib as second line treatment or best supportive care when disease progresses on first line treatments. Companion biomarkers including EGFR ALK ROS1 mutations AN PDL1 expression are routinely performed on diagnostic samples to guide these choices.

	The suite of tests can present problems delivering all the results needed in a timely manner with limited tissue available for testing. Some tests can be carried out on blood samples (liquid biopsies) but this is patchy in its uptake.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidelines 24 updated 2011 The diagnosis and treatment of lung cancer. NICE Technology appraisals TA181; TA190; TA402; TA447 Final appraisal determination – Nivolumab for previously treated non-squamous non-small-cell lung cancer Issue date: September 2017
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is reasonably well defined although emerging treatments particularly in relation to immune-modulatory therapies have provided a major change in modern treatment. How individual agents in this field compare with each other is not very well understood. This is particularly so when considering which therapy and individual patient and their tumour will respond to.
• What impact would the technology have on the current pathway of care?	Improved overall survival and progression free survival compared to docetaxel chemotherapy. Reduced toxicity compared to Nintenamib.
10. Will the technology be used (or is it already used) in	The technology is already in use in clinical practice, but possibly restricted in its use across the UK. Guidance on its use will help drive adoption. Updated guidance on response to differing levels of PD-L1 expression is likely to improve advice to patients and patient choice as to the most appropriate treatment for them.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Predominantly differences in treatment costs. The diagnostic pathway should be already part of standard of care.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Oncology departments as part of specialist cancer care in cancer centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Most of the infrastructure should already be part of the standard of care, but there may be requirements for training in PD-L1 expression if this testing is to be brought in house. Many laboratories outsource this test due lack of experience and capacity. This results in a delay in getting the results needed for clinic appointments.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes I think the technology will improve progression free survival, quality of life and overall survival.
• Do you expect the technology to increase	See above

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	See above
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	no
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	It is already part of care. I do not think wider adoption would cause major problems.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Testing should already be in place, but it may need to adjusted to deliver the correct cut-offs needed to advise treatment. Therefore laboratories may need to adapt the reporting of the PD-L1 expression to include 5%, 10% cut offs. Most laboratories probably do this is already mindful of the need to deliver as much information as possible however the introduction of rules based on levels of PD-L1 expression will mean these cut points need to be incorporated into quality control measures for laboratories.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	no
16. Do you consider the technology to be innovative in	no

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	yes
• Does the use of the technology address any particular unmet need of the patient population?	See comments above
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are a familiar part of all these treatment options. Pneumonistis, Colitis, hepatitis skin rashes,
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Radiological evidence of tumour response, Progression free survival and overall survival
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might	no

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA484]? Please note, the scope from [TA484] is being used in this review, therefore no additional comparators will be considered.	no
21. How do data on real-world experience compare with the trial data?	I think the trial data Is comparable to real world data
Equality	
22a. Are there any potential equality issues that should be	no

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Improved outcome to Docetaxel
- PD-L1 expression helps predict which patients will benefit most and therefore levels of expression are important
-
-
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484) [ID1572]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	ROY CASTLE LUNG CANCER FOUNDATION
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research and work in lung cancer patient care (information, support and advocacy activity) and raising awareness of the disease and issues surrounding it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. 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 15%, 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 solid tumours, such as lung cancer
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of over 55 monthly Lung Cancer Patient Support Groups, patient/carer panel, online forums and its Lung Cancer Information Helpline

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer is 37%. Thus, this group of lung cancer patients, with advanced/metastatic disease have a particularly poor outlook, with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	As above, despite current therapy, outcomes for those with advanced/metastatic disease remains poor. In recent years, immunotherapy has brought a new therapy option.
8. Is there an unmet need for patients with this condition?	Most definitely
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The potential for extensions in life, is of paramount importance to this patient population and their families. This therapy, being available through the CDF has ensured patient access in this indication.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The recorded side effects of this therapy.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Immunotherapy is an important therapy option for patients with non small cell lung cancer
- Having been available in this indication through the CDF, we hope that the necessary data is now available for the Appraisal committee to make a positive recommendation
-
-
-

Thank you for your time.

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Public Health England

Protecting and improving the nation's health

Nivolumab for treating locally advanced or metastatic PD-L positive non-squamous non-small-cell lung cancer

Data review

Commissioned by NHS England

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing and reduce health inequalities. We do this through world-leading science, research, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

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Contents

Executive summary

Introduction

In November 2017, The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of nivolumab for the treatment of patients diagnosed with non-squamous non-small-cell lung cancer (NSCLC). The appraisal committee highlighted clinical uncertainty around estimates of treatment duration and overall survival in the evidence submission. As a result, they recommended commissioning of nivolumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection, to answer the clinical uncertainty.

NHS England commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of nivolumab in the CDF population during the managed access period. This report presents the results of the use of nivolumab, in clinical practice, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to get access to promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and PHE partnership for collecting and following up real-world SACT data in the CDF in England has resulted in analysis of data for the full patient population, with 100% of patients and outcomes reported in the SACT dataset. PHE and NHS England are committed to providing world first high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England’s Blueteq system was used to provide a reference list of all patients with an application for nivolumab for non-squamous NSCLC in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE’s routinely collected SACT data to provide SACT treatment history.

Between September 2017 and December 2018, 59 applications for nivolumab were identified in the NHS England’s Blueteq system. Following appropriate exclusions (see

Figures 1 and 2), 43 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)1.

Results

All 43 (100%) unique patients with CDF applications were reported in the SACT dataset.

Median treatment duration for the analysis cohort was 4.1 months (124 days) [95% CI: 3.0, 8.3]. 47% [95% CI: 31%,61%] of patients were still receiving treatment at 6 months and 21% [95% CI: 9%, 37%] of patients were receiving treatment at 12 months.
The median overall survival (OS) was 9.2 months (279 days). OS at 6 months was 65% [95% CI: 49%,77%], OS at 12 months was 43% [95% CI: 28%,58%].

At data cut off, 72% (N=31) of patients were identified as no longer being on treatment; 55% (N=17) of patients had stopped treatment due to disease progression, 13% (N=4) had stopped treatment due to toxicity, 3% (N=1) of patients chose to end their treatment, 23% (N=7) of patients died (not on treatment) and 6% (N=2) of patients died on treatment.

Sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort. A secondary sensitivity analysis was conducted to show OS by PD-L1 score.

Introduction

Lung cancer is the third most common cancer diagnosed in England and accounts for around 38,906 cancer diagnoses in 2017[2]. There are two main group of lung cancer, small cell lung cancer and non-small-cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer constituting around 12,000 cases diagnosed in males and 10,000 diagnosed in females[3].

Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs (stage III) or metastasised, spreading to distant parts of the body (stage IV). In 2017, results published by National Cancer Registration and Analysis Service[4] showed that 19% of patients diagnosed with lung cancer were diagnosed with stage III and 47% of patients were diagnosed with stage IV[5].

Programmed cell death 1 (PD-1) or its ligand (PD-L1) have been most studied in lung cancer and PD-L1 inhibitors are becoming established agents in the management of NSCLC[6].

Nivolumab is recommended as a treatment option for adult patients diagnosed with PD-L1 positive, locally advanced or metastatic (stage IIIB or IV) NSCLC[7].

Background to this report

The PHE and NHS England partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[8]. From the 29th July 2016, NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical and cost effectiveness. During this period of managed access, ongoing data collection is used to answer the uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[9].

PHE will analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of nivolumab for previously treated non-squamous NSCLC [TA484]

The NICE Appraisal Committee reviewed the evidence for the clinical and cost effectiveness of nivolumab for treating locally advanced or metastatic, PD-L1 positive, non-squamous NSCLC [TA484] and NICE published the guidance for this indication in November 2017[10].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of nivolumab through the CDF for a period of 18 months, from September 2017 to March 2019.

During the CDF funding period, results from ongoing clinical trials, evaluating nivolumab for non-squamous NSCLC in the licensed indication, are likely to answer the main clinical uncertainties raised by the NICE committee. The ongoing trials that will support the evaluation of nivolumab are CheckMate 003 and CheckMate 057. Data collected from the CheckMate 057 clinical trial will act as the primary source of data collection. Data collected from the Checkmate 003 clinical trial will provide supportive data.

Analysis of the SACT dataset will provide information on real-world treatment patterns and outcomes for nivolumab use in non-squamous NSCLC in England during the CDF funding period. This will act as a secondary source of information alongside the results of the CheckMate 003 and CheckMate 057 clinical trials[11,12].

The key areas of uncertainty identified by the committee for re-appraisal at the end of the CDF data collection are:

- treatment duration for the use of nivolumab
- overall survival from the start of a patient's first treatment with nivolumab

Approach

Upon entry to the CDF, representatives from NHS England, NICE, PHE and the company (Bristol-Myers Squibb) formed a working group to agree the Data Collection Agreement (DCA). The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of nivolumab. It also detailed the eligibility criteria for patient access to nivolumab through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications (via Blueteq®) for nivolumab, followed-up in the SACT dataset collected by PHE.

Methods

CDF applications – identification of the cohorts of interest

NHS England collects applications for CDF treatments through their online prior approval system, Blueteq®. The Blueteq application form captures essential baseline demographic and clinical characteristics of patients, needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NHS England shares an extract from the Blueteq database with PHE monthly. This extract contains NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria). The data exchange is governed by a data sharing agreement between NHS England and PHE.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Nivolumab clinical treatment criteria

The criteria for patient access to nivolumab are:

- patient has a confirmed diagnosis of stage IIIB or IV (advanced or metastatic) NSCLC (non-squamous)
- patient has progressed after previously receiving at least 2 cycles of platinum-containing chemotherapy for stage IIIB or IV NSCLC and a targeted treatment if the tumour is EGFR positive or ALK positive
- patient has a performance status of 0 or 1
- patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless received as part of the nivolumab Early Access to Medicines Scheme (EAMS) programme for this indication and meeting all other criteria listed.
- patient has had PD-L1 testing with an approved and validated test to determine the tumour proportion score
- patients tumour expresses PD-L1, with a tumour proportion score ≥1%
- Nivolumab will be administered as monotherapy
- patient has no symptomatically active brain metastases or leptomeningeal metastases
- Nivolumab will be stopped at 2 years of treatment or on disease progression or unacceptable toxicity, whichever occurs first

CDF applications – de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied.
If two trusts apply for nivolumab for locally advanced or metastatic PD-L1 positive non-squamous NSCLC for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

If two trusts apply for nivolumab for locally advanced or metastatic PD-L1 positive non-squamous NSCLC for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust does not match the SACT treating trust.

If two applications are submitted for nivolumab for locally advanced or metastatic PD-L1 positive non-squamous NSCLC and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohort

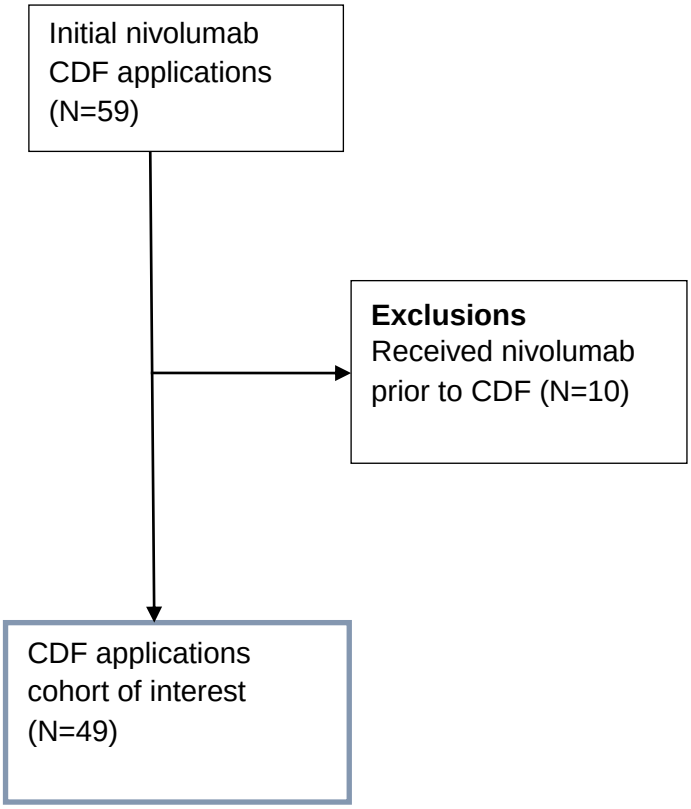
The analysis cohort is limited to the date nivolumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the pharmaceutical company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 20 September 2017 to 19 December 2018. A snapshot of SACT data was taken on 4 May 2019 and made available for analysis on 13 May 2019. The snapshot includes SACT activity up to the 31 January 2019. Tracing the patients' vital status was carried out on 5 June 2019 using the personal demographics service (PDS)[1].

There were 59 applications for CDF funding for nivolumab for locally advanced or metastatic PD-L1 positive non-squamous NSCLC between 20 September 2017 and 19 December 2018 in the NHS England Blueteq database.

10 patients were excluded from these analyses as they appeared to have received nivolumab prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from the initial CDF applications made for locally advanced or metastatic PD-L1 positive non-squamous NSCLC between 20 September 2017 and 19 December 2018



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for nivolumab in NHS England's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application, this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34) are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, separated by an appropriate time delay.

For example; a patient may be on a 3-weekly cycle with treatment being administered on the first and eighth day, but nothing on days 2 to 7 and days 9 to 20. The first day would be recorded as the 'start day of cycle'. The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the first and eighth day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length' which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Nivolumab is administered intra-venously. As such, treatment is administered in a healthcare facility and healthcare professionals are able to confirm that treatment administration has taken place on a specified date. A duration of 13-days has been added to the final treatment date for all patients, this represents the duration between cycles, assuming a single administration on day 1 of the cycle[13].

Treatment duration is calculated for each patient as: Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days).

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as:

- no longer receiving treatment (event), if:
  - the patient has died
  - the outcome summary (SACT data item #41) detailing the reason for stopping treatment has been completed
  - there is no further SACT records for the patient following a 3-month period
- if none of the above apply, the patient is assumed to still be on treatment and is censored

Overall survival

Overall survival (OS) is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead/alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = date of death (or follow up) – treatment start date

The patient is flagged as either:

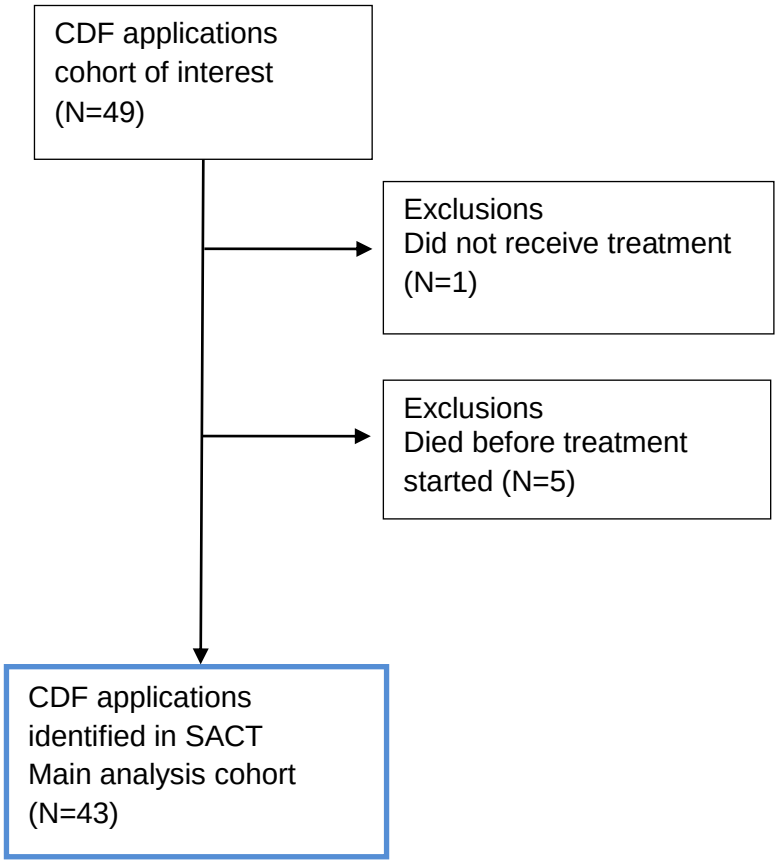
- dead (event) - at the date of death recorded on the PDS
- alive (censored) - at the date patients were traced for their vital status as patients are confirmed as alive on this date

Results

Cohort of interest

Of the 49 new applications for CDF funding for nivolumab for locally advanced or metastatic PD-L1 positive non-squamous NSCLC, one patient did not receive treatment and five patients died before treatment started[1] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for nivolumab for locally advanced or metastatic PD-L1 positive non-squamous NSCLC between 20 September 2017 and 19 December 2018



A maximum of 43 nivolumab records are expected in SACT for patients who were alive and eligible to commence treatment (Figure 2). 100% (43/43) of these applicants for CDF funding have a treatment record in SACT.

[1] The five patients that died before treatment were confirmed by the relevant trusts as deaths before treatment.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is ≥91% for all key items and 100% for primary diagnosis, date of birth, gender and treatment dates.

Table 1: Completeness of key SACT data items for the nivolumab cohort (N=43)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	91%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died or has not received treatment with nivolumab in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 31 patients. Of these, 31 have an outcome summary recorded in the SACT dataset 100% (31/31).

Table 2: Completeness of outcome summary for patients that have ended treatment (N=31)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	100%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. Completeness of PD-L1 score is 100%. A test for PD-L1 status needs to be conducted for each patient commencing treatment with nivolumab. Trusts need to submit this score to the NHS England's Blueteq system.

Table 3: Completeness of PD-L1 score in Blueteq (N=43)

Variable	Completeness (%)
PD-L1 score	100%

Patient characteristics

The median age of the 43 patients receiving nivolumab was 65 years. The median age in males and females was 64 and 68 years respectively.

Table 4: Patient characteristics (N=43)

Patient characteristics[2]		Frequency (N)	Percentage (%)
Sex	Male	29	67%
	Female	14	33%
Age	40-49	1	2%
	50-59	9	21%
	60-69	18	42%
	70-79	13	30%
	80+	2	5%
Performance status	0	9	21%
	1	29	67%
	2	1	2%
	3	0	0%
	4	0	0%
	Missing	4	9%

[2] Figures may not sum to 100% due to rounding.

PD-L1 distribution

The distribution of PD-L1 score in table 5 shows that 19% of patients have a TPS score of ≥1% to <5%, 12% of patients have a score ≥5% to <10%, 67% of patients have a score ≥10%.

