NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483) [ID1559]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483) [ID1559]

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. Roy Castle Lung Cancer Foundation
   b. 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. Addendum

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

7. **Technical engagement response** from Bristol Myers-Squibb Pharmaceuticals
   a. Response form
   b. Appendix A

   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 TA483

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

Document D

Company evidence submission for committee

Final

8 August 2019

File name	Version	Contains confidential information	Date
TA483 Nivolumab in 2L SQ NSCLC Document D_8 August 2019_redacted	1	No	8 August 2019

Contents

Tables and figures

Abbreviations

Term	Definition
ACD	Appraisal Consultation Document
ACM	Appraisal Committee Meeting
AIC	Akaike Information Criterion
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BMS	Bristol-Myers Squibb
CDF	Cancer Drugs Fund
CE	cost-effective
CI	confidence interval
CR	complete response
CrI	credible interval
DSU	Decision Support Unit
ERG	Evidence Review Group
Exp	exponential
FAD	Final Appraisal Determination
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IO	immuno-oncology
KM	Kaplan-Meier
LYG	life-year gained
NA	not available
NC	not calculated
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	non-small-cell lung cancer
OS	overall survival
PAS	patient access scheme
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
RCT	randomised controlled trial
SACT	systemic anticancer therapy
SD	stable disease
SEER	Surveillance, Epidemiology and End Results Program
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 squamous NSCLC in adults after chemotherapy, only if:
- Nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and
  - The conditions in the managed access agreement are followed
  - Based on the committee's preferred assumption, a 3-year data cut from CheckMate 017, and a new commercial access agreement, the committee noted an incremental cost-effectiveness ratio (ICER) of £50,014 per quality-adjusted life-year (QALY) compared with docetaxel for the full squamous NSCLC population, irrespective of programmed death-ligand 1 (PD-L1) status. This provided the plausible cost-effectiveness for a recommendation in the CDF.

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) on the potential appropriate survival extrapolation to use, particularly for overall survival (OS). BMS considered that a log-logistic model, 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 this 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 to existing chemotherapies.

In the first three appraisal committee meetings, the committee concluded that the ERG's approach was appropriate. However, in 2017, OS data from a 3-year database lock from CheckMate 017 and a 4-year database lock from CheckMate 003 were presented. These data were beginning to show the long-term survival benefit provided by nivolumab in this setting. In addition, NICE asked the Decision Support Unit (DSU) to review the available evidence and advise on the most appropriate approach. The DSU considered that an intermediate curve would be appropriate to use, and this was accepted by the appraisal committee. Once it was agreed that the ERG approach to OS extrapolation was too conservative and BMS proposed a commercial access agreement, the committee concluded that nivolumab in the second-line treatment of squamous NSCLC had the plausible potential to be cost-effective and recommended entry to the CDF.

As seen in the analysis presented in this document, the ERG and Committee were over-conservative. The new, long-term data demonstrate that nivolumab is cost-effective and should be funded through routine commissioning.

Table 1. Summary of initial NICE appraisal process for TA483

Step (date)	CheckMate 017 data presented/ considered	Key assumptions	Committee decisions/recommendations	BMS commercial offer
ACM 1: November 2015[2]			**ACD 1: issued December 2015[3]**	
BMS dossier submitted (August 2015)	12-month minimum follow-up All-comers	• OS: proportional hazards, log-logistic • PFS: non-proportional hazards, 2 knots hazard also used for treatment duration • Utility: based on EQ-5D in CheckMate 017 • Base-case ICER: £85,950[a]	• The committee did not recommend, concluding that: – Nivolumab is a clinically effective treatment option for previously treated squamous NSCLC – It was not possible to identify any subgroups for whom nivolumab would provide particular benefits – ERG's approach to extrapolating PFS was appropriate – ERG's modelling of OS was more appropriate for its decision-making – The most appropriate (utility) values would be between those presented by the company and those from the ERG – End of life met • Base-case ICER: between £109,000 and £129,000 per QALY (at list price)	All ICERs based on list price.
ERG report (October 2015)	12-month minimum follow-up	• OS: Kaplan-Meier data for 40 weeks, then exponential • PFS: non-proportional hazards, separate exponentials after 2.2 months • Treatment duration based on TTD • Utility: based on Nafees et al. (2008)[4] • Base-case ICER: £132,989		
ACM 2: February 2016[5]			**FAD withdrawn[6]**	
BMS response to ACD	18-month minimum follow-up All-comers	• Presented new evidence and revised base case – OS: log-logistic remained best fit and was validated vs. 4-year data from CheckMate 003, and with mortality cap – PFS: based on ERG approach – Demonstrated TTD and PFS virtually identical; based treatment duration on PFS • In scenario analysis: – 1- and 2-year stopping rules	• The committee did not recommend, based on: – ERG-preferred OS and PFS assumptions – Utility in between BMS and ERG – Most plausible ICER at least £140,000 • Appraisal suspended at appeal stage and FAD withdrawn unpublished	All ICERs based on list price. BMS requested to submit a PAS.

Step (date)	CheckMate 017 data presented/ considered	Key assumptions	Committee decisions/recommendations	BMS commercial offer
		– Alternative utility values • Base-case ICER: £91,870 • Scenarios: £62,000 to £94,000		
ERG response to BMS new data and analysis	18-month minimum follow-up	• ERG: – OS: stood by their previous analysis and validated vs. SEER not CheckMate 003 – Stood by using TTD for treatment duration – Utility proposed use of van den Hout et al. (2006)[7] for progressed disease state • Base-case ICER: £154,352		
ACM 3: August 2016[6]			**ACD 2: issued October 2016[8]**	
BMS submitted new PAS	18-month minimum follow-up All-comers	• BMS proposed simple discount PAS to apply to all indications, even those already approved as cost-effective at higher price – OS: 2-knot spline hazards (interim curve) – PFS: ERG approach – TTD: for treatment duration (ERG approach) – Utility: based on EQ-5D analysis of CheckMate 017 – Stopping rule • BMS base-case ICER with PAS: £66,100	• The committee did not recommend based on: – The ERG's modelling of OS using the exponential model was more appropriate for its decision-making (than the BMS base-case or interim approach) – Utility values between the ERG and BMS values most likely – It was unable to make recommendations based on a maximum treatment duration of nivolumab therapy (i.e., stopping rule) • Most plausible ICER at least £73,500 (ERG base case) • The committee invited BMS to submit a proposal for inclusion in the CDF, noting that: – It is plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression, and BMS should have presented analysis by PD-L1 threshold	All ICERs based on confidential simple PAS ([redacted]). BMS did not submit a CDF proposal for the PD-L1 subgroup but submitted new evidence for the whole population to address some uncertainties.