Table 5: Distribution of PD-L1 score in Blueteq (N=43)

PD-L1 TPS score (%)	Frequency (N)	Percentage (%)
≥1 to <5	8	19%
≥5 to <10	5	12%
≥10	29	67%
TPS cannot be quantified	1	2%
Total	**43**	**100%**

Treatment duration

Of the 43 patients with CDF applications, 31 (72%) were identified as having completed treatment by 31 January 2019. Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with nivolumab in at least 3 months (see Table 6). The median follow-up time in SACT was 125 days.

Presently, 60% of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended, this provides a maximum follow-up period of 16 months. 40% of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended, this would provide the maximum follow-up period of 17 months. SACT follow-up ends 31 January 2019.

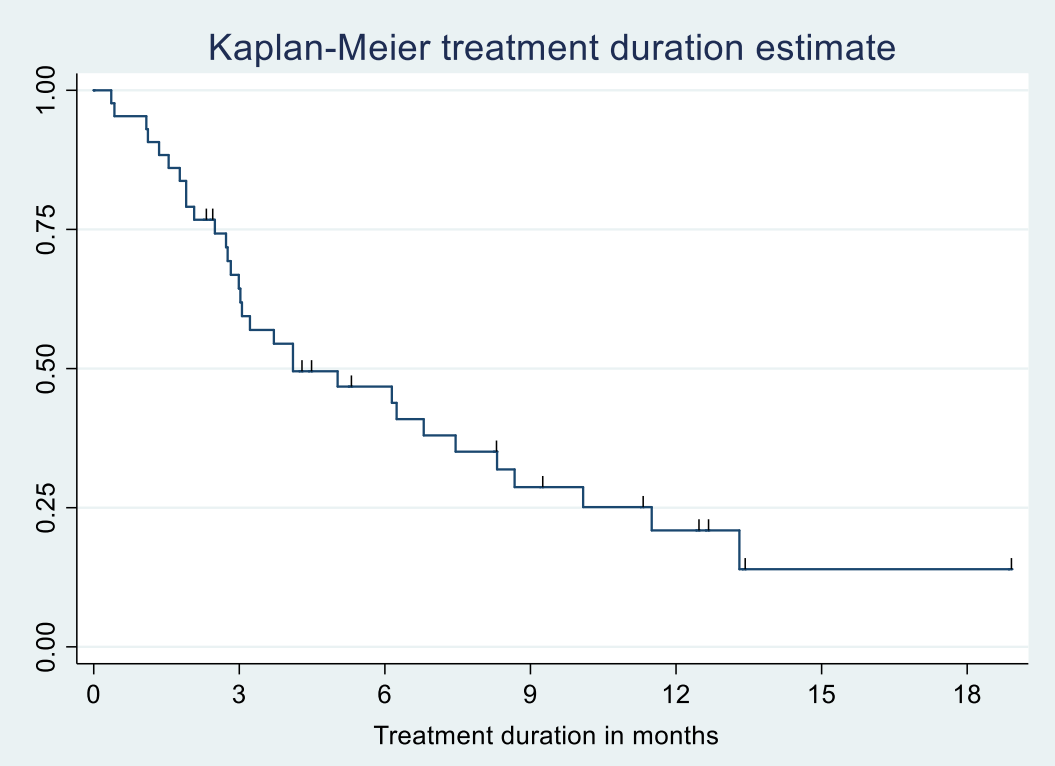
Table 6: Breakdown by patients' treatment status[3,4,5]

Patient status	Frequency (N)	Percentage (%)
Patient died - not on treatment	24	56%
Patient died – on treatment	2	5%
Treatment stopped	5	12%
Treatment ongoing	12	27%
Total	**43**	

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 4.1 months (124 days) [95% CI: 3.0, 8.3] (N=43). 47% of patients were still receiving treatment at 6 months [95% CI: 31%,61%], 21% of patients were receiving treatment at 12 months [95% CI: 9%, 37%].

[3] Figures may not sum to 100% due to rounding.
[4] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 that 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[5] Deaths on treatment and deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

Figure 3: Kaplan-Meier treatment duration (N=43)



Tables 7 and 8 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 16 months (486 days).

Table 7: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Number at risk	43	26	16	9	5	1	1

Table 8 shows that for all patients who received treatment, 12 were still on treatment (censored) at the date of follow-up and 31 had ended treatment (events).

Table 8: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Censored	12	10	7	6	4	1	1
Events	31	16	9	3	1	0	0

Table 9 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 72% (N=31) of patients had ended treatment at 31 January 2019.

Table 9: Treatment outcomes for patients that have ended treatment (N=31) [6,7]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	17	55%
Stopped treatment – acute chemotherapy toxicity	4	13%
Stopped treatment – patient choice	1	3%
Stopped treatment – died on treatment	2	6%
Stopped treatment – died not on treatment	7	23%
Total	**31**	

Table 10: Treatment outcomes and treatment status for patients that have ended treatment (N=31)

Outcome[8]	Patient died [9] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	14	3	
Stopped treatment – acute chemotherapy toxicity	3	1	
Stopped treatment – patient choice		1	
Stopped treatment – died not on treatment	7		
Stopped treatment – died on treatment			2
Total	**24**	**5**	**2**

[6] Figures may not sum to 100% due to rounding.

[7] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 that 'died on treatment', 'died not on treatment' and 'stopped treatment'.

[8] Relates to outcomes submitted by the trust in table 9.

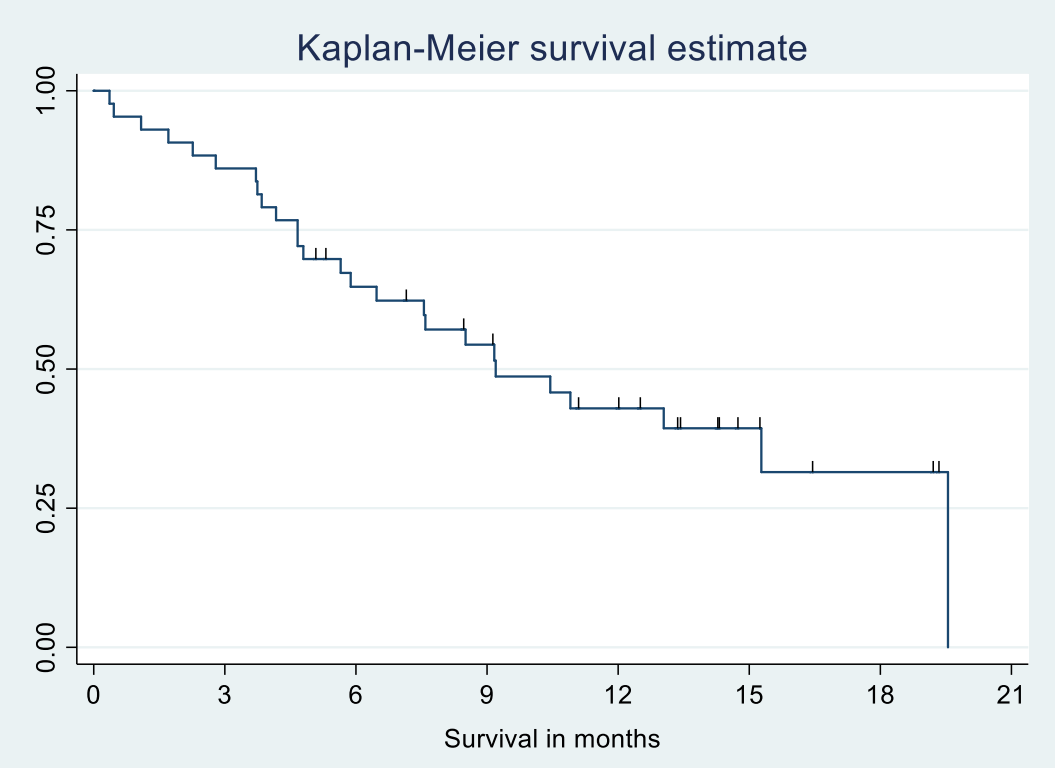
[9] Relates to treatment status in table 6 for those that have ended treatment.

Overall survival

Of the 43 patients with a treatment record in SACT, the minimum follow-up was 5 months (152 days) from the last CDF application. Patients were traced for their vital status on 5 June 2019, this date was used as the follow-up date (censored date) if a patient is still alive.

Figure 4 provides the Kaplan-Meier curve for overall survival, censored at 5 June 2019. The median survival was 9.2 months[10] (279 days) (N=43). Survival at 6 months was 65% [95% CI: 49%,77%], 12 months' survival was 43% [95% CI: 28%,58%].

Figure 4: Kaplan-Meier survival plot (N=43)



[10] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Table 11 and 12 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 20 months (608 days), all patients were traced on 5 June 2019.

Table 11: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-20	3-20	6-20	9-20	12-20	15-20	18-20
Number at risk	43	37	26	20	13	6	3

Table 12 shows that for all patients who received treatment, 17 were still alive (censored) at the date of follow-up and 26 had died (events).

Table 12: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-20	3-20	6-20	9-20	12-20	15-20	18-20
Censored	17	17	15	13	10	4	2
Events	26	20	11	7	3	2	1

Sensitivity analyses

Treatment duration

Sensitivity analyses was carried out on a cohort with at least 6 months' follow-up in SACT. To calculate treatment duration, CDF applications were limited from 20 September 2017 to 31 July 2018 and SACT activity was followed up to the 31 January 2019. 36 patients (84%) were included in these analyses. The median follow-up time in SACT was 125 days

Table 13 shows the results of the sensitivity analysis to evaluate treatment duration for patients with a minimum of 6 months' follow-up in SACT.

Table 13: Median treatment duration, full cohort and sensitivity analysis.

Metric	**Standard analysis: Full cohort**	**Sensitivity analysis: 6 months follow-up cohort**
N	43	36
Median treatment duration	4.1 months (124 days) [95% CI: 3.0, 8.3]	4.1 months (124 days) [95% CI: 2.8, 8.3]

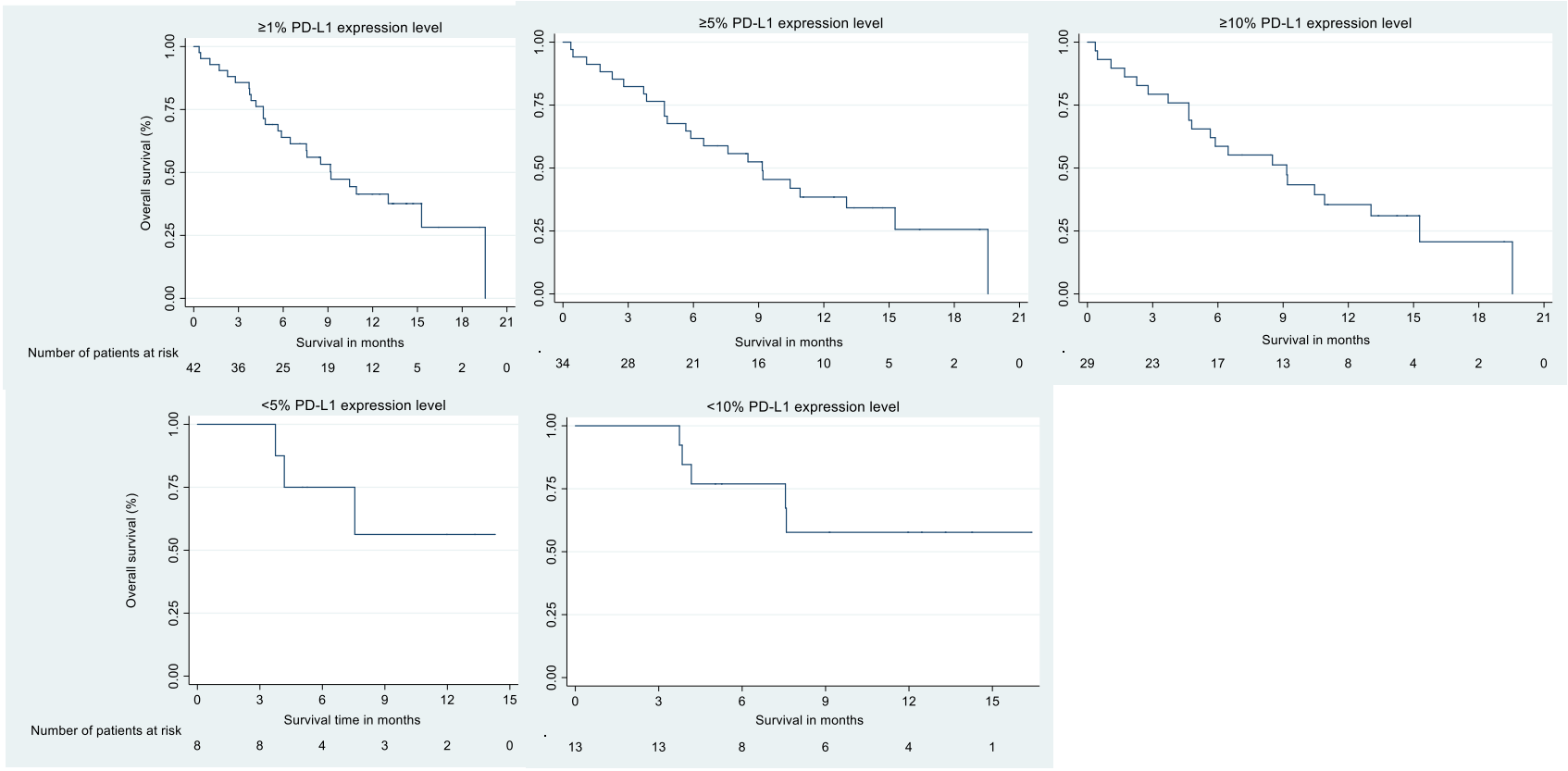
Overall survival

To calculate overall survival (OS), CDF applications were limited from 20 September 2017 to 5 December 2018, however, the last CDF application in the full cohort was 29 November 2018. No patients would be excluded in the sensitivity analysis and OS was not re-calculated.

Overall survival by PD-L1

Figure 5 provides the Kaplan-Meier curves for overall survival by PD-L1 expression level, censored at 5 June 2019.

Figure 5: Kaplan-Meier curve of overall survival by PD-L1 expression level



Conclusions

43 patients received nivolumab for locally advanced or metastatic PD-L1 positive non-squamous NSCLC [TA484] through the CDF between 20 September 2017 and 19 December 2018. All patients were reported to the SACT dataset. For an additional 6 patients, the team at PHE confirmed with the trust responsible for the CDF application that the patient did not receive treatment or died before treatment. For the 43 patients receiving treatment in the approved indication, SACT ascertainment was 100%.

Patient characteristics from the SACT dataset show that proportionally more males received nivolumab treatment compared to females (67% male, 33% female). Most of the cohort was aged between 60 and 79 years (72%) and 88% of patients had a performance status between 0 and 1 at the start of their regimen.

At the end of the data collection period, 31 patients were identified as no longer receiving treatment, of these, 100% (N=31) patients had an outcome submitted by the treating trust to the SACT dataset which detailed the reason why a patient ended their treatment. 55% (N=17) of patients had stopped treatment due to disease progression, 13% (N=4) had stopped treatment due to toxicity, 3% (N=1) patients chose to end their treatment, 23% (N=7) of patients died (not on treatment) and 6% (N=2) of patients died on treatment.

The median treatment duration was 4.1 months (124 days) [95% CI: 3.0, 8.3] The median follow-up was 125 days and the maximum follow-up was 16 months (486 days).

The median OS was 9.2 months (279 days) confidence intervals could not be produced as insufficient events had occurred at the time of this report being produced. The minimum follow-up was 5 months (152 days), the maximum follow-up was 20 months (608 days).

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for this cohort showed no difference in treatment duration (Treatment duration for both cohorts = 4.1 months). Sensitivity analysis was not conducted for OS as all patients in the full cohort had at least 6 months' follow-up.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484) [ID1572]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**BTOG-NCRI-RCP-RCR**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve survival, to improve progression-free survival, to improve response rate, to improve quality of life
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	To improve overall survival, an improvement in median survival for relapsed non-squamous NSCLC by 2 months or an improvement in Hazard Ratio (compared to control treatment) of 0.8. would be regarded as clinically significant.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	At the time of the original NICE review of this indication (relapsed advanced non-squamous NSCLC, TA484), nivolumab was regarded as a step-change in therapy as it was the first immune checkpoint inhibitor to be license by EMA for this indication. Thereafter NICE supported its use in the Cancer Drugs Fund. Since then, additional immune checkpoint inhibitors have also been appraised and approved by NICE for use in this same indication: pembrolizumab (NICE approved, TA428), atezolizumab (NICE approved, TA520). Moreover, clinical practice has rapidly changed and immune checkpoint inhibitors are now preferentially

	used as first-line therapy and not on relapse. First-line immune checkpoint inhibitors are NICE approved (pembrolizumab monotherapy, TA531; pembrolizumab with pemetrexed and carboplatin chemotherapy, TA557) There is therefore only a small unmet need in patients with non-squamous NSCLC that has relapsed that have not received first-line immune checkpoint inhibitor, as most patients eligible for an immune checkpoint inhibitor would have received this first line. There are clinical exceptions, eg those with brain metastases that would not receive a first-line immune checkpoint inhibitor due to active brain metastases but may receive it second line.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Advanced non-squamous NSCLC is currently genotyped for EGFR, ALK, and ROS1. For those with wild-type tumours, ie eligible for immune checkpoint inhibitor, patients receive either pembrolizumab monotherapy, as perTA531, or pembrolizumab with pemetrexed and carboplatin chemotherapy, as per TA557, and as indicated in NICE Lung Cancer Treatment Pathway "Advanced non-squamous (stages IIIB and IV) non-small-cell lung cancer: PD-L1 under 50% (no gene mutation, fusion protein or biomarker)" or "Advanced non-squamous (stages IIIB and IV) non-small-cell lung cancer: PD-L1 50% or over (no gene mutation, fusion protein or biomarker)"
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE clinical guidelines are general used. Other guidelines used include the "Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" and the 2020 ASCO guidelines "Therapy for Stage IV Non-Small Cell Lung Cancer without Driver Alterations"
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	Yes; patients' tumours are all genotyped and tested for PDL1 status. There is no significant differences of opinion on treatment pathways between clinicians in the England

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The technology would have little impact on the current treatment pathway as immune checkpoint inhibitors are currently used as first line therapy. However there are a small but important group of patients for whom immune checkpoint inhibitors are not suitable first line eg active CNS metastases at presentation, for whom immune checkpoint inhibitor therapy may be suitable at time of relapse. It would therefore be important that there is access to an immune checkpoint inhibitor therapy for patients such as these
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	As above, the current treatment pathway is to use immune checkpoint inhibitors currently as first line therapy. However there are a small but important group of patients for whom immune checkpoint inhibitors are not suitable first line eg active CNS metastases at presentation, for whom immune checkpoint inhibitor therapy may be suitable at time of relapse. It would therefore be important that there is access to an immune checkpoint inhibitor therapy for patients such as these
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As per current indication
• What investment is needed to introduce the	No additional investment

technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, this class of therapy is a step change over standard chemotherapy
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is differential activity by PDL1 status. I would expect proportionately more activity in the PDL1 >=50%, than 1-49%, than PDL1 negatives. However, there is heterogeneity of PDL1 expression, resulting in tumour sampling bias (eg a tumour is PDL1 strongly positive but the area that is PDL1 negative is biopsied) and even PDL1 negative patients can have meaningful and long term durable benefit.