Step (date)	CheckMate 017 data presented/ considered	Key assumptions	Committee decisions/recommendations	BMS commercial offer
			– Nivolumab does not have the plausible potential to be cost-effective in the full licensed population but may in high PD-L1 expressers	
ACM 4: April 2017[9]				
DSU input sought by NICE		• The DSU explored extrapolation curves and the rationale for a stopping rule – After carefully reviewing the evidence, the DSU preferred to use the company's "intermediary" curve to extrapolate OS	• Development of the FAD paused to allow BMS and NHS England to have commercial discussions	Based on a new confidential simple PAS ([redacted]).
BMS response	3-year follow-up (plus 5-year from CheckMate 003)	• BMS accounted for DSU findings and provided updated submission based on the whole squamous population: – OS: log-logistic/intermediary curve – PFS: ERG preferred – Waning of treatment effect – Committee's preferred utility – Updated PAS – 2-year stopping rule (implemented for pembrolizumab in TA248 by this time) – Scenarios with "credit" for melanoma and renal cell carcinoma		
ACM 5: August 2017[10]			**FAD: issued September 2017 based on papers from ACM 4 and CDF proposal[11]**	
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 – PD-L1 status is not a good predictor of outcomes	• Nivolumab recommended for use within the CDF as an option for treating locally advanced or metastatic squamous NSCLC in adults after chemotherapy: – With a 2-year stopping rule • In the FAD, the following was noted[11]:	Based on confidential simple PAS [redacted]

Step (date)	CheckMate 017 data presented/ considered	Key assumptions	Committee decisions/recommendations	BMS commercial offer
			– The committee, noting the new evidence and the DSU's expert advice, concluded that the OS extrapolation was uncertain but the DSU's approach (intermediary, generalised gamma curve) was the most appropriate because the tail of the curve more closely reflected the likely continued treatment effect. – Intermediate utility values are most likely. – The committee considered comments on the second ACD that a 2-year stopping rule is acceptable to both patients and clinicians and would be implementable. The committee's concerns were eased by the assurances from NHS England and concluded that a 2-year stopping rule should be applied in the economic model. – Based on the available clinical evidence, it was plausible that, after stopping treatment at 2 years, nivolumab's treatment effect could last up to 3 years.	

ACD = Appraisal Consultation Document; ACM = Appraisal Committee Meeting; CDF = Cancer Drugs Fund; DSU = Decision Support Unit; ERG = Evidence Review Group; FAD = Final Appraisal Determination; ICER = incremental cost-effectiveness ratio; NSCLC = non-small-cell lung cancer; OS = overall survival; PAS = patient access scheme; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; QALY = quality-adjusted life-year; SEER = Surveillance, Epidemiology, and End Results; TTD = time to treatment discontinuation; VAT = value-added tax.

[a] All ICERs presented are cost per QALY for nivolumab vs. docetaxel.

In the 2 years since nivolumab for the second-line treatment of squamous NSCLC entered the CDF, additional database locks have occurred for both CheckMate 017 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.[12,13]

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 as noted under treatment costs, where the labelled dose of nivolumab has changed since CDF entry. In addition to the base case using the committee-preferred assumptions, 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 previously treated locally advanced or metastatic squamous non-small-cell lung cancer after prior chemotherapy.
Comparators	The most appropriate comparator was docetaxel.
Generalisability	The results of CheckMate 017 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 nivolumab showed better effectiveness in the subgroups in which PD-L1 expression was positive, but the results did not suggest a clinically significant difference according to PD-L1 expression. The committee reviewed cost-effectiveness evidence by PD-L1 expression. **The company are expected to submit evidence for the full population as well as by PD-L1 expression level (1%, 5%, and 10%) in the CDF review.**
Extrapolation of OS	The committee noted that the DSU's approach to extrapolate OS using the observed Kaplan-Meier followed by generalised gamma curve was the most appropriate because the tail of the curve more closely reflected the likely continued treatment effect. **It is anticipated that the committee's preferred approach to extrapolation of OS will remain, unless the company can demonstrate that additional data from the trial and SACT justify departure from this approach.** **Note: As detailed in the company response to the terms of engagement, the DSU's approach was to extrapolate OS using generalised gamma for the entire duration (not the observed Kaplan-Meier followed by generalised gamma).**
Extrapolation of PFS	Extrapolating PFS, using the observed Kaplan-Meier followed by exponential curve.
Utilities	A utility value of 0.693 in the progression-free health state was appropriate. A utility value of 0.509 in the progressed-disease health state was reasonable.

Area	Committee-preferred assumptions
Treatment duration	Not limiting docetaxel to a maximum of 4 cycles in the economic model was appropriate.
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	Nivolumab's treatment effect could last up to 3 years.
Treatment costs	Use distributions for body weights and surface areas and the average NHS costs for generic medicines (based on data from the Commercial Medicines Unit's Electronic Market Information Tool). **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; DSU = Decision Support Unit; 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's preferred assumptions remain unchanged.

Sources: NICE (2019)[1]; Bristol-Myers Squibb data on file (2019)[14]

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 the table.

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 any restriction(s) as described in the summary of product characteristics	Nivolumab as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.[15] This indication includes both squamous and non-squamous histologies.
Method of	Intravenous infusion. At the time of the original submission, dosing was

administration and dosage	weight-based (3 mg/kg Q2W). In 2018, dosing was changed to a flat dose of 240 mg Q2W. [redacted]
Additional tests or investigations	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)[15]; NICE (2017)[11]

D.5. Clinical effectiveness evidence

CheckMate 017 was the key study that provided evidence in support of nivolumab in squamous NSCLC (Table 4). Overall survival was the primary outcome in CheckMate 017; 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 017**
Study design	Phase 3, randomised, open-label study
Population	Adults (≥ 18 years) with advanced or metastatic squamous NSCLC after failure of prior platinum doublet-based chemotherapy
Intervention(s)	Nivolumab 3 mg/kg Q2W (n = 135)
Comparator(s)	Docetaxel 75 mg/m^2 Q3W (n = 137)
Outcomes collected that address committee's key uncertainties	**Overall survival** **Progression-free survival** **Time to treatment discontinuation** 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: Brahmer et al. (2015)[17]; NICE (2017)[18]

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[18]. 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).[19]

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 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)[20]; Public Health England (2019)[19]; NICE (2017)[18]

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 017 data from the preferred survival extrapolations, but by the time 3-year data from CheckMate 017 and 4-year

data from CheckMate 003 were available (with some patients followed for up to 4 and 5 years, respectively), it was clear that the ERG's preferred extrapolation severely underestimated OS, and observed survival rates were higher even than those in the company base case. This underestimation was confirmed during the CDF period, during which additional follow-up data from CheckMate 017 and CheckMate 003 were collected. Five-year OS in CheckMate 017 ([redacted]%) is [redacted] than that estimated by BMS (9.77%), [redacted] that estimated by the intermediary curve (6.08%), and [redacted] that estimated by the ERG (3.30%) at the time of the CDF recommendation.

Table 6. Comparison of current 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 017	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
CheckMate 003 (any histology)	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Model estimate for nivolumab overall survival	BMS log-logistic	42.34	23.53	16.08	12.17	9.77	8.16	4.90	3.26
	AC intermediary curve	43.31	22.56	13.53	8.82	6.08	4.37	1.51	0.55
	ERG exponential	42.22	23.25	11.79	6.23	3.30	1.74	0.14	0.01

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

Sources: Bristol-Myers Squibb data on file (2019)[21]; Antonia et al. (2019)[20] NICE (2017)[10]

Figure 1 and Figure 2 depict the committee's preferred OS and progression-free survival (PFS) extrapolations in CheckMate 017, respectively, versus that of BMS and the ERG, 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 017. As a result, updated survival analyses have been conducted to represent the long-term survival outcomes more accurately.

Figure 1. Overall survival committee-, ERG-, and BMS-preferred extrapolations versus 5-year data in CheckMate 017

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

Sources: Bristol-Myers Squibb data on file (2019)[21]; NICE (2015)[2]

Figure 2. Progression-free survival committee- and BMS-preferred extrapolations versus 5-year data in CheckMate 017

ERG = evidence review group; KM = Kaplan-Meier; PFS = progression-free survival.

Note: for PFS, the hybrid exponential is the appraisal committee and ERG-preferred curve.

Sources: Bristol-Myers Squibb data on file (2019)[21]; NICE (2015)[2]

Sections D.6.1 to D.6.4 present further details on results for key outcomes at the time of the original submission and at the 5-year database lock of CheckMate 017. These sections are followed by OS results from the 6-year database lock of CheckMate 003 (Section D.6.5) and the SACT data from the analysis (Section D.6.6).