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No. Using immune checkpoint inhibitors is now clinically routine in the NHS.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional rules beyond that currently approved by NICE for this indication.

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, for those that were unable to access a first-line immune checkpoint inhibitor
• Is the technology a 'step-change' in the management of the condition?	Yes, for those that were unable to access a first-line immune checkpoint inhibitor
• Does the use of the technology address any	Yes, for those that were unable to access a first-line immune checkpoint inhibitor, it addresses poor

particular unmet need of the patient population?	survival, otherwise
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In non-progressors, the technology is likely to improve quality of life and health resource utilization due to benefit. However, immune related adverse events are identified and those of grade 3+ may cause significant reduction in patient quality of life. However, in the overall population, quality of life will be maintained and improve
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, yes this was the primary endpoint of CM057
• If surrogate outcome measures were used, do they adequately predict	A number of secondary endpoints were used, including PFS and response rate, all improved compared to

long-term clinical outcomes?	the comparator docetaxel in the ITT population
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA484?	No
22. How do data on real-world experience compare with the trial data?	Multiple datasets from other countries have generally shown a similar survival compared to that seen in the CM057 trial

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Nivolumab for relapsed non-squamous NSCLC is an important step-change in therapy over docetaxel chemotherapy
- The majority of newly diagnosed advanced non-squamous NSCLC patients already receive an immune checkpoint inhibitor first line, thereby limiting the pool for patients suitable for nivolumab in the relapsed setting
- There remain small numbers of patients that are clinically unsuitable for a first line immune checkpoint inhibitor, and for these patients, nivolumab represents an important step-change in therapy over docetaxel chemotherapy
- Nivolumab is associated with a significant improvement in overall survival over docetaxel chemotherapy
- The magnitude of survival benefit is contingent on the tumour PDL1 status

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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NHS England submission on the NICE re-appraisal of nivolumab monotherapy for the treatment of locally advanced/metastatic non-squamous (NS) non small cell lung cancer (NSCLC) in patients who have been treated with prior platinum-based chemotherapy (ID1572)

1. NHS England notes that the previous CDF recommendation for nivolumab in this indication was only in the PD-L1 positive population. This re-appraisal is therefore confined to this PD-L1 positive NS NSCLC population, this being the consequence of NICE's rules for the re-appraisal of CDF topics. NHS England is aware of the company's wish for re-appraisal to be in the full NS NSCLC population in the marketing authorisation but defers to NICE on this matter.
2. NHS England regards that the only clinically meaningful comparator for nivolumab in this indication is docetaxel. The use of nintedanib in combination with docetaxel is greatly limited by the toxicity of nintedanib and is thus not commonly used.
3. NHS England does not regard the switch of nivolumab from a dose of 3mg/Kg to a fixed dose of 240mg as being an issue of importance in the assessment of clinical and cost effectiveness of nivolumab in this indication. The FDA and EMA have accepted this flat dosing of nivolumab in their revised marketing authorisations. Clinicians have also accepted this change into their clinical practices when nivolumab is used as monotherapy.
4. NHS England notes the sustained 5 year overall survival (OS) rate of [redacted] with nivolumab in Checkmate 057. The [redacted] figure in the docetaxel arm is likely to have been improved by some patients accessing immunotherapy post-progression on docetaxel. This figure of a [redacted] 5 year survival is in keeping with the other long term studies that are mature enough to have reported outcomes in previously treated NSCLC.
5. NHS England notes the continued nivolumab treatment rate of [redacted] and [redacted] at 2 and 5 years in Checkmate 057. Consistent feedback to NHS England has been that NSCLC clinicians are content with the 2 year treatment duration recommended by NICE for all lines of therapy in NSCLC whether this be for nivolumab, pembrolizumab or atezolizumab. The fact that most (12 of 16) of the long term survivors with NSCLC in Checkmate 003 had treatment discontinued at 96 weeks but remained progression free is part of the evidence base which supports the contentment in NHS England in NSCLC therapy of a maximal treatment duration of 2 years. NHS England therefore does not support the use of an open treatment duration in NICE's decision making as to its base case assessment of cost effectiveness.
6. The unsupported remissions of these 12 of 16 long term surviving NSCLC patients in Checkmate 003 supports a substantial continued treatment effect post discontinuation of nivolumab. NHS England therefore regards the previous cautious position of the committee as having treatment effect wane by 3 years post treatment (the '2+3' assumption) as being entirely reasonable at the time of CDF

recommendation. NHS England now regards this as having been a conservative assumption. That there is some waning of treatment effect is evidenced by the continued relapses in patients still on treatment after 2 years in the Checkmate 057 study and in some NSCLC patients in Checkmate 003 who discontinued treatment at 96 weeks.

7. NHS England notes that PD-L1 status does seem to correlate with PFS given that the hazard ratios for PFS steadily diminish as PD-L1 status becomes more positive.
8. The company claim generalisability of the Checkmate 057 population into that treated in the NHS, this being on the basis of similar median durations of treatment discontinuation and OS. However the key issue is where the long term survival plateaus in the OS KM curve in the NHS and the SACT data is not mature enough to give any indications as to this. In addition the constitution of the small numbers of patients with NS NSCLC treated with nivolumab in this indication differs by PD-L1 status: in Checkmate 057, 28% of patients had a PD-L1 status of ≥10% whereas the figure was 67% in the CDF SACT dataset.
9. Should NICE wish to appraise nivolumab in second line NS NSCLC according to its marketing authorisation, NHS England notes the significantly higher company ICER for the PD-L1 negative patients (£54K/QALY) vs PD-L1 positive patients (£33K/QALY).
10. NHS England is surprised at the inclusion of the use of erlotinib in the cost effective modelling. It is not used in this group of patients as 2nd or 3rd line therapy.
11. NHS England does not regard there to be any meaningful clinical difference between the 3 checkpoint inhibitors licensed for S NSCLC in the second line setting.
12. Use of 2nd line immunotherapy in NS NSCLC is falling now that 1st line immunotherapy in combination with chemotherapy is in practice via routine commissioning and CDF recommendations.

Prof Peter Clark

National Clinical lead for the Cancer Drugs Fund

NHS England

March 2020

Cancer Drugs Fund Review

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated non-squamous non-small cell lung cancer [ID1572] (Cancer Drugs Fund update of TA484)

This report was commissioned by the NIHR Systematic Review Programme as project number 129536

Completed 21 January 2020

DOES CONTAIN CIC/AIC

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A MEMBER OF THE RUSSELL GROUP

Title:	Nivolumab for previously treated non-squamous non-small cell lung cancer [ID1572] (Cancer Drugs Fund update of TA484)
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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 Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
James Mahon	Critical appraisal of the economic evidence
Tosin Lambe	Critical appraisal of the economic evidence

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LIST OF ABBREVIATIONS

AC	Appraisal Committee
AE	Adverse event
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
AUC	Area Under the Curve
BIC	Bayesian Information Criterion
BSA	Body surface area
BSC	Best supportive care
CAA	Commercial Access Agreement
CDF	Cancer Drugs Fund
CI	Confidence interval
CS	Company submission
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions Questionnaire
ERG	Evidence Review Group
FAD	Final Appraisal Determination
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
K-M	Kaplan-Meier
MAA	Managed Access Agreement
NICE	National Institute of Health and Care Excellence
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PHE	Public Health England
PS	Performance status
QALY	Quality adjusted life year
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
ToE	Terms of Engagement

EXECUTIVE SUMMARY

1.1 Background

In September 2017, the outcome of the National Institute for Health and Care Excellence (NICE) Technology Appraisal TA484 was to recommend nivolumab as an option for use within the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) in adults after chemotherapy according to the conditions set out in the Managed Access Agreement (MAA). One of the conditions set out in the MAA was that the use of nivolumab should be limited to the treatment of patients whose level of tumour programmed death-ligand 1 (PD-L1) expression was ≥1%.

NICE has issued a Terms of Engagement document. The terms set out within this document, although not binding, outline NICE's expectations in relation to the CDF Review company submission (CS). This Evidence Review Group (ERG) report focuses on the issues outlined in the Terms of Engagement document.

1.1.1 Available evidence

The CheckMate-057 trial (nivolumab versus docetaxel) was the main source of evidence used to inform TA484. This CDF Review has been timed to coincide with the availability of 5-year data cut (May 2019) results from this trial. Data have also been collected from NHS patients who received nivolumab via the CDF (n=43). These data were collected up until January 2019 and are available from the systemic anti-cancer therapy (SACT) database (median follow-up was 125 days).

1.2 Summary of key clinical effectiveness issues

Population

The population recruited to the CheckMate-057 trial was adults with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy. This is a slightly more restricted population than that described in the final scope issued by NICE (i.e., any prior treatment).

Comparators

Direct clinical effectiveness evidence is available from the CheckMate-057 trial for the comparison of treatment with nivolumab versus docetaxel. Clinical advice to the ERG supports the NICE Appraisal Committee (AC) opinion (as set out in the Terms of Engagement document) that docetaxel is the relevant comparator for this CDF Review. Nintedanib+docetaxel was listed as a comparator in the final scope issued by NICE for TA484; however, clinical advice to the ERG is that nintedanib+docetaxel is not commonly used in this indication.

Since publication of the TA484 Final Appraisal Determination (FAD) document, two immunotherapies (IOs), atezolizumab and pembrolizumab, have been recommended by NICE as options for the treatment of previously treated locally advanced or metastatic non-squamous NSCLC after prior chemotherapy. However, as these treatments were not listed as comparators in the final scope issued by NICE for TA484 they are not relevant to this CDF Review.

Clinical effectiveness

CheckMate-057 trial 5-year update median overall survival (OS) results for the 'all-comers' population were [redacted] months (95% confidence interval [CI]: [redacted] to [redacted] months) for patients treated with nivolumab versus [redacted] months (95% CI: [redacted] to [redacted] months) for patients treated with docetaxel. The company has not provided median OS results by level of tumour PD-L1 expression but has provided hazard ratios (HRs). The CheckMate-057 trial 5-year update results demonstrated that, compared to treatment with docetaxel, nivolumab [redacted] OS HRs for subgroups of patients with levels of tumour PD-L1 expression ≥1%, ≥5% and ≥10%. The CheckMate-057 trial 5-year update OS HR results for patients with levels of tumour PD-L1 expression <1%, <5% and <10% were [redacted]. The ERG, therefore, considers that the CheckMate-057 trial 5-year OS HR results do not support any argument that would change the NICE AC's TA484 conclusion that nivolumab should only be prescribed to patients with tumour PD-L1 expression levels ≥1%.

Generalisability

Clinical advice to the ERG is that CheckMate-057 trial data are generalisable to NHS patients treated in England. The company has compared time on treatment and OS Kaplan-Meier (K-M) data from the nivolumab arm of the CheckMate-057 trial 'all-comers' population (42% of whom had confirmed levels of tumour PD-L1 expression ≥1%) with data from the SACT database (n=43, all with level of tumour PD-L1 expression ≥1%, median follow-up=125 days). The ERG considers that it is difficult to draw any conclusions from these comparisons.

1.3 Summary of key issues in cost effectiveness evidence

All ERG comments and revisions relate to 'company base case analysis 3'. The company refers to this within the CDF Review CS as the 'new base case'. Results from this analysis have been generated using the Patient Access Scheme price for nivolumab and list prices for all other treatments.

Model structure

The 'company base case analysis 3' cost effectiveness results have been generated by amending the following aspects of the company model submitted to inform TA484: changes to the modelling of OS, progression-free survival (PFS) and time on treatment, use of a revised utility value to represent health-related quality of life (HRQoL) for patients in the progressed disease health state, and updated nivolumab treatment costs.

The ERG corrected an error in the submitted company model and recalculated the 'company base case analysis 2' and the 'company base case analysis 3' cost effectiveness results; the ERG's correction ensures that the proportion of patients in the PFS health state can never be higher than the proportion of the cohort that is alive. The 'company base case analysis 3' cost effectiveness results for the PD-L1≥1% subgroup were affected by the error.

Population and subgroups

The company has provided cost effectiveness results for the 'all-comers' population, the PD-L1≥1% subgroup and the PD-L1<1% subgroup.

Extrapolation of OS and PFS

The company implemented approaches to modelling OS and PFS that differed from the NICE AC's preferred approaches as the NICE AC preferred approaches generated curves that were not good fits (statistically or visually) to the 5-year CheckMate-057 trial K-M data. The ERG considers that the 'company base case analysis 3' model incorporated approaches to modelling OS and PFS that, for the purposes of decision making, are adequate.

Utilities

The company did not use the AC's preferred utility value to represent the HRQoL of patients in the progressed disease health state. Instead, the company used a higher value generated from results collected as part of the CheckMate-057 trial. The ERG, after correcting the error in the company model, has generated cost effectiveness results using the AC's preferred utility value (results provided in Section 1.4).

Stopping rule

A treatment stopping rule was not included in the CheckMate-057 trial protocol. However, in line with NICE AC preference, the 'company base case analysis 3' model did include a 2-year stopping rule. The ERG, after correcting the error in the company model, has explored the effect on cost effectiveness results of assuming that treatment with nivolumab is continued up until 5 years (results provided in Section 1.4).

Treatment waning

The company has assumed that the effect of treatment with nivolumab lasts for the patient's lifetime, even if treatment is stopped at 2 years, i.e., the company has not applied a treatment waning effect. The trial evidence presented by the company does not fully discount the possibility that the effect of treatment with nivolumab will wane after treatment is stopped. However, the ERG considers that the modelling of treatment waning to inform this CDF Review can only be arbitrary and any plausible approaches to modelling would have little effect on estimates of the relative cost effectiveness of treatment with nivolumab versus docetaxel.

Treatment costs

In 2018, the nivolumab dosing regime was changed from being based on patient weight to a flat dose of 240mg every 2 weeks (Q2W).

1.4 Exploratory cost effectiveness estimates

The ERG considers that, for the purposes of decision-making, after the model error has been corrected, 'company base case analysis 3' results are adequate. The ERG has, however, carried out two exploratory analyses to assess the effect on the ERG corrected 'company base case analysis 3' cost effectiveness results of:

- using the NICE AC's preferred utility value to represent HRQoL for patients in the progressed disease health state
- no nivolumab treatment stopping rule.

Results from these analyses are provided in the table below.

ERG corrected 'company base case analysis 3' and alternative cost effectiveness results (nivolumab PAS price)

	'All comers' population	PD-L1≥1% subgroup	PD-L1<1% subgroup
'Company base case analysis 3'	***£38,703***	***£33,191***	***£53,907***
ERG corrected 'company base case analysis 3'	***£41,420***	***£33,191***	***£64,278***
NICE AC preferred utility value	£42,331	£34,940	£66,636
No stopping rule	£62,296	£47,591	£88,576

AC=Appraisal Committee; NICE=National Institute for Health and Care Excellence; PAS=Patient Access Scheme; PD-L1=programmed death-ligand 1

1.5 End of life

Available CheckMate-057 5-year update median OS results, which have only been provided in the CS for the 'all-comers' population, are presented in the table below. Mean OS results, generated by the 'company base case analysis 3' model, are also presented in the table below. These results suggest that, [redacted]

	Nivolumab		Docetaxel		NICE criteria	
	Mean OS months	Median OS months	Mean OS months	Median OS Months	Short life expectancy	3-month OS gain
'All-comers' population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1≥1% subgroup	[redacted]	Not provided	[redacted]	Not provided	[redacted]	[redacted]
PD-L1<1% subgroup	[redacted]	Not provided	[redacted]	Not provided	[redacted]	[redacted]

* Estimate generated using the 'company base case analysis 3' model
** CheckMate-057 trial 5-year update results (CDF Review CS, p18)
OS=overall survival

1.6 ERG conclusions

1.6.1 Clinical effectiveness

The clinical components of the company CDF Review CS adhere to the NICE AC's preferred clinical assumptions (as set out in the Terms of Engagement document).

The 5-year CheckMate-057 trial data provided in the CDF Review CS do not contradict the NICE AC's conclusion (based on 2-year CheckMate-057 trial data) that nivolumab should only be prescribed to patients with levels of tumour PD-L1 expression ≥1%.

Clinical advice to the ERG is that docetaxel is the most appropriate comparator and that results from the CheckMate-057 trial are generalisable to clinical practice in England.

It is difficult to draw firm conclusions from the SACT data as they were only collected from a small number of patients (n=43) over a short period of time (median follow-up=125 days).

1.6.2 Cost effectiveness

The ERG considers that, after correcting for an error in the company model, the 'company base case analysis 3' cost effectiveness results are robust. Any appropriate modelling of the remaining uncertainty around OS and PFS beyond 5 years, or around the magnitude of the treatment waning effect with a 2-year stopping rule, is unlikely to have a major impact on these results.

The ERG corrected 'company base case analysis 3' cost effectiveness results for the 'all-comers' population and for the PD-L1≥1% subgroups are less than £42,000 per quality adjusted life year (QALY) gained. The results for the PD-L1<1% subgroup were based on improvements in OS and PFS for nivolumab versus docetaxel from the CheckMate-057 trial that [redacted]. However, even when the CheckMate-057 trial numerical OS and PFS advantage for nivolumab versus docetaxel for this subgroup is modelled, the 'company base case analysis 3' incremental cost effectiveness ratio (ICER) per QALY gained is greater than £50,000.

2 EVIDENCE REVIEW GROUP REPORT

2.1 Introduction

In September 2017, nivolumab was recommended[1] by the National Institute for Health and Care Excellence (NICE) for use within the Cancer Drugs Fund (CDF) as an option for treating locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) in adults after chemotherapy, only if:

- their tumours were programmed death-ligand 1 (PD-L1) positive (expression level ≥1%)
- nivolumab was stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression
- the conditions in the Managed Access Agreement (MAA[2]) were followed.

This recommendation followed a lengthy appraisal process that included five NICE Appraisal Committee (AC) meetings. One of the main areas of uncertainty during the original appraisal was the validity of the overall survival (OS) projections put forward by the company and the Evidence Review Group (ERG). The key trial data used by the company to provide evidence to support treatment with nivolumab was from the CheckMate-057 trial. At the time of the TA484[3] company submission (CS) to NICE, OS projections were based on 12 months of follow-up data. By the time of the 5th NICE AC meeting, minimum follow-up data from the CheckMate-057 trial was 24 months. To inform this CDF Review, the company has provided 5-year follow-up data from the CheckMate-057 trial. Further data, from patients (n=43) who received nivolumab via the CDF, are now also available from the systemic anti-cancer therapy (SACT) database (median follow-up time was125 days).

2.2 Nivolumab

Key facts about nivolumab:

- nivolumab (Opdivo®) is a programmed death-1 (PD-1) inhibitor
- nivolumab is indicated as a monotherapy for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults; the indication includes both squamous and non-squamous histologies[4]
- approval by the European Medicines Agency (EMA) was granted in July 2017[4]
- nivolumab is administered by intravenous infusion. At the time of the original CS, dosing was based on weight, but the dosing regime was changed to 240mg every 2 weeks (Q2W) in 2018
- nivolumab is available to the NHS at a discounted price via a Patient Access Scheme (PAS).

2.3 Effectiveness of nivolumab and comparators

Key points relating to the clinical effectiveness of nivolumab and comparator treatments that were raised by the ERG during TA484,[3] and which remain relevant to this CDF Review, are summarised in Box 1.

Box 1 Clinical effectiveness issues

- The population recruited to the CheckMate-057 trial was adults with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy, which is a slightly more restricted population than that described in the final scope issued by NICE (i.e., any prior treatment)
- Clinical advice to the ERG was that the characteristics of patients included in the CheckMate-057 trial (nivolumab versus docetaxel) reflected those of patients treated in the NHS
- Clinical advice to the ERG was that docetaxel was the relevant comparator and nintedanib+docetaxel was rarely used in the NHS
- Results from the company's ITC (calculated using RMST differences) showed no statistically significant differences in PFS or OS for the comparison of treatment with nivolumab versus nintedanib+docetaxel
- Results from subgroup analyses (CheckMate-057 data) suggested that nivolumab is statistically significantly more effective in patients with higher levels of tumour PD-L1 expression than in those with lower levels of tumour PD-L1 expression.

CS=company submission; ERG=Evidence Review Group; NHS=National Health Service; ITC=indirect treatment comparison; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival; RMST=restricted mean survival time
Source: ERG TA484 Report[3]

3 CLINICAL DECISION PROBLEM

The NICE AC's preferred clinical assumptions (as set out in the Terms of Engagement document[5]) are presented in Table 1.

Table 1 NICE Appraisal Committee's preferred clinical assumptions

Area	Summary of NICE AC's preferred clinical assumptions
Population	*People with PD-L1 positive previously treated locally advanced or metastatic non-squamous NSCLC after prior chemotherapy*
Comparators	*The most appropriate comparators for this appraisal are docetaxel monotherapy, nintedanib+docetaxel (for people with adenocarcinoma only) and BSC*
Generalisability	*The results of CheckMate-057 are generalisable to clinical practice in England*
Subgroups	*The AC considered that it is plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression* *The AC reviewed cost effectiveness evidence by PD-L1 expression*

AC=Appraisal Committee; BSC=best supportive care; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1
Source: NICE Terms of Engagement document (2019)[5]

3.1 Population and subgroups

Box 2 NICE Appraisal Committee's preferred clinical assumption: population and subgroups

Population

People with PD-L1 positive previously treated locally advanced or metastatic non-squamous NSCLC after prior chemotherapy

Subgroups

The company are expected to submit evidence by PD-L1 expression level in the CDF review

Source: NICE Terms of Engagement document (2019)[5]

Results for key clinical outcomes from the CheckMate-057 trial are provided in Table 2. These results have been calculated using data from the 'all-comers' population (i.e., including all patients irrespective of level of tumour PD-L1 expression). The initial database lock for the CheckMate-057 trial took place in March 2015 (12 months follow-up) and a targeted database lock (minimum of 5 years follow-up) took place in May 2019. Results from analyses of CheckMate-057 trial data showed that, for the comparison of treatment with nivolumab versus docetaxel in the 'all-comers' population, median OS was statistically significantly longer for patients treated with nivolumab (hazard ratio [redacted]).

Table 2 Key effectiveness results from the CheckMate-057 trial ('all-comers' population)

Database lock March 2015		Database lock May 2019	
Nivolumab (n=292)	**Docetaxel (n=290)**	**Nivolumab (n=292)**	**Docetaxel (n=290)**
Median overall survival (95% CI)*			
12.2 months (9.7 to 15.0 months)	9.4 months (8.1 to 10.7 months)	[redacted] months ([redacted] to [redacted] months)	[redacted] months ([redacted] to [redacted] months)
HR=0.73 (95% CI: 0.59 to 0.89) P=0.002		[redacted] (95% CI: [redacted]) [redacted]	
Median progression-free survival (95% CI)**			
2.3 months (2.2 to 3.3 months)	4.2 months (3.5 to 4.9 months)	-	-
HR=0.92 (95% CI: 0.77 to 1.11; p=0.39)		-	
Median time to treatment discontinuation (95% CI)†			
NR	NR	[redacted] months ([redacted] to [redacted] months)	[redacted] months ([redacted] to [redacted] months)
NR			

CI=confidence interval; HR=hazard ratio; NR=not reported
Source: CDF Review CS (*p18, **p19, †p20)

Survival results (HRs) by level of tumour PD-L1 expression calculated using 1-year CheckMate-057 data are provided in Figure 1 and updated OS HRs from the 5-year analyses are provided in Figure 2. The OS HR results from both sets of analyses suggest that, compared with treatment with docetaxel, the OS benefit for patients treated with nivolumab is statistically significantly improved for patients with tumour PD-L1 expression levels ≥1%, ≥5% and ≥10% but is not statistically significantly improved for patients with tumour PD-L1 expression levels <1%, <5% and <10%. The ERG, therefore, considers that the CheckMate-057 trial 5-year OS HR results do not support any argument that would change the NICE AC's TA484 conclusion that nivolumab should only be prescribed to patients with tumour PD-L1 expression levels ≥1%.

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)	

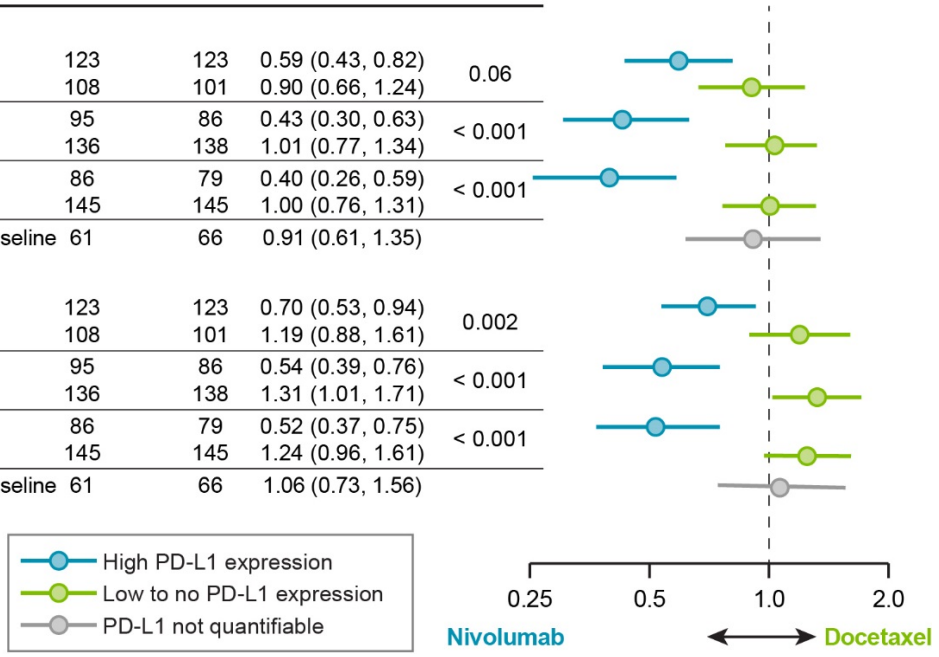

Figure 1 CheckMate-057 trial OS and PFS by level of PD-L1 expression: 1-year analysis

Source: CDF Review CS, Figure 6

Figure 2 CheckMate-057 trial OS by level of PD-L1 expression: 5-year update

Source: CDF Review CS, Figure 7

3.2 Comparators

Box 3 NICE Appraisal Committee's preferred clinical assumption: comparators

The most appropriate comparators for this appraisal are docetaxel monotherapy, nintedanib+docetaxel (for people with adenocarcinoma only) and BSC

Source: NICE Terms of Engagement document (2019)[5]

Direct evidence is available from the CheckMate-057 trial for the comparison of treatment with nivolumab versus docetaxel. The company has not provided any evidence for the comparison of the effectiveness of nivolumab versus nintedanib+docetaxel as clinical advice to the company is that nintedanib+docetaxel is not commonly used in this indication. Clinical advice to the ERG supports the clinical advice provided to the company.

During the period of time since the original appraisal (TA484[3]), other immunotherapies (IOs), i.e., pembrolizumab and atezolizumab, have been recommended by NICE for the treatment of advanced or metastatic NSCLC after chemotherapy, namely:

- pembrolizumab (TA428[6]) for treating locally advanced or metastatic PD-L1 positive NSCLC in adults who have had at least one chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]- positive tumour)
- atezolizumab (TA520[7]) for treating locally advanced or metastatic NSCLC in adults who have had chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour).

However, these treatments are not relevant to this CDF Review as they were not listed as comparators in the final scope issued by NICE for TA484.[3]

3.3 Generalisability

Box 4 NICE Appraisal Committee's preferred clinical assumption: generalisability

Results of CheckMate-057 are generalisable to clinical practice in England

Source: NICE Terms of Engagement document (2019)[5]

During TA484,[3] clinical advice to the ERG was that the baseline characteristics of patients recruited to the CheckMate-057 trial reflected those of patients treated in the NHS. The SACT data (patients who received nivolumab via the CDF) are described and discussed in Section 3.4. The company has only provided Kaplan-Meier (K-M) data that allow comparisons of time on treatment and OS between the CheckMate-057 trial 'all-comers' population (42% of whom had confirmed levels of tumour PD-L1 expression ≥1%) and the SACT database population

(patients with tumours with levels of PD-L1 expression ≥1%, n=42, median follow-up=125 days). The ERG considers that it is difficult to draw any conclusions from these comparisons.

3.4 SACT database outcomes

Public Health England (PHE) provided a SACT report[8] for NHS England based on data collected from patients with a nivolumab CDF application from 20 September 2017 to 19 December 2018. These 43 patients were followed up until 31 January 2019.

The MAA[2] includes the criteria that needed to be met for patients to be prescribed nivolumab via the CDF, namely:

- patient has a confirmed diagnosis of stage IIIB or IV non-small cell lung cancer (non-squamous)
- patient has progressed after previously receiving at least 2 cycles of platinum-containing chemotherapy for stage IIIB or IV non-small cell lung cancer and also a targeted treatment if the tumour is EGFR positive or ALK positive
- patient has a performance status of 0 or 1
- patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless received as part of the nivolumab Early Access to Medicines Scheme (EAMS) programme for this indication and meeting all other criteria listed
- patient has had PD-L1 testing with an approved and validated test to determine the Tumour Proportion Score
- patients' tumour expresses PD-L1, that is with a Tumour Proportion Score ≥1%
- nivolumab will be administered as monotherapy
- patient has no symptomatically active brain metastases or leptomeningeal metastases
- nivolumab will be stopped at 2 years of treatment or on disease progression or unacceptable toxicity, whichever occurs first.

These criteria are more restrictive than those outlined in the NICE Final Appraisal Determination (FAD) document[1] and describe a subgroup of the patients recruited to the CheckMate-057 trial.

Summary characteristics of the 43 unique patients included in the SACT analysis are described in Table 3 The OS data from the SACT analyses are presented in Table 4.

Table 3 SACT database: patient summary characteristics

Characteristic	Patients with CDF application (n=348)
Male	29 (67%)
Age, median	65 years
PS 0	21%
PS 1	67%
PD-L1≥1%	42 (98%)
PD-L1 expression not available	1 (2%)
Patients who had completed tx by Jan 2019	31 (72%)
Median follow-up time in SACT Range	4.1 months (95% CI: 3.0 to 8.3 months) 125-486 days
Median treatment duration	3.5 months (95% CI: 3.0 to 4.1 months)
Proportion of patients receiving tx at 6 months	38% (95% CI: 23% to 53%)
Proportion of patients receiving tx at 12 months	21% (95% CI: 9% to 37%)

CDF=Cancer Drugs Fund; CI= confidence interval; PD-L1=programmed death-ligand 1; PS=performance status; tx=treatment; SACT=systemic anti-cancer treatment
*PS of remaining patients is not reported
Source: CDF Review CS, Section D.6.6

The company highlights that median treatment duration for patients who received nivolumab via the CDF was longer than that observed for patients in the CheckMate-057 trial (Figure 3). However, the ERG highlights that SACT data only relate to patients with levels of tumour PD-L1 expression ≥1% and the CheckMate-057 trial data used in this comparison are the 'all-comers' population.

Figure 3 Treatment duration (SACT data)
Source: CDF Review CS Figure 10

One of the criteria relating to receipt of nivolumab via the CDF was that treatment with nivolumab would be stopped at 2 years of treatment or on disease progression or unacceptable toxicity, whichever occurred first. However, due to the short follow-up period (median follow-up was 125 days), the effect of treatment stopping at 2 years was not captured by the SACT data.

Key SACT OS information is provided in Table 4, whilst SACT and CheckMate-057 (nivolumab arm, 'all-comers' population) OS K-M trial data are reproduced in Figure 4. The ERG highlights that whilst the survival curves follow a similar trajectory, the SACT data have only been obtained from 43 patients and only relate to patients with tumour levels of PD-L1 expression ≥1%.

Table 4 SACT database: overall survival data

Survival	Estimate
Median OS	9.2 months (95% CI could not be estimated due to insufficient number of events)
Follow-up range (minimum to maximum)	5 months to 20 months
Survival at 6 months	62% (95% CI: 46% to 75%)
Survival at 12 months	43% (95% CI: 28% to 58%)
Alive/dead at date of follow up	17/26

confidence interval=CI; OS=overall survival
Source: CDF Review CS, Section D.6.6

Figure 4 CheckMate-057 trial and SACT overall survival Kaplan-Meier data
Source: CDF Review CS Figure 11

3.4.1 ERG comments on SACT analyses

It is difficult to draw firm conclusions from the SACT data as they were only collected from a small number of patients (n=43) over a short period of time (median follow-up=125 days).

3.4.2 Conclusions of the clinical effectiveness section

The clinical components of the company CDF Review CS adhere to the NICE AC's preferred clinical assumptions (as set out in the Terms of Engagement document[5]).

Key outcomes from the CheckMate-057 trial (nivolumab versus docetaxel) are presented for a population with previously treated locally advanced or metastatic non-squamous NSCLC. The company has focused on presenting clinical effectiveness evidence for the full ('all-comers') population but has also provided some results by level of tumour PD-L1 expression. The 5-year CheckMate-057 trial data provided in the CDF Review CS do not contradict the NICE AC's conclusion that nivolumab should only be prescribed to patients with levels of tumour PD-L1 expression ≥1%.

Clinical advice to the ERG is that docetaxel is the most appropriate comparator and that results from the CheckMate-057 trial are generalisable to clinical practice in England.

It is difficult to draw firm conclusions from the SACT data as they were only collected from a small number of patients (n=43) over a short period of time (median follow-up=125 days).

4 COST EFFECTIVENESS DECISION PROBLEM

The NICE AC's preferred economic assumptions, as set out in the Terms of Engagement document,[5] are presented in Table 5. Further information relating to each assumption is provided in the text following the table.

All ERG comments and revisions relate to 'company base case analysis 3'. The company refers to this within the CDF Review CS as the 'new base case'. Results from this analysis have been generated using the Patient Access Scheme price for nivolumab and list prices for all other treatments.

Table 5 NICE Appraisal Committee's preferred economic assumptions

Area	Summary of NICE AC's economic assumptions
Model structure	*The company's model structure was accepted*
Subgroups	*The committee considered that it is plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression.* *The committee reviewed cost effectiveness evidence by PD-L1 expression*
Extrapolation of OS	*The observed Kaplan-Meier followed by the exponential model is an appropriate method for extrapolating OS*
Extrapolation of PFS	*Using the observed data followed by an exponential extrapolation is the most appropriate method to estimate PFS*
Utilities	*A utility value of 0.569 should be used for the progressed-disease health state* *A utility value of 0.713 should be used for the progression-free health state*
Stopping rule	*A 2-year stopping rule was not included in the SmPC* *A stopping rule was considered acceptable and implementable to both patients and clinicians*
Continued treatment effect	*After stopping treatment at 2 years, nivolumab's treatment effect could last up to 3 years*
Dose intensity reduction	*It is reasonable to adjust the dose intensity for both the intervention and the comparator*
Treatment costs	*Committee accept the ERG's cost corrections to the dose of nivolumab, and the calculation of administration costs*
End of life	*Nivolumab met the criteria to be considered a life-extending, end-of-life treatment*

AC=Appraisal Committee; PD-L1=programmed death-ligand 1; PFS=progression-free survival; OS=overall survival; SmPC=Summary of Product Characteristics Source: NICE Terms of Engagement document (2019)[5]

4.1 Model structure

Box 5 NICE Appraisal Committee's preferred clinical assumption: model structure

The company's model structure was accepted

Source: NICE Terms of Engagement document (2019)[5]

The ERG has been able to use the company model to replicate the cost effectiveness results that are reported in the NICE FAD document.[1] An error, relating to an assumed relationship between OS and PFS was identified in the company model. The modelling error meant that if, at any time point, there were more patients alive in the PFS health state than were modelled to be alive by the OS extrapolation, then the OS extrapolation was adjusted to match the PFS extrapolation. This error has been corrected by the ERG such that, when necessary, the PFS extrapolation is adjusted so that the proportion of patients in the PFS health state is never higher than the proportion of the cohort that is alive.

4.2 Subgroups

Box 6 NICE Appraisal Committee's preferred clinical assumption: subgroups

The committee considered that it is plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression *The committee reviewed cost effectiveness evidence by PD-L1 expression*

Source: NICE Terms of Engagement document (2019)[5]

The company has submitted cost effectiveness evidence for the 'all-comers' population and for two subgroups differentiated by level of tumour PD-L1 expression (≥1% and <1%) which, combined, make up the 'all-comers' population. 'Company base case analysis 3' cost effectiveness estimates for the comparison of treatment with nivolumab versus docetaxel, for the 'all-comers' population, the PD-L1≥1% subgroup and the PD-L1<1% subgroup were £38,703, £33,191 and £53,907 per quality adjusted life year (QALY) gained respectively. When the ERG corrected the error in the company model, the ICERs per QALY gained for nivolumab versus docetaxel for the 'all-comers' population and the PD-L1<1% subgroup were £41,420 and £64,278 respectively. Cost effectiveness analysis results for the PD-L1≥1% subgroup were not affected by the model error.