D.6.1. Overall survival: 5-year database lock, CheckMate 017

The initial database lock for CheckMate 017 took place in December 2014. The median OS was 9.2 months (95% confidence interval [CI], 7.3-13.3 months) for the 135 patients in the nivolumab group versus 6.0 months (95% CI, 5.1-7.3 months) for the 137 patients in the docetaxel group (hazard ratio [HR], 0.59; 95% CI, 0.44-0.79; $P < 0.001$). The 1-year OS rate was 42% (95% CI, 34%-50%) with nivolumab versus 24% (95% CI, 17%-31%) with docetaxel.[17] 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).[21] The 5-year OS rate for the nivolumab group ([redacted]%; 95% CI, [redacted]) was at least [redacted] times that for the docetaxel group ([redacted]%; 95% CI, [redacted]) (Table 7).[21] 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 probably underestimated because of this.

Figure 3. Kaplan-Meier of overall survival in CheckMate 017 (all randomised patients): 5-year update

CI = confidence interval.

Source: Bristol-Myers Squibb data on file (2019)[21]

Table 7. Overall survival rates by 6-month intervals up to 5 years in CheckMate 017 (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)[21]

D.6.2. Progression-free survival: 5-year database lock, CheckMate 017

At the time of submission to NICE, results from the initial 12-month database lock in December 2014 were presented. Treatment with nivolumab reduced the risk of death or disease progression by 38% when compared with docetaxel (HR, 0.62; 95% CI, 0.47-0.81; $P < 0.001$).[17] The median PFS was 3.5 months (95% CI, 2.1-4.9 months) for patients receiving nivolumab compared with 2.8 months (95% CI, 2.1-3.5 months) for patients receiving docetaxel.[17] The PFS rate at 12 months was more than three times higher for the nivolumab group compared with the docetaxel group (21% vs. 6%, respectively).[17] The 5-year PFS rate for the nivolumab group was [redacted]% 95% CI, [redacted]%) (Figure 4, Table 8).[21]

Figure 4. Kaplan-Meier of progression-free survival in CheckMate 017 (all randomised patients): 5-year update

CI = confidence interval.

Source: Bristol-Myers Squibb data on file (2019)[21]

Table 8. Progression-free survival rates by 6-month intervals up to 5-years in CheckMate 017 (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; NC = not calculated.

Source: Bristol-Myers Squibb data on file (2019)[21]

D.6.3. Time to treatment discontinuation: 5-year database lock, CheckMate 017

Time to treatment discontinuation (TTD) was not included in the original squamous NSCLC submission to NICE, and results are not included in the main Brahmer et al. (2015)[17] 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.[21] The 5-year TTD rate for the nivolumab group was [redacted]% (95% CI, [redacted]%) (Figure 5, Table 9).[21]

Figure 5. Kaplan-Meier of time to treatment discontinuation in CheckMate 017 (all randomised patients): 5-year update

[redacted]

Source: Bristol-Myers Squibb data on file (2019)[21]

Table 9. Time to treatment discontinuation rates by 6-month intervals up to 5-years in CheckMate 017 (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]

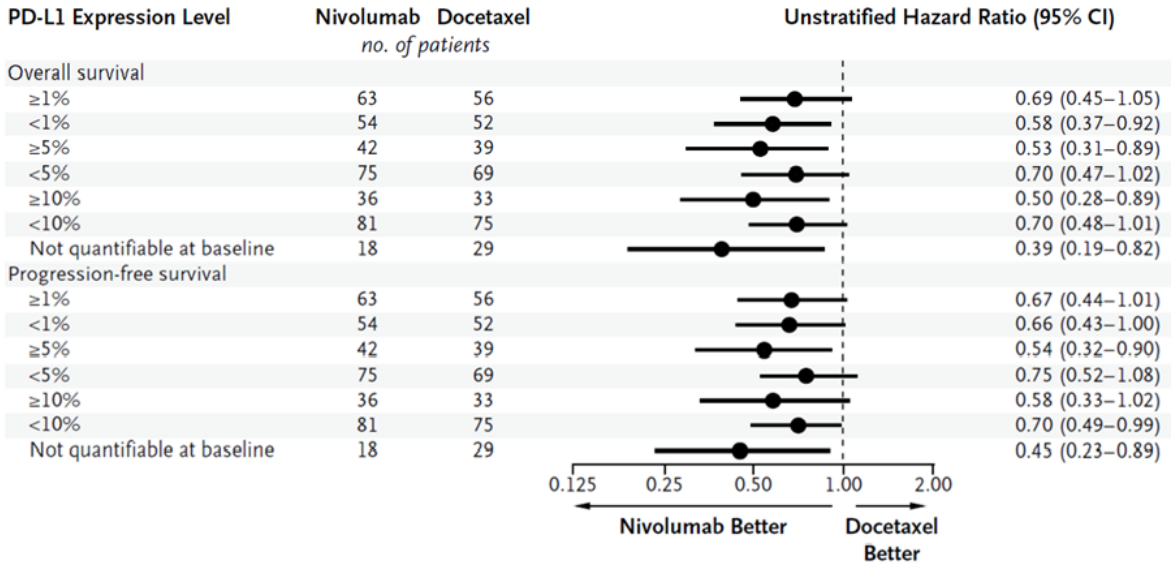
CI = confidence interval.

Source: Bristol-Myers Squibb data on file (2019)[21]

D.6.4. Efficacy in PD-L1 subgroups: 5-year database lock, CheckMate 017

At the time of the original submission, nivolumab had been shown to be effective across all PD-L1 expression level subgroups, and PD-L1 was not considered predictive of outcome (Figure 6).[17] Brahmer et al. (2015)[17] concluded that, "PD-L1 expression was neither prognostic nor predictive of benefit in the population of patients with squamous-cell NSCLC". Furthermore, in the original technology appraisal guidance (paragraph 4.29) the committee concluded, "that the results did not suggest a clinically significant difference according to PD-L1 expression". PD-L1 subgroup was not predictive of clinical outcomes in the squamous population.[22] This is confirmed by the 5-year database lock (Figure 7).[23]

Figure 6. Forest plot of overall survival and progression-free survival in CheckMate 017 by PD-L1 subgroup: 1-year analysis



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

Source: Brahmer et al. (2015)[17]

Figure 7. Forest plot of overall survival in CheckMate 017 by PD-L1 subgroup: 5-year update

Source: Bristol-Myers Squibb data on file (2019)[23]

Kaplan-Meier plots by PD-L1 subgroup are presented in Figure 8.

Figure 8. Kaplan-Meier for overall survival in CheckMate 017 by PD-L1 subgroup: 5-year update

PD-L1 = programmed death-ligand 1.

Source: Bristol-Myers Squibb data on file (2019)[23]

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

At the time of the original submission, 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).[24] At the 3 mg/kg dose, 1-, 2-, and 3-year OS rates were 56% (95% CI, 38%-71%), 42% (95% CI, 24%-58%), and 27% (95% CI, 12%-43%), respectively. Median OS and survival rates were similar in patients with squamous and non-squamous histologies (1-, 2-, and 3-year OS rates for squamous NSCLC at 3 mg/kg: 49%, 35%, and 28%, respectively).[24]

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).[20] The estimated 6-year OS rate was [redacted]% for all treated patients (n = 129) (Figure 9).

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

CI = confidence interval; OS = overall survival.

Source: Antonia et al. (2019)[20]

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, signifying continued treatment effect up to 3 years after 2 years of nivolumab treatment.[25] 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, 389 new applicants for CDF funding for nivolumab in squamous NSCLC were received; after appropriate exclusions, 348 unique patients were included in the analysis.[19]

Overall, 66% (n = 230) were male and 34% (n = 118) were female; the median age was

70 years, and most patients had a performance status of 0 (17%) or 1 (71%). PD-L1 expression was < 1% in 69% (n = 241), ≥ 1% in 14% (n = 49), and not available in 17% of patients (n = 58).

Of the included patients, 278 (80%) had completed treatment by 31 January 2019. The median follow-up time in SACT was 97 days and the maximum follow-up was 487 days; the median treatment duration was 3.5 months (95% CI, 3.0-4.1 months) (Figure 10). Overall, 30% of patients were still receiving treatment at 6 months (95% CI, 25%-35%) while 16% of patients were still receiving treatment at 12 months (95% CI, 12%-21%) Of note, the median treatment duration in SACT was similar to that in CheckMate 017 and the two KM curves are similar (overlaid in Figure 10); suggesting the TTD trial data are generalisable to the real world.[19]

Figure 10. Kaplan-Meier for treatment duration in the SACT database and CheckMate 017

SACT = systemic anticancer therapy.

Source: Public Health England (2019)[19], Bristol-Myers Squibb data on file (2019)[21].

At the time of analysis, the median OS was 8.4 months (95% CI, 7.2-9.7 months) (Figure 11). Survival at 6 months was 57% (95% CI, 51%-62%), 12-months survival was 35% (95% CI, 30%-41%) The minimum follow-up in SACT was 5 months and the maximum follow-up period for survival was 20 months. For all patients who received treatment, 111 were still alive (censored) at the date of follow-up and 237 had died.[19] Notably, the median OS in SACT was similar to the median OS in CheckMate 017 (9.2 months) and the curves are similar (overlaid in Figure 11) suggesting the trial data are generalisable to the real world.

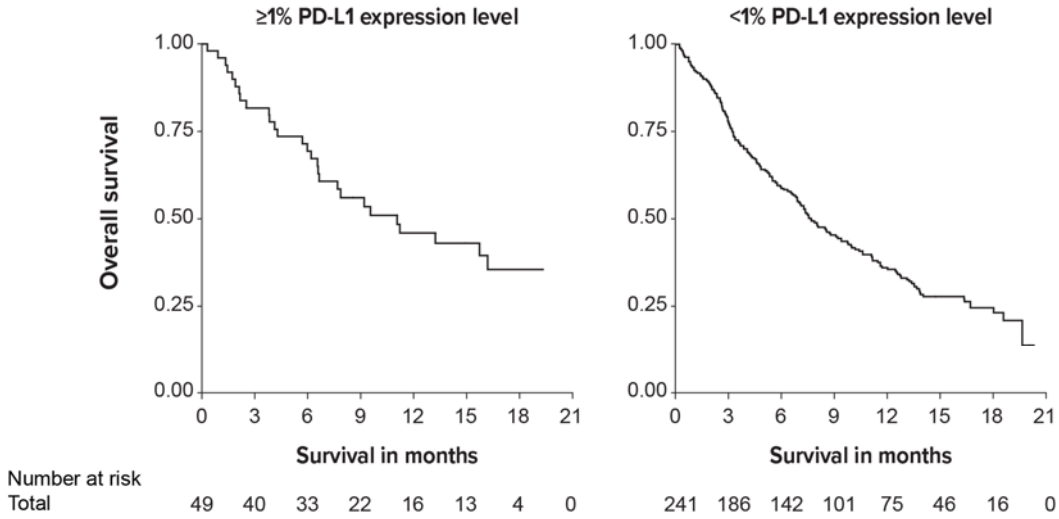
Figure 11. Kaplan-Meier for overall survival in the SACT database and CheckMate 017

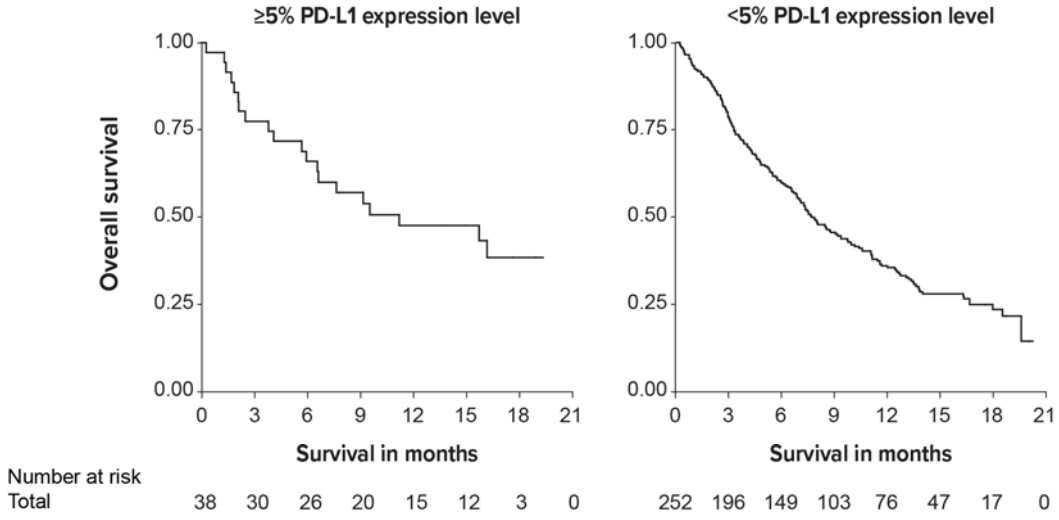
SACT = systemic anticancer therapy.

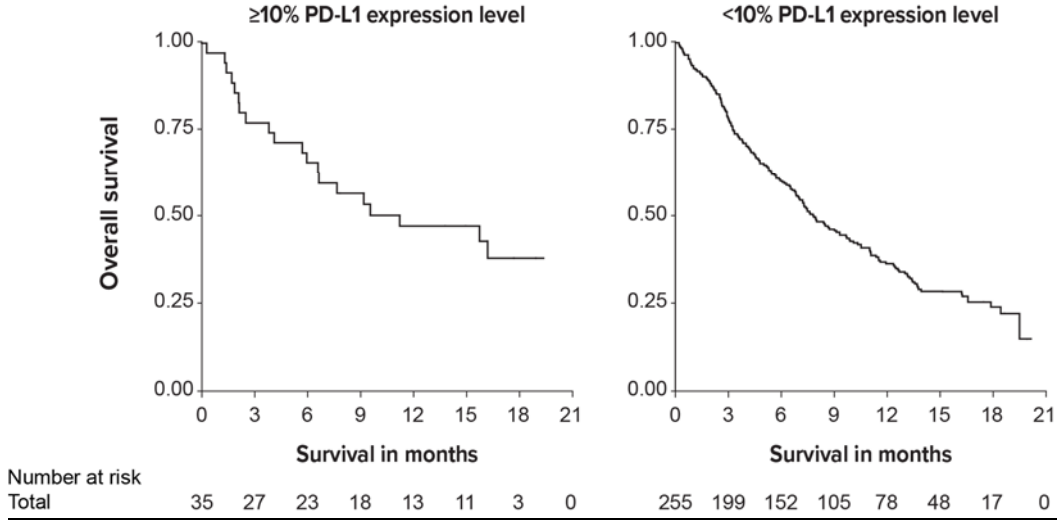
Source: Public Health England (2019)[19], Bristol-Myers Squibb data on file (2019)[21].

Figure 12 provides the Kaplan-Meier curves for OS by PD-L1 expression level, censored at 5 June 2019. These support the results of the original and 5-year analyses of the CheckMate 017 study, in which nivolumab was shown to be effective across all PD-L1 expression level subgroups and PD-L1 was not considered predictive of outcome.