Cost effectiveness results by other levels of tumour PD-L1 expression were not provided in the CS, nor were they provided in response to a clarification request. The company argued that provision of these results was unnecessary as there were no clinically or statistically meaningful differences between CheckMate-057 trial OS results for (i) patients with levels of tumour PD-L1 expression ≥1%, ≥5%, ≥10% or (ii) patients with levels of tumour PD-L1

expression <1%, <5%, <10% (see Figure 2 and OS response rates provided in response to clarification letter Question B2).

4.3 Extrapolation of overall survival

Box 7 NICE Appraisal Committee's preferred economic assumption: extrapolation of overall survival

The observed Kaplan-Meier followed by the exponential model is an appropriate method for extrapolating OS

Source: NICE Terms of Engagement document (2019)[5]

The company concluded, based on visual inspection, that the NICE AC preferred approach for modelling OS (OS K-M data followed by an exponential curve) was not a good fit to the 'all-comers' population 5-year CheckMate-057 trial OS K-M data and carried out a curve fitting exercise to identify the best fitting extrapolations to the trial nivolumab and docetaxel data. The 17 different curves fitted by the company were assessed statistically (using the Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC] statistics) and by assessing visual fit to the CheckMate-057 trial OS K-M data for the 'all-comers' population and for the PD-L1≥1% and PD-L1<1% subgroups. Based on these assessments, the company's preferred distributions were the log-normal for the 'all-comers' population and the PD-L1≥1% subgroup, and the spline normal 1 knot for the PD-L1<1% subgroup (CDF Review CS, p 41). However, the ERG highlights that, in 'company base case analysis 3', a log-normal distribution was used to generate incremental cost effectiveness ratios (ICERs) per QALY gained for the PD-L1<1% subgroup. In response to a clarification request, in addition to the 17 distributions already considered, the company provided an updated model that included the option to model hybrid extrapolations using the CheckMate-057 trial OS K-M data for up to 60 months, followed by a parametric distribution (exponential, Weibull, gompertz, generalised-gamma, gamma, log-logistic or log-normal).

The ERG notes that the maturity of the OS data from the CheckMate-057 trial means that the distribution choice makes little difference to cost effectiveness results when distributions with implausible tails (i.e., those that generate mortality hazards that rapidly fall below background mortality) or those that are a poor fit to the CheckMate-057 trial OS K-M data, are excluded. Using the corrected 'company base case analysis 3' model, the ICERs per QALY gained for all the plausible distributions, including the hybrid extrapolations at 36, 48 or 60 months, were up to £6,000 lower for the 'all-comers' population, ranged from £500 higher to £4,000 lower for the PD-L1≥1% subgroup and varied by ± £2,000 for the PD-L1≤1% subgroup. As it is not possible to differentiate robustly between any of the plausible distributions, the ERG considers that, for the purposes of decision making, the company's preferred OS extrapolations are

adequate (including use of the log-normal distribution to model OS for the PD-L1<1% subgroup).

4.4 Extrapolation of progression-free survival

Box 8 NICE Appraisal Committee's preferred economic assumption: extrapolation of progression-free survival

Using the observed data followed by an exponential extrapolation is the most appropriate method to estimate PFS

Source: NICE Terms of Engagement document (2019)[5]

The company concluded, based on visual inspection, that the AC's preferred distribution (CheckMate-057 trial PFS K-M data followed by an exponential distribution) was not a good fit to the 'all-comers' population 5-year CheckMate-057 trial progression-free survival (PFS) K-M data and carried out a curve fitting exercise to identify the best fitting extrapolations. The company fitted independent survival distributions to the CheckMate-057 trial PFS K-M data for nivolumab and docetaxel. The 17 different curves fitted by the company were assessed statistically (using the AIC and the BIC statistics) and by assessing visual fit to the CheckMate-057 trial PFS K-M data for the 'all-comers' population, for the PD-L1≥1% and PD-L1<1% subgroups. The company concluded that the best distributions to use to model PFS for patients treated with nivolumab and for those treated with docetaxel were the spline odds 2 knot for the 'all-comers' population and the PD-L1<1% subgroup, and the spline normal 1 knot for the PD-L1≥1% subgroup.

In addition to the 17 distributions already considered, the company model also included the option to model PFS using hybrid exponential extrapolations using the observed CheckMate-057 trial PFS K-M data followed by an exponential curve (the approach described in the NICE Terms of Engagement document[5]). However, the maturity of the PFS K-M data from the CheckMate-057 trial means that, when distributions which are not a good fit to the CheckMate-057 trial PFS K-M data are excluded, the choice of distribution makes little difference to cost effectiveness results. As was the case with OS projections, for the 'all-comers' population, the PD-L1≥1% subgroup and the PD-L1<1% subgroup, all the plausible distributions, including the hybrid extrapolations at 36, 48 or 60 months, generated ICERs per QALY gained that were within £1,000 of the ERG corrected 'company base case analysis 3' cost effectiveness results. The ERG, therefore, considers that, for the purposes of decision making, the company's preferred PFS extrapolations are adequate.

4.5 Utilities

Box 9 NICE Appraisal Committee's preferred economic assumption: utilities

A utility value of 0.569 should be used for the progressed-disease health state *A utility value of 0.713 should be used for the progression-free health state*

Source: NICE Terms of Engagement document (2019)[5]

'Company base case analysis 3' model has been populated with a utility value of 0.688 to represent health-related quality of life (HRQoL) for patients in the progressed disease health state. This value has been generated from CheckMate-057 trial data. No justification, or new evidence, has been provided in the CDF Review CS to explain why this value, rather than the NICE AC's preferred utility value (0.569), has been used in this analysis.

Compared to results generated using the ERG corrected 'company base case analysis 3', using the AC preferred progressed disease utility value (0.569) results in ICERs per QALY gained for the comparison of the cost effectiveness of nivolumab versus docetaxel for the 'all-comers' population, the PD-L1≥1% subgroup and the PD-L1<1% subgroup of £42,331, £34,940 and £66,636 respectively.

4.6 Stopping rule and continued treatment effect

Box 10 NICE Appraisal Committee's preferred economic assumption: stopping rule

Stopping rule *A 2-year stopping rule was not included in the SmPC* *A stopping rule was considered acceptable and implementable to both patients and clinicians* **Continued treatment effect (waning)** *After stopping treatment at 2 years, nivolumab's treatment effect could last up to 3 years*

Source: NICE Terms of Engagement document (2019)[5]

Treatment stopping rule

A treatment stopping rule is not included in the CheckMate-057 trial protocol. However, in line with the NICE AC preference, 'company base case analysis 3' included a 2-year stopping rule.

Details provided in Table 6 show the proportions of patients in the CheckMate-057 trial still receiving nivolumab at 2, 3 and 5 years (CheckMate-057 trial time to treatment discontinuation K-M data). If treatment with nivolumab were continued up until 20 years (the model time horizon), then the ICERs per QALY gained, generated using the ERG corrected 'company base case analysis 3' assumptions, for the comparison of the cost effectiveness of nivolumab versus docetaxel, for the 'all-comers' population, the PD-L1≥1% subgroup and the PD-L1<1% subgroup would be £62,296, £47,591 and £88,576 respectively.

Table 6 CheckMate-057 trial patients receiving nivolumab at different time points

Population	Proportions of CheckMate-057 trial patients receiving nivolumab		
	2 years	3 years	5 years
All-comers	[redacted]	[redacted]	[redacted]
PD-L1≥1%	[redacted]	[redacted]	[redacted]
PD-L1<1%	[redacted]	[redacted]	[redacted]

Source: CheckMate-057 time to treatment discontinuation (TTD) Kaplan-Meier data in company model

Treatment waning effect

The company has assumed that the effect of treatment with nivolumab lasts for the patient's lifetime, even if treatment is stopped at 2 years, i.e., the company has not applied a treatment waning effect. The company's justification is that, in the CheckMate-003 trial (CDF Review CS, p38), where the protocol stipulated that treatment with nivolumab should be stopped at 2 years, 75% of patients with NSCLC (squamous and non-squamous disease) who received nivolumab and were still alive at 5 years were progression free, and OS rates for these patients at 3 years ([redacted]) and 5 years ([redacted]) were similar to OS rates at 3 years ([redacted]) and 5 years ([redacted]) for all patients randomised to the nivolumab arm of the CheckMate-057 trial.

The evidence from the CheckMate-057 and CheckMate-003 trials does not fully discount the possibility of a treatment waning effect occurring. However, the length of time that any treatment effect might continue is unknown. In addition, as patients randomised to the docetaxel arm of the CheckMate-057 trial could cross over to receive nivolumab on progression, it is not possible to determine the mortality and progression rates that should be used once any benefits from having been treated with nivolumab have ended.

In this appraisal, the following factors are important when considering how to model the effect of treatment waning for nivolumab:

- the uncertainty around treatment waning
- a treatment waning effect is likely to only affect a small proportion of patients
- choice between the selection of OS and PFS extrapolations considered by the company has little effect on cost effectiveness results.

Due to these factors, the ERG considers that any modelling of the treatment waning effect to inform this CDF Review can only be arbitrary and any plausible approaches to modelling waning would have little effect on estimates of the relative cost effectiveness of treatment with nivolumab versus docetaxel.

4.7 Dose intensity reduction

Box 11 NICE Appraisal Committee's preferred economic assumption: dose intensity reduction

It is reasonable to adjust the dose intensity for both the intervention and the comparator

Source: NICE Terms of Engagement document (2019)[5]

The company has applied dose intensity reductions to nivolumab and docetaxel as in the original company model.

4.8 Treatment costs

Box 12 NICE Appraisal Committee's preferred economic assumption: treatment costs

Committee accept the ERG's cost corrections to the dose of nivolumab, and the calculation of administration costs

Source: NICE Terms of Engagement document (2019)[5]

At the time of the original CS, the dose of nivolumab was calculated based on patient weight. However, in 2018, the dosing regime was changed to a flat dose of 240mg every 2 weeks (Q2W) and this is the dose that is used in 'company in base case analysis 3'.

4.9 End of life

Box 13 NICE Appraisal Committee's preferred economic assumption: end-of-life

Nivolumab met the criteria to be considered a life-extending, end-of-life treatment

Source: NICE Terms of Engagement document (2019)[5]

The NICE end of life criteria[9] are:

- treatment is indicated for patients with a short life expectancy, normally less than 24 months
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Available CheckMate-057 5-year update median OS results, which have only been provided in the CS for the 'all-comers' population, are presented in Table 7. Mean OS results, generated by the 'company base case analysis 3' model, are also presented in Table 7. These results suggest that, [redacted]

Table 7 End of life estimates

	Nivolumab		Docetaxel		NICE criteria	
	Mean OS months	**Median OS months**	**Mean OS months**	**Median OS Months**	**Short life expectancy**	**3-month OS gain**
'All-comers' population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1≥1% subgroup	[redacted]	Not provided	[redacted]	Not provided	[redacted]	[redacted]
PD-L1<1% subgroup	[redacted]	Not provided	[redacted]	Not provided	[redacted]	[redacted]

* Estimate generated by the 'company base case analysis 3' model
** CheckMate-057 trial 5-year update results (CDF Review CS, p18)
OS=overall survival
Source: CDF Review CS and 'company base case analysis 3' model

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company has presented results from a number of different deterministic cost effectiveness analyses (see CDF Review CS, Table 26). Different combinations of study data, survival extrapolations and nivolumab doses have been used to generate cost effectiveness results.

'Company base case analysis 3', the new company base case, generated using the flat dose for nivolumab and the [redacted] PAS price (cost effectiveness analysis 3) generated ICERs per QALY gained of £38,703 ('all-comers population), £33,191 (PD-L1≥1%) and £53,907 (PD-L1<1%) as shown in Table 8 to Table 10.

After the ERG corrected the PFS/OS extrapolation error in the company model, the 'company base analysis 3' ICERs per QALY gained changed to £41,420 ('all-comers population), £33,191 (PD-L1≥1%) and £64,278 (PD-L1<1%) as shown in Table 8 to Table 10. Cost effectiveness analysis results for the PD-L1≥1% subgroup were not affected by the model error. The ERG has only corrected the error in the models that use CheckMate-057 trial 5-year survival data (i.e., company cost effectiveness analyses 2 and 3).

Table 8 Company's cost effectiveness results for 'all-comers' population

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Cost effectiveness analysis 1a: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF ([redacted])PAS							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£16,032	0.44	0.32	£49,936[a]
Cost effectiveness analysis 1b: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF ([redacted])PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£18,025	0.44	0.32	£56,141
Cost effectiveness analysis 1c: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with ([redacted]) PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£26,552	0.44	0.32	£82,702
Cost effectiveness analysis 2: analysis that demonstrated plausible potential for cost-effectiveness at CDF entry, with ([redacted]PAS and incorporating updated OS and PFS hybrid exponential fitted to CheckMate-057 5-year data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£26,073	0.51	0.37	£70,017
Cost effectiveness analysis 2: COMPANY MODEL CORRECTED BY THE ERG							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£30,505	1.21	0.72	£42,104
Cost effectiveness analysis 3: new company base case with [redacted]PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£28,360	1.23	0.73	£38,703
Cost effectiveness analysis 3: COMPANY MODEL CORRECTED BY THE ERG							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£28,041	1.09	0.68	£41,420

[a] Revised ICER after a programming error was corrected during preparation of current submission CDF=Cancer Drugs Fund; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year Source: CDF Review CS, Table 25

Table 9 Company's cost effectiveness results for the PD-L1≥1% subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Cost effectiveness analysis 1a: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF PAS ([redacted]							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£22,645	1.11	0.72	£31,589
Cost effectiveness analysis 1b: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF PAS ([redacted] and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£25,196	1.11	0.72	£35,147
Cost effectiveness analysis 1c: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with [redacted]PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£36,116	1.11	0.72	£50,381
Cost effectiveness analysis 2: analysis that demonstrated plausible potential for cost-effectiveness at CDF entry, with [redacted]PAS and incorporating updated OS and PFS hybrid exponential fitted to CheckMate-057 5-year data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£38,410	1.27	0.80	£47,793
Cost effectiveness analysis 2: COMPANY MODEL CORRECTED BY THE ERG							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£41,416	1.57	0.98	£42,200
Cost effectiveness analysis 3: new company base case with [redacted]PAS and nivolumab flat dose**							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£43,128	2.24	1.30	£33,191

[a] Revised ICER after a programming error was corrected during preparation of current submission

** [redacted]

CDF=Cancer Drugs Fund; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year
Source: CDF Review CS, Table 27

Table 10 Company's cost effectiveness results for the PD-L1<1% subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Cost effectiveness 1a: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF PAS ([redacted]							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£10,647	0.18	0.15	£68,694
Cost effectiveness analysis 1b: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with CDF PAS ([redacted] and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£12,249	0.18	0.15	£79,024
Cost effectiveness analysis 1c: replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry with [redacted]PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£19,102	0.18	0.15	£123,239
Cost effectiveness analysis 2: analysis that demonstrated plausible potential for cost-effectiveness at CDF entry, with [redacted]PAS and incorporating updated OS and PFS hybrid exponential fitted to CheckMate-057 5-year data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£19,885	0.25	0.19	£103,741
Cost effectiveness analysis 2: COMPANY MODEL CORRECTED BY THE ERG							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£18,371	0.28	0.22	£84,457
Cost effectiveness analysis 3: new company base case with [redacted]PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£18,811	0.56	0.35	£53,907
Cost effectiveness analysis 3: COMPANY MODEL CORRECTED BY THE ERG							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£18,458	0.42	0.29	£64,278

[a] Revised ICER after a programming error was corrected during preparation of current submission CDF=Cancer Drugs Fund; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year Source: CDF Review CS, Table 26

6 ERG COST EFFECTIVENESS ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has provided results to show the effect, on the ERG corrected 'company base case analysis 3' results, of using the NICE AC's preferred utility value, rather than the value used by the company, to represent the HRQoL life of patients in the progressed disease health state. The effect of this change is to increase the ERG corrected 'company base case analysis 3' cost effectiveness results by £911, £1,749 and £2,358 for the 'all-comers' population, the PD-L1 ≥1% subgroup and the PD-L1<1% subgroup, respectively.

The ERG has not made any amendments to the ways in which the company has modelled time on treatment, OS or PFS. The ERG considers that changes are unnecessary because the maturity of the CheckMate-057 trial K-M data means that time on treatment data are complete, and the choice of method used to extrapolate available OS and PFS data has little impact on model cost effectiveness results.

6.2 Conclusions of cost effectiveness section

The ERG considers that 'company base case analysis 3' cost effectiveness results, when generated using the NICE AC's preferred progressed disease utility values and after correcting the PFS/OS error in the model, are robust. Any appropriate modelling of the remaining uncertainty around OS and PFS beyond 5 years, or around the magnitude of the 'treatment waning effect' with a 2- year stopping rule, is unlikely to have a major impact on the ERG corrected 'company's base case analysis 3' cost effectiveness results.

The ERG corrected 'company base case analysis 3' cost effectiveness results for the 'all-comers' population and for the PD-L1≥1% subgroups are less than £42,000 QALY gained. The results for the PD-L1<1% subgroup were based upon improvements in OS and PFS for nivolumab versus docetaxel from the CheckMate-057 trial that did not reach statistical significance. Even when the numerical OS and PFS advantage of nivolumab versus docetaxel for the PD-L1<1% subgroup from the CheckMate-057 trial is modelled, the ICER per QALY gained for treatment with nivolumab versus docetaxel is over £50,000.

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UNIVERSITY OF LIVERPOOL

ERRATUM: Nivolumab for previously treated non-squamous non-small cell lung cancer [1D1572]

Cancer Drugs Fund update of TA484

This document contains the following information:

- Instructions required to correct company model error (Table 1)
- ERG corrected 'company cost effectiveness analysis 2' results for the 'all-comers' population (Table 2). The ERG is unable to correct the results for patients with PD-L1≥1% and PD-L1<1% expression levels.
- The ERG noted an error in Table 8 of the submitted ERG report. Total costs for nivolumab should be £[redacted] (instead of £[redacted]).

Table 1 Instructions to correct company model error

Sheet	Cells	Modified formulae
Patient flow - 1	J14	=MIN(H8*'Response and survival'!$CC39, 'Response and survival'!CE39) Copy cell formula to range J15:J1054
	L14	=1-J14-N14 Copy cell formula to range L15:L1054

Table 2 Company's cost effectiveness results for 'all-comers' population

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Cost effectiveness analysis 2: analysis that demonstrated plausible potential for cost-effectiveness at CDF entry, with ([redacted] PAS and incorporating updated OS and PFS hybrid exponential fitted to CheckMate-057 5-year data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£26,073	0.51	0.37	£70,017
Cost effectiveness analysis 2: COMPANY MODEL CORRECTED BY THE ERG - INCORRECT							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£30,505	1.21	0.72	£42,104
Cost effectiveness analysis 2: COMPANY MODEL CORRECTED BY THE ERG - REVISED							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£25,890	0.45	0.34	£76,061

CDF=Cancer Drugs Fund; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Liverpool Reviews and Implementation Group

27 January 2020

Confidential appendix 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated non-squamous non-small cell lung cancer [ID1572]

Cancer Drugs Fund update of TA484

Additional analyses (treatment waning) requested by NICE generated using discounted price of nivolumab

This report was commissioned by the NIHR Systematic Reviews Programme as project number 129536

Completed 27 January 2020

CONTAINS COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

This document contains ERG responses to two requests from NICE for additional information.

1 In an email dated 20 Jan 2020, NICE asked the ERG to list the PFS and OS distributions that the ERG considers to have implausible tails or have a poor fit to the K-M data.

OS: 'All-comers' population, PD-L1<1% subgroup and PD-L1≥1% subgroup

Exponential

Weibull

PFS: All-comers and PD-L1<1%

Exponential

Weibull

Log-logistic

Log-normal

Generalised-gamma

PFS: PD-L1>1% subgroup

Exponential

Weibull

Log-logistic

Log-normal

2 During a telephone call held on 24 January 2020, NICE asked the ERG to generate results from analyses exploring the effect of treatment waning on 'company cost effectiveness analysis 3'. The results from these scenarios are provided in Table 1.

Table 1 ERG corrected 'company cost effectiveness analysis 3', with PAS prices for nivolumab only and 'continued treatment after 2-year stopping rule' set to 3 years

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
All-comers							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£26,924	0.76	0.52	£51,856
PD-L1≥1% subgroup							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£39,030	1.39	0.90	£43,270
PD-L1<1% subgroup							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£18,050	0.30	0.23	£78,889

ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Nivolumab for treating previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484)

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

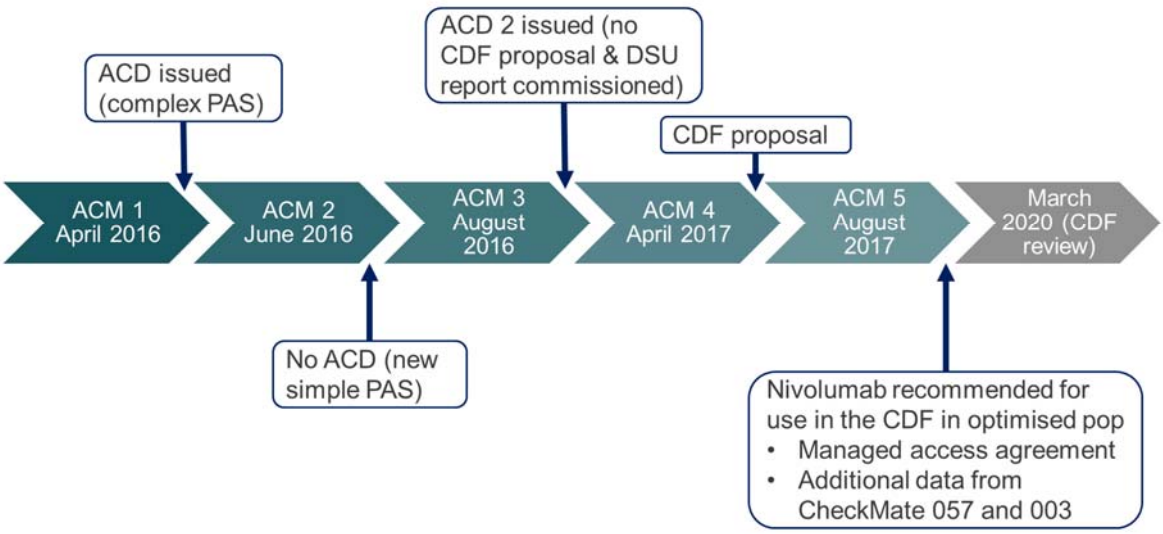
- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: February 2020

1. Topic background

1.1 Summary of original appraisal TA484



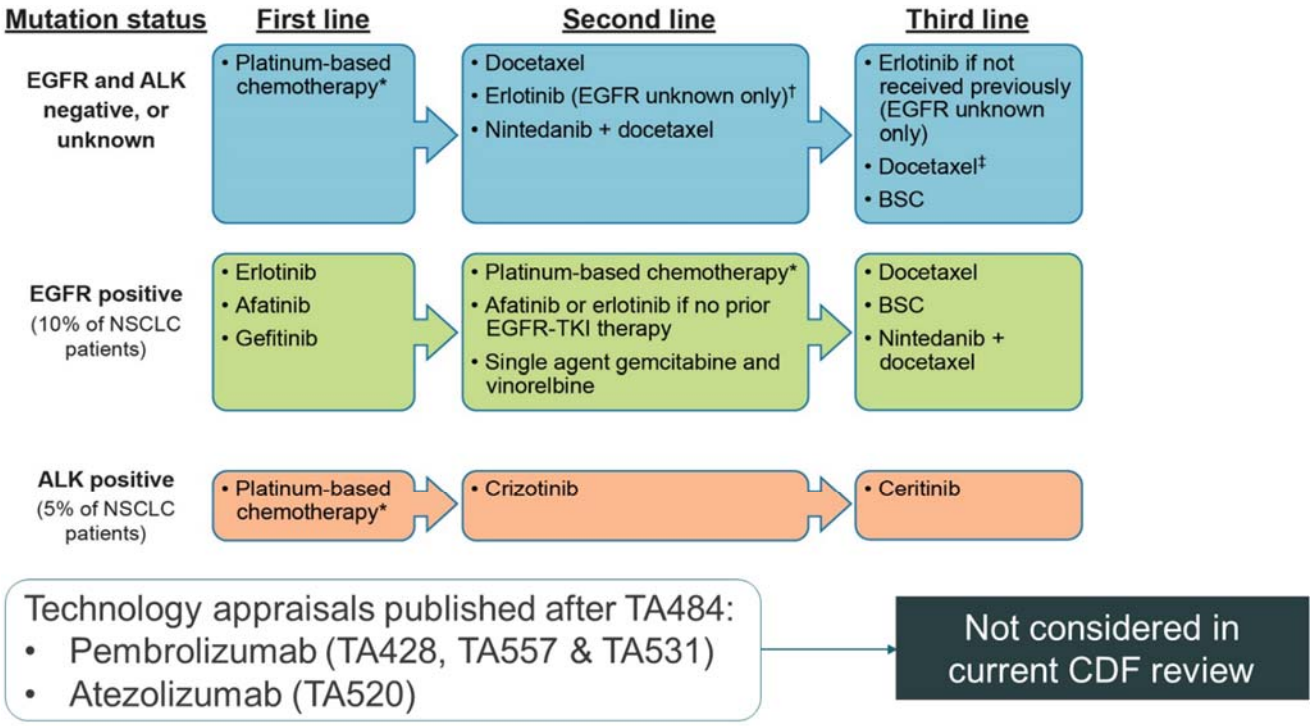
1.2 Appraisal background

Nivolumab marketing authorisation: treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

TA484 recommendation: Nivolumab is recommended in CDF for locally advanced or metastatic non-squamous NSCLC after chemotherapy only if: • tumours are PD-L1 positive • nivolumab is stopped at 2 years of uninterrupted treatment, or disease progression, • the conditions in the managed access agreement are followed

	Original appraisal (TA484)	ID1572 CDF review
Population	CDF recommendation restricted to PD-L1 positive disease	Company include analyses for ITT population, PD-L1 ≥1% & PD-L1 <1%. Only the PD-L1 ≥1% subgroup is relevant for this CDF review in line with the recommendation in TA484
Comparator	• nintedanib plus docetaxel (for adenocarcinoma – considered relevant despite high toxicity but the indirect comparison is not reliable) • docetaxel monotherapy • Best supportive care (BSC) – no ICERs presented	Company only compare nivolumab with docetaxel monotherapy
Clinical data	3-year data from CheckMate 057	• 5-year data from CheckMate 057 • SACT data from 43 people (Sept 2017 to Dec 2018)

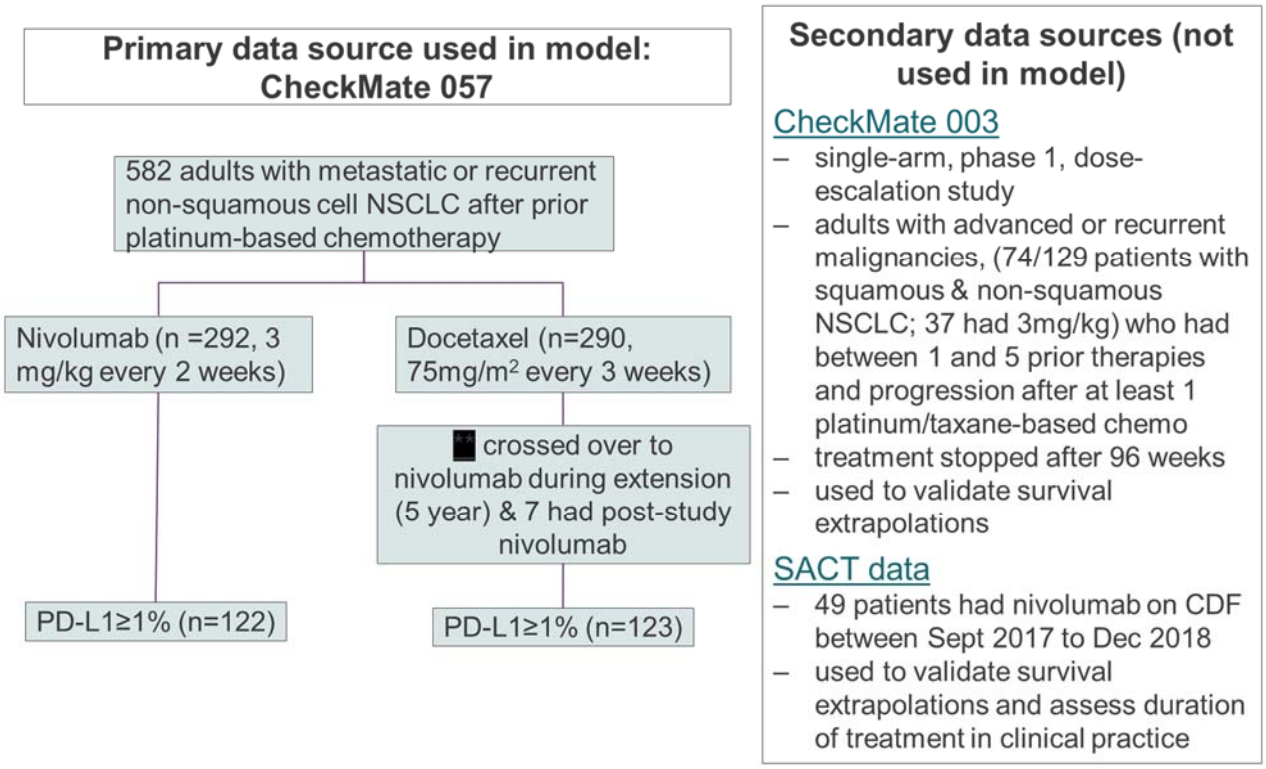
1.3 Treatment pathway from TA484



1.4 Key considerations for TA484 in people with PD-L1≥1%

	Committee preferred in TA484	Company base case in CDF review
Comparator	Docetaxel monotherapy, nintedanib plus docetaxel (for adenocarcinoma) & BSC	Docetaxel monotherapy
OS extrapolation	Hybrid exponential model using 3-year Kaplan-Meier data from CheckMate 057 then exponential curve.	Lognormal curve fitted to 5-year KM data (scenario: spline with 3 knots)
PFS extrapolation	Hybrid exponential using 2-year Kaplan-Meier data then exponential curve	Spline normal 1 knot fitted to the 5-year KM data
Time to treatment discontinuation	2-year Kaplan-Meier data & 2 year stopping rule	5-year Kaplan-Meier data & 2 year stopping rule
Utility values	• Progressed disease 0.569 (midpoint of company & ERG preferred) • Progression-free 0.713	Post-progression (0.688) from 5-year CheckMate 057 data and no change to progression-free
Duration of continued treatment effect	• Nivolumab's effectiveness is continued for 3 years after treatment is stopped • Treatment effect from docetaxel arm applied thereafter	Lifetime treatment effect for nivolumab after it is stopped
Dose	3 mg/kg body weight and it is reasonable to adjust dose intensity for both nivolumab & comparator	240 mg every 2 weeks (SmPC change in 2018). No changes to dose intensity

1.5 Key clinical data sources



1.6 Key trial results for PD-L1≥1% subgroup

Outcome	Original appraisal TA484		CDF review		
	CheckMate 057 (3-year data)		CheckMate 057 (5-year data)		SACT (n=43)
	Nivolumab	Docetaxel	Nivolumab	Docetaxel	
Median OS	17.7†	9.0	Not reported		9.2*
OS	HR 0.59 (0.43 to 0.82)**		[redacted]		Not reported
1-year OS	Not reported		[redacted]	[redacted]	43% (28 to 58)
3-year OS	Not reported		[redacted]	[redacted]	Not reported
5-year OS	N/A		[redacted]	[redacted]	Not reported
Median PFS	4.2	4.5	Not reported	Not reported	Not reported
PFS	HR 0.70 (0.53 to 0.94)**		Not reported	Not reported	Not reported

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival
All data reported are in months unless otherwise indicated
* insufficient data for confidence interval; ** 1-year data; † based on 18-month data

2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 Nintedanib plus docetaxel may be a relevant comparator for people with non-squamous NSCLC and adenocarcinoma

Issue 2 The company's extrapolations fitted to the updated 5-year OS and PFS data from CheckMate 057 are plausible, but so are some alternative distributions.

Issue 3 The technical team prefers to use previously accepted utility values from TA484, because the updated data from CheckMate 057 are likely to be influenced by the same type of selection bias as the original data.

Issue 4 The technical team prefers to use the previously accepted 3-year duration of treatment effect for nivolumab, because the exact duration is unknown, and assuming a lifelong effect is likely to underestimate cost-effectiveness estimates. It is unclear if a 2-year stopping rule is appropriate.

2.2 The technical team recognised that the following uncertainties would remain in the CDF review analyses and could not be resolved:

- The effect of changing the licensed dosing regimen to a fixed dose as opposed to weight-based pricing is unknown.

2.3 The cost-effectiveness results for nivolumab vs. docetaxel alone include a commercial arrangement (patient access scheme) for nivolumab. A confidential appendix includes a discount for erlotinib which is used as a subsequent treatment for some patients.

2.4 For nivolumab vs. docetaxel, the technical team's preferred incremental cost-effectiveness ratios (ICERs) is £60,321 per quality-adjusted life year (QALY) gained (see table 2) by using the previously accepted utility values (see issue 3), the previously accepted 3-year treatment duration of

treatment effect for nivolumab after it's stopped and removing the 2-year treatment stopping rule (see issue 4). This estimate does not include the commercial arrangement for erlotinib because this is confidential and cannot be reported here. Estimates that include this commercial arrangement would be higher than those reported above. The cost-effectiveness estimates for nivolumab vs. nintedanib plus docetaxel are unknown.

2.5 Nivolumab meets the end-of-life criteria (see Nivolumab for previously treated non-squamous non-small-cell lung cancer). The updated data support this conclusion from TA484.

2.6 Nivolumab is considered to be innovative and a step-change in managing non-squamous NSCLC because of its novel mechanism of action, which is associated with fewer adverse reactions than the currently available treatment options. The committee concluded that there were no additional benefits in health-related quality of life that had not been already captured in the QALY calculations.

2.7 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Comparator

Questions for engagement	1. Is nintedanib plus docetaxel used in clinical practice in the NHS in England to treat people with non-squamous non-small cell lung cancer and adenocarcinoma? a. Approximately what proportion of people would have nintedanib plus docetaxel in clinical practice?
Background/description of issue	**Original appraisal TA484** • In the original appraisal the committee heard from clinical experts that around 70% of people with non-squamous NSCLC have adenocarcinoma, for which nintedanib plus docetaxel is a recommended treatment option. It noted that 90% of patients had adenocarcinoma in the full population of CheckMate 057. It understood that nintedanib plus docetaxel is associated with high levels of toxicity and only those able to tolerate 4 cycles of docetaxel were likely to have nintedanib. Despite this, the committee considered nintedanib plus docetaxel to be a relevant comparator. • The most plausible ICER for nivolumab vs. nintedanib plus docetaxel was over £100,000 per QALY gained (exact ICERs are confidential and cannot be reported because this includes commercial discounts for nivolumab and nintedanib). The committee noted considerable uncertainty in the clinical and cost-effectiveness for this comparison, and concluded that nivolumab had plausible potential to be cost effective in the subgroup of patients whose

	tumours were PD-L1 positive when further long-term data are collected for comparison with nintedanib plus docetaxel. • BSC was also considered to be relevant, but no cost-effectiveness results were presented comparing nivolumab with BSC, therefore the committee could not make any recommendations. **CDF review** **The company** do not report cost-effectiveness results comparing nivolumab with nintedanib plus docetaxel because it considers docetaxel alone to be the most appropriate comparator. Clinical advice to **the ERG** supports the company's view that nintedanib plus docetaxel is not commonly used to treat non-squamous NCSLC. **The technical team** is concerned that nivolumab may not be a cost-effective treatment option for people with non-squamous NSCLC and PD-L1≥1% who are eligible for treatment with nintedanib plus docetaxel.
Why this issue is important	The cost-effectiveness estimates comparing nivolumab with nintedanib plus docetaxel are unknown.
Technical team preliminary judgement and rationale	The technical team considers that nintedanib plus docetaxel may be a relevant comparator for people with non-squamous non-small cell lung cancer and adenocarcinoma.