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







PD-L1 = programmed death-ligand 1; SACT = systemic anticancer therapy.

A number of studies assessing the real world efficacy of IO therapies in general and nivolumab in particular have been published. Like 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.[26-28] 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 to the survival in CheckMate 017 and 057. Dixmier A et al. (2018)[28] 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 5-year follow-up data from CheckMate 017 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.

It also 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.

With increasing length of survival data being collected, we are seeing increasing numbers of network meta-analyses looking at checkpoint inhibitors in the postprogression NSCLC indication. A recent network meta-analysis by Almutairi et al. (2019)[29] 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%. However, some toxicity differences were seen favouring nivolumab to atezolizumab in terms of risk of anaemia, constipation, and nausea. In an analysis of all patients (regardless of histology or PD-L1 expression level), pairwise comparisons did not show statistically significant differences in OS between pembrolizumab, nivolumab and atezolizumab, suggesting a histology agnostic analysis of the benefit of nivolumab might be relevant.[29]

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 DSU guidelines with fitting both standard parametric functions and spline models. The number of knots for the spline models was limited to 2 in line with the original submission to avoid overfitting the data. In addition to updating standard parametric and spline models, updated hybrid exponential functions were also fitted based on this being the ERG-preferred extrapolation for OS, and the committee-preferred extrapolation for PFS.

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 017 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.[30] Similarly, based on Raftery's rule of thumb[31], 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.

D.7.1. Overall survival

The committee-preferred generalised gamma extrapolation for OS selected after input from the DSU is shown in Figure 1 together with the ERG-preferred hybrid exponential overlaid with the 5-year Kaplan-Meier data from CheckMate 017. As shown in Figure 1, the hybrid exponential model results in a poor visual fit to the CheckMate 017 study data for both docetaxel and nivolumab. However, the committee-preferred generalised gamma does provide a much closer fit to the CheckMate 017 data, although it underestimates the later part of the 5-year CheckMate 017 Kaplan-Meier data. These findings confirm the conclusion from the DSU assessment and, as argued by the company from the initial submission, that a declining hazard would be plausible and represent a more accurate extrapolation compared with the hybrid exponential argued by the ERG. In fact, it shows that the generalised gamma (argued to be too optimistic by the ERG) underestimates the long-term survival for nivolumab but is well aligned with the long-term docetaxel data (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). Therefore, survival analyses have been run on the 5-year data to identify best-fitting survival extrapolations accounting for the additional CDF evidence collected as well as re-predicting the committee-preferred generalised gamma extrapolation with the additional evidence now available.

As for the original analysis of OS, whether proportional hazard could be assumed was explored based on log-cumulative hazards and log-cumulative odds plots to determine if parallel lines were evident (Figure 13 and Figure 14). As seen in the figures, the arms cross over at the very start of the study but the lines are close to parallel over time. In addition, the Grambsch and Therneau's correlation test was applied, which confirmed the null hypothesis of proportional hazards could not be ruled out for OS (P = 0.88). Thus, consistent with the method in the original submission, survival models with treatment as a covariate were fitted to the CheckMate 017 data.

Figure 13. Log-cumulative hazard plot of CheckMate 017: 5-year survival data

Figure 14. Log-odds plot of CheckMate 017: 5-year survival data

Table 10 summarises the AIC and BIC values for the parametric distributions explored for OS for docetaxel and nivolumab. Table 10 demonstrates that, in terms of statistical fit assessed by AIC, only spline hazard 2 knots and spline normal 2 knots provided AIC values within 4 of the best-fitting distribution. Both of these distributions also had a BIC difference of less than 10 compared with the distribution with the lowest BIC. The other best-fitting curves based on BIC had an AIC difference greater than 4 compared with spline hazard 2 knots and therefore were not considered for the base-case analysis.

Table 10. Summary of goodness-of-fit statistics for extrapolations for 5-year overall survival

Distribution	AIC	BIC
Spline hazard 2 knots	1,786.3	1,804.3
Spline normal 2 knots	1,789.7	1,807.7
Spline odds 2 knots	1,791.0	1,809.1
Spline hazard 1 knot	1,792.0	1,806.4
Spline odds 1 knot	1,793.9	1,808.4
Log-logistic	1,794.5	1,805.3
Generalised F	1,794.8	1,812.8
Lognormal	1,800.6	1,811.4
Dependent spline normal 1 knot	1,801.6	1,816.0
Gompertz	1,802.0	1,812.8
Generalised gamma	1,802.0	1,816.5
Weibull	1,843.8	1,854.6
Gamma	1,852.1	1,862.9
Exponential	1,853.9	1,861.1

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

All curves were assessed with respect to visual fit to the Kaplan-Meier data. From the visual inspection, it was clear that the statistically best-fitting distribution also provided the best visual fit to the data. Figure 15 shows the visual fit of spline hazard 2 knots normal to the CheckMate 017 OS data for docetaxel and nivolumab. Figure 16 shows the long-term extrapolation of the same distribution. As shown in the figures, this distribution provides good visual fit to the data. Therefore, spline hazard 2 knots has been selected for the updated company base case. However, it is important to note that Figure 16 does show that the 2-knot spline does not fully follow the observed plateau and may provide an underestimate of the long-term benefit of nivolumab.

Figure 15. Overall survival in CheckMate 017: 5-year KM data and updated extrapolations

KM = Kaplan-Meier; K2 = 2 knots.

Figure 16. Overall survival in CheckMate 017: long-term extrapolations based on 5-year data

KM = Kaplan-Meier; K2 = 2 knots.

Comparison to long-term data

As shown in Table 11, spline hazard 2 knots distribution selected as the company-preferred distribution provided a good fit to both the 5-year study data and the CheckMate 003 survival data.

Table 11. Overall survival estimates from nivolumab studies compared with 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	Spline hazard 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AC generalised gamma (based on 5-year data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERG hybrid exponential (based on 5-year data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model estimates for docetaxel OS	Spline hazard 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AC generalised gamma (based on 5-year data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERG hybrid exponential (based on 5-year data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CheckMate 017	Nivolumab OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA
	Docetaxel OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA
CheckMate 003	Nivolumab OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA

AC = Appraisal committee; ERG = Evidence Review Group; NA = not available; OS = overall survival.
Sources: Bristol-Myers Squibb data on file (2019)[21]; Antonia et al. (2019)[20]

D.7.2. Progression-free survival

The committee-preferred assumption regarding PFS was a hybrid exponential in which the exponential distribution was fitted from a 2.2-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. Thus, it is clear new extrapolations would be warranted based on the new data collected. Therefore, 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 in the original analysis, independent parametric survival models fitted separately to the nivolumab (Table 12) and docetaxel (Table 13) arms were considered because of the crossover in PFS survival curves.