Issue 2 – Extrapolation of overall survival and progression-free survival

Questions for engagement	2. For the PD-L1 ≥1% subgroup, what is the most appropriate extrapolation method for overall survival? a. In clinical practice, approximately what proportion of people (who are treated with nivolumab for 2 years) would you expect to survive at 10, 15 and 20 years? 3. For the PD-L1 ≥1% subgroup, what is the most appropriate extrapolation method for progression-free survival?
Background/description of issue	**<u>Original appraisal TA484</u>** • In the original appraisal, the committee's preferred extrapolations for OS and PFS were hybrid exponential models using the 3-year Kaplan-Maier data from CheckMate 057. For the full population, the committee accepted the ERG's approach: ➢ for OS, the nivolumab and docetaxel curves crossed at around 7 months ➢ the ERG noted that the mortality hazard over time differed for patients who had nivolumab after disease progression and those who did not ➢ the ERG calculated the hazards of both nivolumab subgroups (with and without post-progression treatment) after around 7 months ➢ the ERG noted that the long-term hazards in these nivolumab subgroups were similar, and that most of the difference in survival occurred before 10 months; therefore, it used an 8-month 'break point' to define the timepoint from which the exponential curves should be fitted to the data ➢ in the cost-effectiveness model, the ERG used Kaplan-Meier data for the first 18 months, then applied the exponential curves afterwards, in a mixed approach assuming that 25% of people would have nivolumab as a post-progression treatment. • The DSU explained that in implementing the ERG's approach, the company did the following: ➢ For the full population, it calculated an exponential curve using survival data from 8 months onwards, then in the cost-effectiveness model it used the Kaplan-Meier data for the first 3 years followed by the exponential curve.

	➢ For the PD-L1≥1% subgroup, it used a similar method but used a 27 month 'break point', then in the cost-effectiveness model used Kaplan-Meier data for the first 27 months followed by the exponential curve. The committee was aware of uncertainty in this extrapolated survival, because beyond 27 months only a small number of patients remained at risk. • The committee accepted corrections from the DSU to cap PFS to OS when the 2 curves cross **CDF review** **The company** prefers to use a single lognormal curve to model OS, and a spline normal 1 knot curve for PFS, fitted to the updated 5-year Kaplan-Meier data (see figures 3 and 4). The company advised that the TA484 committee's preferred method for extrapolating OS and PFS (using Kaplan-Meier data followed by an exponential curve) does not produce a good fit to the 5-year data for the full ITT population or the PD-L1≥1% subgroup (see figure 4 in company's clarification response). **The ERG** noted that the survival data from CheckMate 057 are now relatively mature. It advised that some of the company's alternative survival curves had implausible tails, predicting mortality hazards that rapidly fall below background mortality, and others are clearly a poor fit to the Kaplan-Meier data from CheckMate 057. However, the choice of distribution from the remaining plausible options, including the company's base-case curves, does not have a large impact on cost-effectiveness results. As it is not possible to robustly differentiate between the plausible distributions, the ERG considers that the company's preferred OS and PFS extrapolations are adequate for decision making. **The technical team** agrees that the TA484 committee's preferred hybrid exponential extrapolation does not provide a good fit to the updated survival data for the PD-L1≥1% subgroup. It notes that there are other plausible extrapolations, but understands it is difficult to robustly differentiate between these and the company's preferred estimates. The technical team notes that some uncertainty regarding the extrapolation of OS and PFS may remain, because: • Like in TA484, the company has not produced cost-effectiveness results using the TA484 committee's preferred ERG approach for extrapolating OS, which split the nivolumab arm

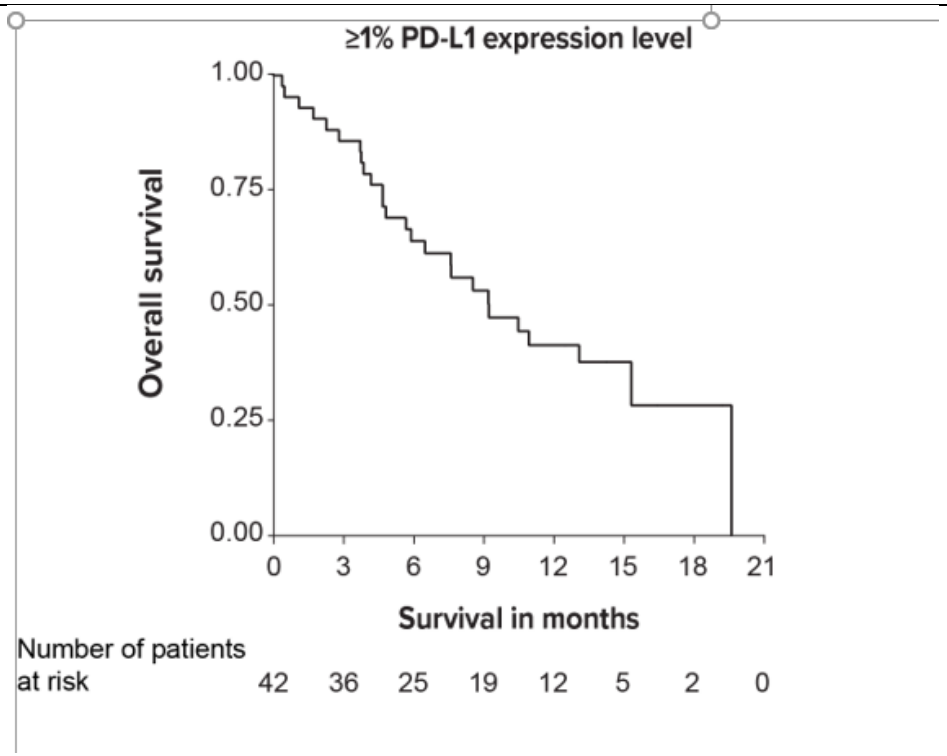
into 2 subgroups based on post-progression treatment, estimate long-term survival separately for each subgroup, and apply in the cost-effectiveness model after 18 months.

- The only hybrid model explored for PFS was the company's exponential model from TA484.

Figure 1. Updated 5-year Kaplan-Meier data from CheckMate 057 for overall survival in PD-L1≥1% subgroup

Data source: figure 8 from company submission

Figure 2 SACT data for PD-L1≥1%



Data source: figure 12 from company submission

Figure 3 Updated OS from PD-L1≥1% subgroup of company preferred extrapolation (5-year data and lognormal curve)

	 Data source: figure 24 from company submission **Figure 4 Updated PFS from PD-L1≥1% subgroup of company preferred extrapolation (5-year data and spline normal 1 knot curve)**

	 Data source: figure 27 from company submission
Why this issue is important	The company's preferred extrapolation method predicts that around [redacted] of people with PD-L1≥1% who had nivolumab for 2 years will survive for 20 years. It predicts a mean OS in the nivolumab arm of [redacted] months in the PD-L1≥1% subgroup and [redacted] months in the docetaxel arm. Using other plausible survival extrapolations alone does not have a large impact on the cost-effectiveness results. However, when combined with the cumulative impact of changing the extrapolations alongside other plausible assumptions (for utility values [see issue 3] and the duration of treatment effect after nivolumab is stopped [see issue 4]), the choice of extrapolation could become a more important decision.

Technical team preliminary judgement and rationale	The company's extrapolations fitted to the updated 5-year OS and PFS data from CheckMate 057 are plausible, but so are some alternative distributions. The technical team notes that there are still some uncertainties regarding the OS and PFS estimates, but these relate to reproducing the TA484 committee's preferred approached. If the company's extrapolations fitted to the new 5-year data are acceptable, then these uncertainties may be less important for decision making.

Issue 3 – Utility values

Questions for engagement	4. Should the TA484 committee's preferred post-progression utility value (0.569) be used?
Background/description of issue	**Original appraisal TA484** • In the original appraisal, the committee's preferred utility values were 0.713 for progression-free health state and 0.569 for the progressed disease health state. • The committee understood that EQ-5D values were available from CheckMate 057 but the post-progression values were likely to be influenced by selection bias; therefore, its preferred utility for progressed disease was the mid-point between the ERG's (0.480) and company's (0.657) preferred values. **CDF review** **The company** used a post-progression health state utility of 0.688 from updated CheckMate 057 data. **The ERG** explained that the company does not provide justification or new evidence to support using this post-progression value, rather than the TA484 committee's preferred utility value (0.569). **The technical team** is concerned that utility values from updated CheckMate 057 data are influenced by same selection bias that was present in the original data. If this is the case, the company's preferred utility for the post-progression health state is likely to be an overestimate.
Why this issue is important	The company's base-case ICER for the PD-L1≥1% population increases from £33,191 to £34,940 per QALY gained when the TA484 committee's preferred utility values are used.
Technical team preliminary judgement and rationale	The technical team prefers to use previously accepted utility values from TA484, because new evidence has not been presented to justify changing the committee's preference. Also, the updated data from CheckMate 057 are likely to be influenced by the same type of selection bias as the original data.

Issue 4 – Duration of treatment effect after nivolumab is stopped & stopping rule

Questions for engagement	5. Should the TA484 committee's preferred treatment effect duration be used (i.e. the treatment benefit of nivolumab is maintained for 3 years after treatment is stopped)? a. If nivolumab is given for 2 years and then stopped, is it clinically plausible that its treatment benefit continues for a lifetime? 6. Is a 2-year stopping rule appropriate?
Background/description of issue	**<u>Original appraisal TA484</u>** • In the original appraisal, the committee noted that it was biologically plausible for nivolumab's treatment effect to continue after treatment had stopped, but the exact duration was uncertain. • The committee agreed that a 2-year stopping rule should be applied in the economic model. However, CheckMate 057 study protocol did not include a maximum duration of treatment, therefore the clinical evidence in the economic model was based on patients that could continue to receive nivolumab after 2 years. • The committee considered it plausible that after stopping treatment at 2 years (stopping rule), nivolumab's treatment effect was uncertain but could last for up to 3 additional years. • The DSU explained that the company had applied the committee's accepted 3-year continued treatment effect for nivolumab to OS, but not PFS. The DSU preferred to be consistent and assume that after 3-years, patients in the PFS health state moved to progressed disease at the same rate as the docetaxel arm. • The committee accepted corrections from the DSU to apply the docetaxel hazard rate to the nivolumab arm after the committee's preferred 3-year duration of treatment effect for PFS as well as OS • It also heard from the ERG that the way in which patients are censored in Checkmate 003 means that the long-term survival profile beyond 4 years is obscured. This is because the number of patients that remain in the trial is too small beyond this time point to detect the risk of an event, not because there is no risk of an event.

- The committee noted that the company had an ongoing study (CheckMate 153) investigating the effect of a 1-year maximum treatment duration which could substantiate whether a stopping rule is appropriate.

CDF review

The company prefers to assume that nivolumab's effectiveness lasts for a lifetime, even if treatment is stopped at 2 years. The company suggests this is supported by:

- 5-year data from CheckMate 057 that shows a long-term OS benefit for nivolumab, even though only [redacted] are still having nivolumab after 5 years
- 6-year data from CheckMate 003 (included n=37 with squamous or non-squamous NSCLC) that shows:
  - a long-term OS benefit for nivolumab after it was stopped at 1.8 years
  - 12 (75%) of the 5-year survivors who had no subsequent therapy, were still alive at 5 years and were progression free
  - long-term survival on the nivolumab arms of CheckMate 057 and CheckMate 003 are very similar, despite differences in duration of therapy (see table 1)

Table 1: Overall survival results

	Proportion alive at each year (%, 95% confidence interval)					
Data source	**1**	**2**	**3**	**4**	**5**	**6**
CheckMate 057 full population† (n=292)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 057 PD-L1≥1% (n=122)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SACT data for PD-L1≥1% (n=43)	43 (28 to 58)	-	-	-	-	-
Company preferred analysis for PD-L1≥1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CheckMate 003 (n=122)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* values determined by technical team using the 5-year Kaplan-Meier data in the ERG-corrected model

† [redacted] and [redacted] were on nivolumab at 2, 3 and 5 years (see table 6 in ERG report)

¥ values determined by technical team using the ERG-corrected model

Data source: Tables 8 and 9 clarification response and figure 9 in company submission

The ERG explained that the evidence from the CheckMate 057 and CheckMate 003 trials does not fully discount the possibility of a continued treatment effect after nivolumab is stopped, and notes that the duration of any continued treatment effect is unknown. In addition, as patients randomised to the docetaxel arm of the CheckMate 057 trial could cross over to receive nivolumab on progression, it is not possible to determine the mortality and disease progression rates that should be used once any benefits from having nivolumab have ended.

The ERG considers that the following factors are important when considering how to model the long-term effectiveness of nivolumab:

- the inherent uncertainty around the continued treatment effect after nivolumab is stopped
- a continued treatment effect is likely to only affect a small proportion of patients
- choice between the selection of OS and PFS extrapolations considered by the company has little effect on cost effectiveness results.

Because of these factors, the ERG suggests any assumptions about a continued treatment effect would be arbitrary, and any plausible changes are unlikely to have a large impact on the cost-effectiveness results.

The technical team is concerned that there is no evidence to support a lifetime treatment effect after nivolumab is stopped at 2 years. It notes that data from the SACT database of 43 patients with PD-L1 positive disease who were treated with nivolumab for 2 years as part of the CDF shows a median overall survival of 9.2 months with 43% (95% confidence interval 28 to 58%) surviving at 1 year and only 3 people remaining at risk after 18 months.

It also notes that data from CheckMate 003 may be limited because:

	• it included a mixed population of people with squamous and non-squamous NSCLC (n=74/129), of which only 37 had 3mg/kg of nivolumab • data censoring obscured long-term survival • overall survival was lower compared with the PD-L1≥1% subgroup of CheckMate 057 (see table 1) The technical highlight that for PFS, it appears that the company's model does not apply the docetaxel hazard rate to the nivolumab arm after the committee's preferred 3-year duration of treatment effect, despite this DSU correction being accepted by the committee in TA484. The technical team also note that no further evidence for the stopping rule from CheckMate 153 has been submitted.
Why this issue is important	Cost-effectiveness results increase when using the committee's preferred 3-year duration of continued nivolumab treatment effect and when removing the 2-year stopping rule (see table 2).
Technical team preliminary judgement and rationale	The technical team prefers to use the previously accepted 3-year duration of treatment effect for nivolumab after it is stopped. However, it recognises that there is uncertainty in determining the most appropriate assumption about what happens to the treatment effect when treatment has stopped but assuming a lifelong effect is likely to underestimate cost-effectiveness results. Given the lack of evidence, the technical team consider it is uncertain if the 2-year stopping rule remains appropriate.

4. Issues for information

Tables 2 to 4 are provided to stakeholders for information only and are not included in the technical report comments table provided.

Table 2: Technical team preferred assumptions and impact on the cost-effectiveness estimate for nivolumab vs. docetaxel for PD-L1≥1%

Alteration	Technical team rationale	ICER	Change from base case
Company assumptions for PD-L1≥1%	**–**	**£33,191**	**-**
1. Alternative extrapolations of OS and PFS	Alternative extrapolations may also plausible (see issue 2)	Various plausible alternatives but minimal ICER impact likely	
2. Committee's preferred utility from TA484	This value was previously accepted in TA484 (see issue 3)	£34,940	+£1,749
3. 3-year continued treatment effect for nivolumab	This value was previously accepted in TA484 (see issue 4)	£43,270	+£10,079
4. Remove 2-year stopping rule for nivolumab	A 2-year stopping rule may not be appropriate (see issue 4)	£47,591	+£14,400
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate (2 to 4 above)	**–**	**£60,321***	**+£27,130**
*ICER run by the technical team using the ERG's corrected model			

Table 3: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate on PD-L1≥1% subgroup
Change of dosing schedule	In the original appraisal, dosing was weight based (3mg/kg every 2 weeks) but this has since changed in the summary of product characteristics to a flat dose of 240mg every 2 weeks. The company assume that this dose will have equivalent clinical effectiveness.	Reversing this change in dosing regimen decreases the company preferred ICER to £30,048 per QALY gained.
[redacted]	[redacted]	[redacted]

Table 4: Other issues for information

Issue	Comments
Subgroup analyses by PD-L1 expression	The Managed Access Agreement for TA484 states subgroup analyses by PD-L1 expression level will be undertaken by 1%, 5% and 10% expression levels. The subgroup analyses and associated cost-effectiveness estimates will be provided to NICE as part of the evidence submission when the guidance is reviewed. The company submitted evidence for the full population independent of PD-L1 status and by PD-L1 status ≥1% and ≤1%). For the present CDF review, the PD-L1 ≥1% subgroup is appropriate because it reflects the recommendations in TA484.
Innovation	The company considers the drug to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equalities issues have been identified by the company, consultees and their nominated clinical experts and patient experts.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for treating previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484) [ID1572]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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Deadline for comments: **5pm** on **Monday 17 February 2020**

Thank you for your time.

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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol Myers Squibb Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Comparator	
1. Is nintedanib plus docetaxel used in clinical practice in the NHS in England to treat people with non-squamous non-small cell lung cancer and adenocarcinoma? a. Approximately what proportion of people would have nintedanib plus docetaxel in clinical practice?	• We have been advised by UK clinicians that since IO therapies have been recommended in 2L NSCLC, nintedanib has rarely been used. • In the appraisal of atezolizumab in 2L NSCLC [TA520] published in May 2018, it states "At the third committee meeting, the Cancer Drugs Fund clinical lead and the clinical expert explained that docetaxel and nintedanib plus docetaxel (for the adenocarcinoma population only) are considered relevant treatments only for PD-L1-negative disease. **Comments received at consultation suggested that nintedanib plus docetaxel is used only for a small number of people in clinical practice, which the committee accepted"** • We therefore do not consider nintedanib plus docetaxel a relevant comparator

Issue 2: Extrapolation of overall survival and progression-free survival	
2. For the PD-L1 ≥1% subgroup, what is the most appropriate extrapolation method for overall survival?	• There will always be some uncertainty around survival extrapolation, however the additional data now available mean that is reduced. • In the Company Submission, the lognormal was used in the base case extrapolation due to the AIC/BIC statistics, although we acknowledged that it didn't provide a really good fit to the middle section or the tail of the nivolumab arm, and therefore potentially leads to underestimation of long-term survival. • Alternative models, such as spline 3-knot hazard were explored but did not provide good statistical fit to the docetaxel data and used only in a scenario analysis for nivolumab and resulted in a lower ICER. • The ERG concluded that the company's preferred OS and PFS extrapolations are adequate for decision making and that choice of curve has minimal impact on ICERs.
a. In clinical practice, approximately what proportion of people (who are treated with nivolumab for 2 years) would you expect to survive at 10, 15 and 20 years?	• Clinical expert to provide to NICE.
3. For the PD-L1 ≥1% subgroup, what is the most appropriate extrapolation method for progression-free survival?	• Spline normal 1 knot distribution used in the base case based on good visual fit to both treatment arms. • Spline normal 1 knot distribution also provided best statistical fit (based on AIC and BIC) when compared to other plausible distributions such as the spline hazard 1 knot. However, the impact on the ICER of the different distributions was minimal. • Standard parametric distributions were also considered but none were a good fit to both treatment arms, and in particular were a poor fit to the nivolumab arm.
Issue 3: Utility values	

4. Should the TA484 committee's preferred post-progression utility value (0.569) be used?	• In line with the NICE reference case, for the original submission BMS provided utility values based on EQ-5D collected in the CheckMate-057 trial. • The ERG considered that these utilities were too high and suggested an approach using utilities from van den Hout 2006, a Dutch study that assessed alternative palliative radiotherapy delivery models for patients with NSCLC and was thus in a different patient population. • The ERG considered that in reality, the utilities for each health state are probably in between those proposed by BMS and the ERG. • BMS consider that the committee-preferred post-progression utility value is somewhat arbitrary, and it is preferable to base model health-state utility inputs on recent EQ-5D data collected in the pivotal trial, rather than assumptions.
Issue 4: Duration of treatment effect after nivolumab is stopped & stopping rule	
5. Should the TA484 committee's preferred treatment effect duration be used (i.e. the treatment benefit of nivolumab is maintained for 3 years after treatment is stopped)? a. If nivolumab is given for 2 years, is it clinically plausible that its treatment benefit continues for a lifetime?	• 5-year follow-up confirms a long-term OS benefit for patients treated with nivolumab, even though patients in the docetaxel arm had switched over to nivolumab as subsequent treatment. • Only [redacted] of PD-L1 +ve patients remained on treatment after 5-years in CheckMate 057, but a survival rate of [redacted] at 5-year follow-up suggests there is a durable treatment effect lasting at least 3-years. • As shown in the submission, only about 50% of patients alive remain on treatment at 2 years in CheckMate 057 but there is still a clear benefit for the proportion not on treatment. By 60 months, only one-quarter of patients who are alive remain on treatment. The other three-quarters of patients continue to show long-term benefit from the earlier treatment with nivolumab. • Using a 3-year waning of treatment effect results in a clinically implausible (kinked) curve and is therefore not appropriate, as discussed in the technical engagement teleconference. • Notably, in CheckMate 003, nivolumab treatment was stopped after 96 weeks (1.8 years). Long-term survival of nivolumab in CheckMate 057 and CheckMate 003 is very similar despite differences in duration of therapy. 75% of the 5-year survivors (12/16) in CheckMate 003 received no subsequent therapy and were without evidence of progressive disease at the last follow-up. This confirms that implementation of a 2-year

stop is practical and demonstrates long-term durable treatment effect of nivolumab with a similar stopping rule to that agreed for nivolumab for the UK.

- Table 1 presents the incremental cost-effectiveness ratios for both All-Comers and PD-L1≥1% populations, based on the settings presented in the "Additional analyses (treatment waning) requested by NICE generated using discounted price of nivolumab" in the Technical Engagement Papers.

Table 1. Cost-effectiveness results: Duration of treatment benefit of 3-years following 2-year stopping rule with company-preferred utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
All-Comers							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£26,924	0.76	0.52	£51,856
PD-L1≥1%							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£39,030	1.39	0.90	£43,270

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

- Table 2 presents the incremental cost-effectiveness ratios for both All-Comers and PD-L1≥1% populations, based on the settings presented in the "Additional analyses (treatment waning) requested by NICE generated using discounted price of nivolumab" document in the Technical Engagement Papers. These ICERs also implement the committee-preferred utility value for progressed-disease.

Table 2. Cost-effectiveness results: Duration of treatment benefit of 3-years following 2-year stopping rule with committee-preferred utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
All-Comers							

Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£26,924	0.76	0.51	£52,791
PD-L1≥1%							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£39,030	1.39	0.88	£44,547

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

- As currently implemented in the model, after 3-years following the stopping rule, all patients switch instantly to the same hazard of death as patients in the docetaxel arm leading to an abrupt and implausible shift in the survival curve generated in the model.
- Exploratory analyses have added to the model to include an adjustment to the proportion of patients switching to docetaxel hazard after this 3-year period in order to increase the model's ability to reflect patients who continue to benefit for a longer-period of time, as seen in both CheckMate 057 and 003.
- Scenarios are included in Table 3 to Table 4 for the All-Comers population and Table 5 to Table 6 for the PD-L1≥1% population and show the impact of including a proportion of patients likely to continue to benefit from treatment for longer than 3-years following the 2-year stopping rule.
- A range of scenarios are presented, potentially the most relevant being the scenario in which 44% of patients continue to benefit from treatment beyond 3-years, based on the proportion of patients experiencing complete response, partial response, or stable disease in the CheckMate-057 clinical trial (Borghaei et al., 2015).
- Cells shaded green indicate ICERs below the end-of-life threshold of £50,000 per QALY.

Table 3. Cost-effectiveness results: All-Comers Population (Company-Preferred Utility)

Proportion of patients who continue to benefit	Duration of additional benefit after 3-years			
	3-Years	5-Years	10-Years	20-Years
0%	£51,856	£51,856	£51,856	£51,856
25%	£50,384	£49,986	£49,636	£49,579

44%	£49,243	£48,501	£47,814	£47,694
75%	£47,364	£45,991	£44,612	£44,340
100%	£45,840	£43,937	£41,868	£41,420

Table 4. Cost-effectiveness results: All-Comers Population (Committee-Preferred Utility)

Proportion of patients who continue to benefit	Duration of additional benefit after 3-years			
	3-Years	5-Years	10-Years	20-Years
0%	£52,791	£52,791	£52,791	£52,791
25%	£51,326	£50,912	£50,548	£50,489
44%	£50,201	£49,428	£48,714	£48,589
75%	£48,382	£46,948	£45,509	£45,224
100%	£46,935	£44,972	£42,800	£42,331

Table 5. Cost-effectiveness results: PD-L1≥1% Population (Company-Preferred Utility)

Proportion of patients who continue to benefit	Duration of additional benefit after 3-years			
	3-Years	5-Years	10-Years	20-Years
0%	£43,270	£43,270	£43,270	£43,270
25%	£41,875	£41,476	£41,123	£41,064
44%	£40,792	£40,043	£39,913	£39,178
75%	£38,991	£37,659	£36,152	£35,809
100%	£37,513	£35,694	£33,644	£33,191

Table 6. Cost-effectiveness results: PD-L1≥1% Population (Committee-Preferred Utility)

Proportion of patients who continue to benefit	Duration of additional benefit after 3-years			
	3-Years	5-Years	10-Years	20-Years
0%	£44,547	£44,547	£44,547	£44,547
25%	£43,177	£42,751	£42,374	£42,312
44%	£42,138	£41,347	£40,566	£40,422
75%	£40,447	£39,112	£37,527	£37,156
100%	£39,090	£37,331	£35,347	£34,940

6. Is a 2-year stopping rule for nivolumab appropriate?	• Yes, a 2 year stop is in our opinion appropriate. • A two-year stopping rule has been consistently accepted in other TAs for IO therapies, and was supported by NHSE • In TA520 (atezolizumab in 2L NSCLC) the company argued that it would prefer to have no stop of treatment. However, clinicians were concerned for continuing treatment longer. In the FAD, "The committee further noted that NICE guidance for other immunotherapies for previously treated NSCLC (pembrolizumab and nivolumab) include 2-year stopping rules. It concluded that it would prefer a 2-year stopping rule in the economic model." • Only a small proportion of patients remain on treatment in the clinical trials after 2-years (11.8% on nivolumab treatment at 2-years in Checkmate 057). • As described above, the CheckMate 003 trial confirms that implementation of a 2-year stop is practical and demonstrates long-term durable treatment effect of nivolumab with a similar stopping rule to that agreed for nivolumab for the UK.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for treating previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484) [ID1572]

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Comparator	
1. Is nintedanib plus docetaxel used in clinical practice in the NHS in England to treat people with non-squamous non-small cell lung cancer and adenocarcinoma? a. Approximately what proportion of people would have nintedanib plus docetaxel in clinical practice?	The combination of Docetaxel Nintendinib is used in England, the introduction of immunotherapy is pushing the use of the combination into the third line setting so it is less widely prescribed and the overall proportion of NSCLC patients receiving this treatment is probably now less than 5%.
Issue 2: Extrapolation of overall survival and progression-free survival	
2. For the PD-L1 ≥1% subgroup, what is the most appropriate extrapolation method for overall survival? a. In clinical practice, approximately what proportion of people (who are treated with nivolumab for 2 years) would you expect to survive at 10, 15 and 20 years?	Pooled analysis for the long term (ie 5yr) survival data suggests up to 15 % for those receiving nivolumab treatment. Therefore, we would estimate the 10 + year survival to be around 5%.
3. For the PD-L1 ≥1% subgroup, what is the most appropriate extrapolation method for progression-free survival?	
Issue 3: Utility values	
4. Should the TA484 committee's preferred post-progression utility value (0.569) be used?	Yes
Issue 4: Duration of treatment effect after nivolumab is stopped & stopping rule	

5. Should the TA484 committee's preferred treatment effect duration be used (i.e. the treatment benefit of nivolumab is maintained for 3 years after treatment is stopped)? a. If nivolumab is given for 2 years, is it clinically plausible that its treatment benefit continues for a lifetime?	It is clinically plausible that the immune system could be 'reset' and hence benefit from treatment be maintained for years after the nivolumab is stopped at 2 years.
6. Is a 2-year stopping rule for nivolumab appropriate?	It is not an evidence based recommendation and we are awaiting outcomes from clinical trials that are addressing the optimal duration of these treatments

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Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol Myers Squibb Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

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ERG comment	• Clinical advice to the ERG is that nintedanib+docetaxel is not commonly used in NHS clinical practice

Issue 2: Extrapolation of overall survival and progression-free survival	
2. For the PD-L1 ≥1% subgroup, what is the most appropriate extrapolation method for overall survival?	• There will always be some uncertainty around survival extrapolation, however the additional data now available mean that is reduced. • In the Company Submission, the lognormal was used in the base case extrapolation due to the AIC/BIC statistics, although we acknowledged that it didn't provide a really good fit to the middle section or the tail of the nivolumab arm, and therefore potentially leads to underestimation of long-term survival. • Alternative models, such as spline 3-knot hazard were explored but did not provide good statistical fit to the docetaxel data and used only in a scenario analysis for nivolumab and resulted in a lower ICER. • The ERG concluded that the company's preferred OS and PFS extrapolations are adequate for decision making and that choice of curve has minimal impact on ICERs.
ERG comment	• No further comments
a. In clinical practice, approximately what proportion of people (who are treated with nivolumab for 2 years) would you expect to survive at 10, 15 and 20 years?	• Clinical expert to provide to NICE.
ERG comment	• No comment
3. For the PD-L1 ≥1% subgroup, what is the most appropriate extrapolation method for progression-free survival?	• Spline normal 1 knot distribution used in the base case based on good visual fit to both treatment arms. • Spline normal 1 knot distribution also provided best statistical fit (based on AIC and BIC) when compared to other plausible distributions such as the spline hazard 1 knot. However, the impact on the ICER of the different distributions was minimal. • Standard parametric distributions were also considered but none were a good fit to both treatment arms, and in particular were a poor fit to the nivolumab arm.
ERG comment	• No further comments
Issue 3: Utility values	

4. Should the TA484 committee's preferred post-progression utility value (0.569) be used?	• In line with the NICE reference case, for the original submission BMS provided utility values based on EQ-5D collected in the CheckMate-057 trial. • The ERG considered that these utilities were too high and suggested an approach using utilities from van den Hout 2006, a Dutch study that assessed alternative palliative radiotherapy delivery models for patients with NSCLC and was thus in a different patient population. • The ERG considered that in reality, the utilities for each health state are probably in between those proposed by BMS and the ERG. • BMS consider that the committee-preferred post-progression utility value is somewhat arbitrary, and it is preferable to base model health-state utility inputs on recent EQ-5D data collected in the pivotal trial, rather than assumptions.
ERG comment	• For clarity, it was the NICE AC, not the ERG, who reached the conclusion that the most appropriate utility values to use in TA484 probably lay between the van den Hout values and the BMS values • NICE's expectation in relation to the CDF Review CS are outlined within the Terms of Engagement document. The Terms of Engagement document includes details of the NICE AC's preferred utility values. Whilst the terms are not binding, the ERG highlights that the company has not provided any new evidence to support deviating from the NICE AC preferred utility values
Issue 4: Duration of treatment effect after nivolumab is stopped & stopping rule	
5. Should the TA484 committee's preferred treatment effect duration be used (i.e. the treatment benefit of nivolumab is maintained for 3 years after treatment is stopped)? a. If nivolumab is given for 2 years, is it clinically plausible that its treatment benefit continues for a lifetime?	• 5-year follow-up confirms a long-term OS benefit for patients treated with nivolumab, even though patients in the docetaxel arm had switched over to nivolumab as subsequent treatment. • Only [redacted] of PD-L1 +ve patients remained on treatment after 5-years in CheckMate 057, but a survival rate of [redacted] at 5-year follow-up suggests there is a durable treatment effect lasting at least 3-years. • As shown in the submission, only about 50% of patients alive remain on treatment at 2 years in CheckMate 057 but there is still a clear benefit for the proportion not on treatment. By 60 months, only one-quarter of patients who are alive remain on treatment. The other three-quarters of patients continue to show long-term benefit from the earlier treatment with nivolumab. • Using a 3-year waning of treatment effect results in a clinically implausible (kinked) curve and is therefore not appropriate, as discussed in the technical engagement teleconference. • Notably, in CheckMate 003, nivolumab treatment was stopped after 96 weeks (1.8 years). Long-term survival of nivolumab in CheckMate 057 and CheckMate 003 is very similar despite differences in duration of therapy. 75% of the

5-year survivors (12/16) in CheckMate 003 received no subsequent therapy and were without evidence of progressive disease at the last follow-up. This confirms that implementation of a 2-year stop is practical and demonstrates long-term durable treatment effect of nivolumab with a similar stopping rule to that agreed for nivolumab for the UK.

- Table 1 presents the incremental cost-effectiveness ratios for both All-Comers and PD-L1≥1% populations, based on the settings presented in the "Additional analyses (treatment waning) requested by NICE generated using discounted price of nivolumab" in the Technical Engagement Papers.

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PD-L1≥1%							
Nivolumab	[redacted]	[redacted]	[redacted]				
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ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

- Table 2 presents the incremental cost-effectiveness ratios for both All-Comers and PD-L1≥1% populations, based on the settings presented in the "Additional analyses (treatment waning) requested by NICE generated using discounted price of nivolumab" document in the Technical Engagement Papers. These ICERs also implement the committee-preferred utility value for progressed-disease.

Table 2. Cost-effectiveness results: Duration of treatment benefit of 3-years following 2-year stopping rule with committee-preferred utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
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ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

- As currently implemented in the model, after 3-years following the stopping rule, all patients switch instantly to the same hazard of death as patients in the docetaxel arm leading to an abrupt and implausible shift in the survival curve generated in the model.
- Exploratory analyses have added to the model to include an adjustment to the proportion of patients switching to docetaxel hazard after this 3-year period in order to increase the model's ability to reflect patients who continue to benefit for a longer-period of time, as seen in both CheckMate 057 and 003.
- Scenarios are included in Table 3 to Table 4 for the All-Comers population and Table 5 to Table 6 for the PD-L1≥1% population and show the impact of including a proportion of patients likely to continue to benefit from treatment for longer than 3-years following the 2-year stopping rule.
- A range of scenarios are presented, potentially the most relevant being the scenario in which 44% of patients continue to benefit from treatment beyond 3-years, based on the proportion of patients experiencing complete response, partial response, or stable disease in the CheckMate-057 clinical trial (Borghaei et al., 2015).
- Cells shaded green indicate ICERs below the end-of-life threshold of £50,000 per QALY.

Table 3. Cost-effectiveness results: All-Comers Population (Company-Preferred Utility)

Proportion of patients who continue to benefit	**Duration of additional benefit after 3-years**			
	3-Years	5-Years	10-Years	20-Years
0%	£51,856	£51,856	£51,856	£51,856
25%	£50,384	£49,986	£49,636	£49,579
44%	£49,243	£48,501	£47,814	£47,694

75%	£47,364	£45,991	£44,612	£44,340
100%	£45,840	£43,937	£41,868	£41,420

Table 4. Cost-effectiveness results: All-Comers Population (Committee-Preferred Utility)

Proportion of patients who continue to benefit	Duration of additional benefit after 3-years			
	3-Years	5-Years	10-Years	20-Years
0%	£52,791	£52,791	£52,791	£52,791
25%	£51,326	£50,912	£50,548	£50,489
44%	£50,201	£49,428	£48,714	£48,589
75%	£48,382	£46,948	£45,509	£45,224
100%	£46,935	£44,972	£42,800	£42,331

Table 5. Cost-effectiveness results: PD-L1≥1% Population (Company-Preferred Utility)

Proportion of patients who continue to benefit	Duration of additional benefit after 3-years			
	3-Years	5-Years	10-Years	20-Years
0%	£43,270	£43,270	£43,270	£43,270
25%	£41,875	£41,476	£41,123	£41,064
44%	£40,792	£40,043	£39,913	£39,178
75%	£38,991	£37,659	£36,152	£35,809
100%	£37,513	£35,694	£33,644	£33,191

Table 6. Cost-effectiveness results: PD-L1≥1% Population (Committee-Preferred Utility)

Proportion of	Duration of additional benefit after 3-years

	patients who continue to benefit	3-Years	5-Years	10-Years	20-Years
	0%	£44,547	£44,547	£44,547	£44,547
	25%	£43,177	£42,751	£42,374	£42,312
	44%	£42,138	£41,347	£40,566	£40,422
	75%	£40,447	£39,112	£37,527	£37,156
	100%	£39,090	£37,331	£35,347	£34,940
ERG comment	• Please note that the ICER value of £39,913 (10yrs at 44%) in Table 5 should be £39,313 • The ERG highlights that, for all of the company's scenarios for the PD-L1≥1% population, the ICERs per QALY gained are all less that £50,000				
6. Is a 2-year stopping rule for nivolumab appropriate?	• Yes, a 2 year stop is in our opinion appropriate. • A two-year stopping rule has been consistently accepted in other TAs for IO therapies, and was supported by NHSE • In TA520 (atezolizumab in 2L NSCLC) the company argued that it would prefer to have no stop of treatment. However, clinicians were concerned for continuing treatment longer. In the FAD, "The committee further noted that NICE guidance for other immunotherapies for previously treated NSCLC (pembrolizumab and nivolumab) include 2-year stopping rules. It concluded that it would prefer a 2-year stopping rule in the economic model." • Only a small proportion of patients remain on treatment in the clinical trials after 2-years (11.8% on nivolumab treatment at 2-years in Checkmate 057). • As described above, the CheckMate 003 trial confirms that implementation of a 2-year stop is practical and demonstrates long-term durable treatment effect of nivolumab with a similar stopping rule to that agreed for nivolumab for the UK.				
ERG comment	• There is currently no robust evidence demonstrating the optimal duration of treatment with nivolumab for the population being considered in this CDF Review				