Table 12. Summary of goodness-of-fit statistics for nivolumab extrapolations for progression-free survival 5-year data

Distribution	AIC	BIC
Spline hazard 1 knot	683.2	691.9
Spline odds 1 knot	683.2	691.9
Spline hazard 2 knots	685.0	696.7
Spline odds 2 knots	685.4	697.0
Spline normal 1 knot	685.9	694.6
Spline normal 2 knots	686.1	697.8
Generalised gamma	687.9	696.7
Gompertz	696.4	702.2
Log-logistic	698.5	704.3
Lognormal	700.7	706.5
Weibull	739.1	744.9
Gamma	755.3	761.1
Exponential	778.9	781.8
Spline hazard 1 knot	683.2	691.9

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

Table 13. Summary of goodness-of-fit statistics for docetaxel extrapolations for progression-free survival 5-year data

Distribution	AIC	BIC
Lognormal	574.9	580.7
Log-logistic	576.1	582
Generalised gamma	576.8	585.6
Spline normal 1 knot	576.9	585.6
Spline hazard 1 knot	577.5	586.2
Spline odds 1 knot	578	586.8
Spline normal 2 knots	578.8	590.4
Generalised F	578.8	590.5
Spline odds 2 knots	579.2	590.9
Spline hazard 2 knots	579.5	591.2
Gamma	589.1	595
Weibull	594.3	600.2
Exponential	597.6	600.5

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

As shown by the AIC and BIC values for the variety of independent parametric distributions explored for PFS for docetaxel and nivolumab, the three distributions providing the best statistical fit to docetaxel (lognormal, log-logistic, and generalised gamma) did not provide a statistical fit to the nivolumab arm within the predefined criteria. However, the best-fitting curve to nivolumab (spline hazard 1 knot) also fulfilled the selection criteria set for AIC and BIC for docetaxel. Therefore, this was determined to be the best option for the base-case selection of extrapolations based on AIC and BIC. From visual inspection, it was also clear that the spline hazard 1 knot provided a good visual fit for both arms. Lognormal, log-logistic, generalised gamma, and spline hazard 1 knot all provided close to identical fit to the docetaxel data. For nivolumab, the best-fitting distribution of the non-spline distributions was generalised gamma; however, as shown in Figure 17, generalised gamma did not provide as good a fit as the spline hazard 1 knot.

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

KM = Kaplan-Meier; K1 = 1 knot.

Based on this analysis, spline hazard 1 knot was selected as a common distribution for PFS for both docetaxel and nivolumab in the updated company base case.

D.7.3. Duration of treatment effect and time to treatment discontinuation

As shown in Figure 16, 5-year follow-up confirms a long-term OS benefit for patients treated with nivolumab, although 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 017 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), and six-year survival was [redacted] (vs. CheckMate 017: [redacted] 5-year survival), showing that a maximum of 1.8 year of nivolumab treatment contributes to a significant long-term survival. As reported by Gettinger et al. (2018)[25], 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 017 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 017 remain on treatment (Figure 18). After 3 years, [redacted] % of the study population were still on treatment and at 5 years [redacted] % remained on treatment.

Figure 18. 5-year overall survival and time to treatment discontinuation in CheckMate 017

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

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 017.

When comparing the original committee-preferred extrapolation of TTD (hybrid exponential as proposed by the ERG) with the 5-year follow-up, it is clear that the original extrapolation provided a reasonable fit to the TTD KM data for nivolumab but underestimated the TTD for docetaxel (Figure 19). 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 further extrapolation. This follows a similar principle to that used in the committee-preferred analysis and the analyses do not require any assumptions related to extrapolation.

Figure 19. Time to discontinuation: committee-preferred extrapolation versus 5-year data

ERG = Evidence Review Group; KM = Kaplan-Meier; TTD = time to treatment discontinuation.

D.8. Key model assumptions and inputs

Committee- and company-preferred original model assumptions are presented in Table 14, and key model assumptions and inputs for this submission are presented in Table 15.

Table 14. Committee-preferred and company-preferred original model assumptions and inputs

Model input/assumption	Committee-preferred parameter/assumption	Company-preferred parameter/ assumption
Overall survival extrapolation	Generalised gamma (based on input from DSU)	Log-Logistic (3-year February 2017 CheckMate 017 database lock)
Progression-free survival	Hybrid exponential with Kaplan-Meier data up to 2.2 months followed by exponential	Spline 2-knots hazard preferred, though hybrid exponential with Kaplan-Meier data up to 2.2 months followed by exponential agreed to facilitate decision making
Continued treatment effect beyond 2 years	Treatment waning over 3 years after treatment discontinuation	Continued treatment effect preferred though treatment waning over 3 years after treatment discontinuation agreed to facilitate decision making

DSU = Decision Support Unit.

Table 15. Key model assumptions and inputs

Model input	Original parameter/ assumption	Updated parameter/ assumption	Source/justification
Overall survival	Generalised	2-knot spline	Goodness-of-fit statistics and visual inspection

Model input	Original parameter/ assumption	Updated parameter/ assumption	Source/justification
extrapolation	gamma (3-year February 2017 CheckMate 017 database lock)	hazards model (5-year May 2019 CheckMate 017 database lock)	demonstrate that the 2-knot spline hazards model is the best-fitting extrapolation for the updated clinical data. Figure 20 shows that the original generalised gamma extrapolation severely underestimates the tail of the nivolumab data.
Progression-free survival extrapolation	Hybrid exponential (2-year CheckMate 017 database lock)	1-knot spline hazards model (5-year May 2019 CheckMate 017 database lock)	Goodness-of-fit statistics and visual inspection demonstrate that the 1-knot spline hazards model is the best-fitting extrapolation for the updated clinical data. Figure 21 shows that the original hybrid exponential extrapolation underestimates the tail of the nivolumab arm.
Treatment duration	Hybrid exponential (2-year CheckMate 017 database lock)] and 2-year stopping rule	KM data (5-year May 2019 CheckMate 017 database lock) 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.
Continued treatment effect beyond 2 years	Treatment waning over 3 years after treatment discontinuation	Continued treatment effect	Continued follow-up of patients throughout data collection period shows no evidence of a waning of the treatment effect associated with nivolumab.

KM = Kaplan-Meier.

Figure 20. Overall survival: original versus updated extrapolation

AC = appraisal committee; KM = Kaplan-Meier.

Figure 21. Progression-free survival: original versus updated extrapolation

AC = appraisal committee; KM = Kaplan-Meier.

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 16 shows the initial cost-effectiveness results that demonstrated plausible cost-effectiveness at CDF entry with the CDF agreed patient access scheme discount for nivolumab (1a). Results 1b and 1c shows the results when incorporating the updated flat dosing of Nivolumab and the standard patient access scheme discount for nivolumab. Unless otherwise specifically noted both of these changes has been included in all following results presented. Results 2 and 3 shows the results with updates made to the original committee-preferred parameters for decision making using the 5-year CheckMate 017 data, and the updated company base case.

To illustrate the impact of each individual change in model parameters, Table 17 shows the impact changing each individual parameter has on the ICER when compared with the updated company base case.

Table 16. Cost-effectiveness results

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]	£23,076	0.80	0.46	£49,826[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]	£23,153	0.80	0.46	£49,992
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]	£31,881	0.80	0.46	£68,838
Cost-effectiveness analysis 2: analysis that demonstrated plausible potential for cost-effectiveness at CDF entry, with [redacted] PAS and incorporating updated OS (generalised gamma) and PFS (hybrid exponential) fitted to 5-year CheckMate-017 data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£29,683	0.66	0.43	£69,647
Cost-effectiveness analysis 3: new company base case with [redacted] PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£31,281	1.49	0.88	£35,657

[a] This ICER deviates slightly from the £49,982 ICER at CDF entry. This is due to a programming error in the model identified during the preparation of the current submission. The error related to how the ERG hybrid exponential PFS curve was incorporated into the model and has been corrected in the updated model.

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 17. Impact on the ICER of individual parameter changes to the committee preferred assumptions

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 (analysis 1c)		**£68,838**
OS extrapolation	OS modelled with updated base case: spline hazards 2 knots extrapolation (5-year May 2019 CheckMate 017 database lock).	-£11,486
PFS extrapolation	PFS modelled with updated base case: spline hazards 1 knot extrapolation (5-year May 2019 CheckMate 017 database lock).	-£33,464
Time to treatment discontinuation	Time to treatment discontinuation modelled with KM data (5-year May 2019 CheckMate 017 database lock), with 2-year stopping rule	£891
Duration of effect	Duration of treatment effect modelled with no waning of effect.	-£5,576

ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival;

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 18. The probabilistic ICER for the new company base case was £35,278 per QALY gained compared with £35,657 per QALY gained in the deterministic analysis.

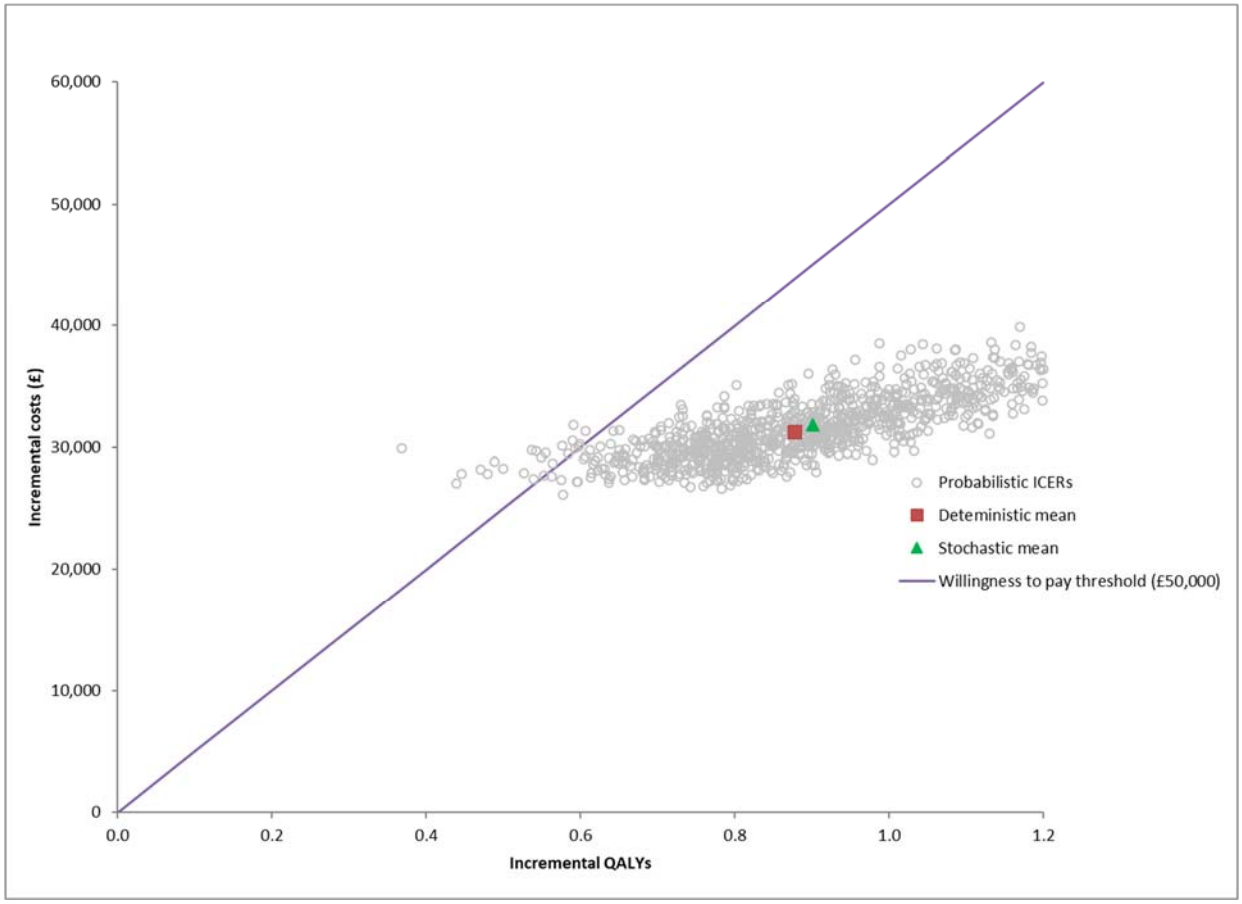
Figure 22 presents the cost-effectiveness plane, which shows that most of the 1,000 iterations fall below the willingness to pay threshold for an end-of-life therapy (£50,000 / QALY).

Table 18. Updated company base-case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Nivolumab	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	£31,794	0.90	£35,280

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

Figure 22. Scatterplot of probabilistic results

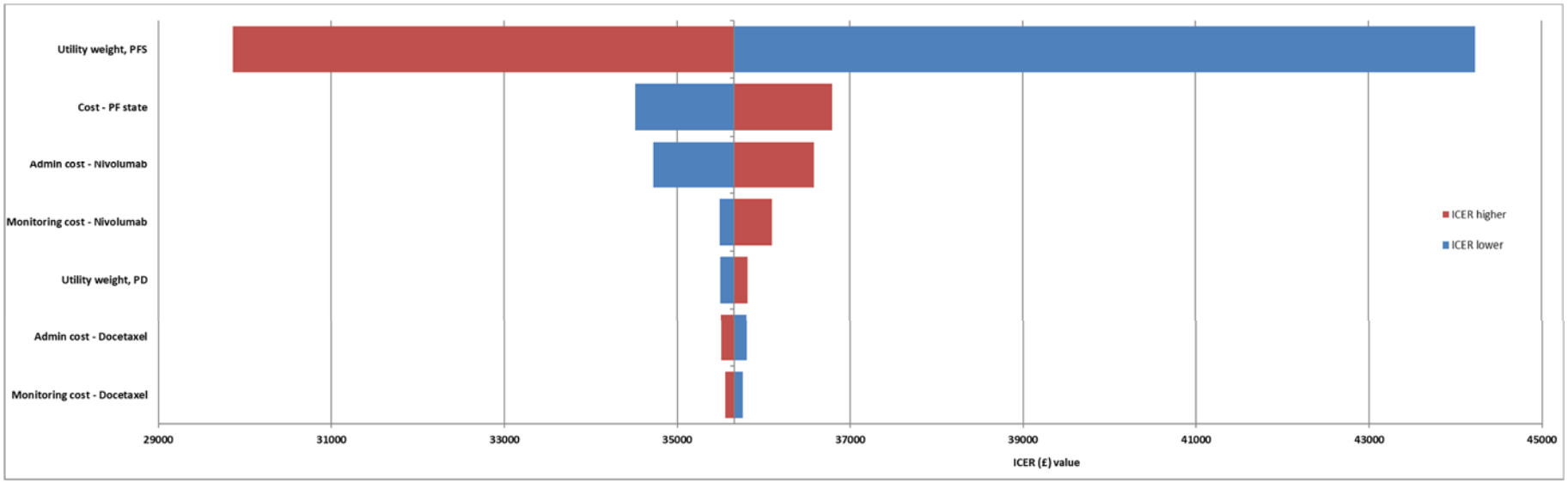


ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

D.11. Key sensitivity and scenario analyses

Figure 23 presents a tornado diagram showing the results of the deterministic sensitivity analyses.

Figure 23. Tornado diagram



ICER = incremental cost-effectiveness ratio

Scenario analyses were undertaken to investigate the effect of certain model inputs on the ICERs. All undertaken scenario analyses are presented in Table 19.

Table 19. Key scenario analyses: impact on base-case ICER

Scenario and cross-reference	Scenario detail	Brief rationale	ICER (change from base case)
New company base case			**£35,657**
[redacted]	[redacted]	[redacted]	[redacted]
2-year OS extrapolation for docetaxel	Using committee preferred generalised gamma fitted to the 2-year data cut for the docetaxel arm.	This scenario is included to imitate the docetaxel arm in the absence of crossover to IO (allowed after year 2 and on progression in CheckMate 017). By using the 2-year data cut the effect of subsequent IO treatment is not influencing the docetaxel survival extrapolation to the same extent as for the 5-year data cut.	£34,210 (-£1,447)
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	£37,442 (£1,785)

ICER = incremental cost-effectiveness ratio; IO = immuno-oncology; NSCLC = non-small-cell lung cancer; OS = overall survival.

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 017 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). The data clearly show that the original ERG- and appraisal committee-preferred extrapolations for both OS and PFS significantly underestimated the 5-year survival from CheckMate 017. Further the data show that the BMS base case was the most appropriate although still an under-estimate 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 017 are likely to underestimate the true benefit of nivolumab in the active treatment arm compared with a situation with no nivolumab treatment.

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. 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 patients with squamous NSCLC and should be available to patients in England through routine commissioning.

D.13. References

1. NICE. Terms of engagement for CDF review of TA483: nivolumab for previously treated squamous non-small-cell lung cancer. 2019.
2. NICE. Committee papers 1: nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483] National Institute for Health and Care Excellence; 2015. Available at: https://www.nice.org.uk/guidance/ta483/documents/committee-papers. Accessed 24 July 2019.
3. NICE. Appraisal consultation document 1: nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483] National Institute for Health and Care Excellence; 2015. Available at: https://www.nice.org.uk/guidance/ta483/documents/appraisal-consultation-document. Accessed 24 July 2019.
4. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008 Oct 21;6:84.
5. NICE. Committee papers 2: nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483] National Institute for Health and Care Excellence; 2016. Available at: https://www.nice.org.uk/guidance/ta483/documents/committee-papers-4. Accessed 24 July 2019.
6. NICE. Committee papers 3: nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483] National Institute for Health and Care Excellence; 2016. Available at: https://www.nice.org.uk/guidance/ta483/documents/committee-papers-3. Accessed 24 July 2019.
7. van den Hout WB, Kramer GW, Noordijk EM, Leer JW. Cost-utility analysis of short- versus long-course palliative radiotherapy in patients with non-small-cell lung cancer. J Natl Cancer Inst. 2006 Dec 20;98(24):1786-94.
8. NICE. Appraisal consultation document 2: nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483] National Institute for Health and Care Excellence; 2016. Available at: https://www.nice.org.uk/guidance/ta483/documents/appraisal-consultation-document-2. Accessed 24 July 2019.
9. NICE. Committee papers 4: nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483] 2017. Available at: https://www.nice.org.uk/guidance/ta483/documents/1. Accessed 24 July 2019.
10. NICE. Committee papers 5: nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483] National Institute for Health and Care Excellence; 2017. Available at: https://www.nice.org.uk/guidance/ta483/documents/committee-papers-5. Accessed 24 July 2019.
11. NICE. Final appraisal determination: nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483] National Institute for Health and Care Excellence; 2017. Available at: https://www.nice.org.uk/guidance/ta483/documents/final-appraisal-determination-document. Accessed 24 July 2019.
12. NICE. TA520. Chair's presentation: atezolizumab for treating locally advanced or metastatic non-small cell lung cancer after chemotherapy. 3rd appraisal committee meeting. National Institute for Health and Care Excellence; 23 January 2018. Available at: https://www.nice.org.uk/guidance/ta520/documents/1-3. Accessed 11 July 2019.
13. NICE. TA520. Final Appraisal Determination. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. 2018. Available at: https://www.nice.org.uk/guidance/ta520/documents/final-appraisal-determination-document. Accessed July 30, 2019.

14. Bristol-Myers Squibb data on file. Company CDF review engagement form for TA483: nivolumab for previously treated squamous non-small-cell lung cancer 2019.
15. EMA. Opdivo: summary of product characteristics. European Medicines Agency; 4 June 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf. Accessed 18 June 2019.
16. Bristol-Myers Squibb data on file. Nivolumab (BMS-936558) [redacted]
17. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015 Jul 9;373(2):123-35.
18. NICE. Cancer Drugs Fund Managed Access Agreement: Nivolumab for previously treated squamous non-small-cell lung cancer. 2017. Available at: https://www.nice.org.uk/guidance/ta483/resources/managed-access-agreement-november-2017-pdf-4659350653. Accessed August 2, 2019.
19. Public Health England. Nivolumab for treating locally advanced or metastatic squamous non-small cell lung cancer - data review [TA483]. 2019.
20. Antonia S, Borghaei H, Ramalingam S, Horn L, De Castro Carpeño J, Pluzanski A. Pooled analysis of long-term survival with nivolumab in patients with previously treated advanced non-small cell lung cancer: Impact of disease control and response on outcomes. Accepted, Lancet Oncology. 2019.
21. Bristol-Myers Squibb data on file. 5-year update on advanced non-small cell lung cancer (NSCLC) patients from the CheckMate 017 and CheckMate 057 phase 3 clinical trials. OR Nivo 176. 2019.
22. NICE. Nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483]. 1 November 2017. Available at: https://www.nice.org.uk/guidance/ta483. Accessed 5 July 2019.
23. Bristol-Myers Squibb data on file. 5-year overall survival update for squamous (SQ) advanced non-small cell lung cancer (NSCLC) patients in CheckMate 017 by tumor PD-L1 expression level. (OR NIVO 180). 2019.
24. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol. 2015 Jun 20;33(18):2004-12.
25. Gettinger S, Horn L, Jackman D, Spigel D, Antonia S, Hellmann M, et al. Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: Results from the CA209-003 study. J Clin Oncol. 2018 Jun 10;36(17):1675-84.
26. Schwartzberg L, Korytowsky B, Penrod JR, Zhang Y, Le TK, Batenchuk C, et al. Real-World Clinical Impact of Immune Checkpoint Inhibitors in Patients With Advanced/Metastatic Non-Small Cell Lung Cancer After Platinum Chemotherapy. Clin Lung Cancer. 2019 Jul;20(4):287-96 e4.
27. Juergens RA, Mariano C, Jolivet J, Finn N, Rothenstein J, Reaume MN, et al. Real-world benefit of nivolumab in a Canadian non-small-cell lung cancer cohort. Curr Oncol. 2018 Dec;25(6):384-92.
28. Dixmier A DD, Raspaud C, Auliac JB, Benoit N, Bombaron P, Asselain B, et al. A French observational study of nivolumab-treated lung cancer patients in a real-world setting: initial results on 1394 advanced non-small lung cancer patients. Presented at the ESMO; 2018.
29. Almutairi AR, Alkhatib N, Martin J, Babiker HM, Garland LL, McBride A, et al. Comparative efficacy and safety of immunotherapies targeting the PD-1/PD-L1 pathway for previously treated advanced non-small cell lung cancer: A Bayesian network meta-analysis. Crit Rev Oncol Hematol. 2019 Jul 10;142:16-25.
30. Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. Sociol Methods Res. 2004;33(2):43.
31. Raftery A. Bayesian model selection in social research. Sociol Methodol. 1995;25:111-63.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483) [ID1559]

Clarification questions

16 December 2019

File name	Version	Contains confidential information	Date
ID1559 Nivolumab SQ NSCLC Clarification Letter to Company 16122019 Redacted	1	No	16 December 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

No ERG questions

Section B: Clarification on cost-effectiveness data

B1. Priority request. Please provide a copy of the MS Excel model that was used to generate the ICER per QALY gained that informed the NICE FAD issued in September 2017 (based on papers from ACM 4 and the CDF proposal). Please also provide a copy of the instructions that are needed to convert that model to the model provided as part of the CS for this appraisal.

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 14 and Table 15 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.

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” sheet was 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 range “list_OS_analysis” in the “Survival Inputs” sheet was updated to ensure that all options for OS are linked to the updated “Doc_OS” sheet.

Similarly, the “Nivo_PFS” and “Doc_PFS” sheets were updated with the progression-free survival parameters from the updated analysis. Further, “Survival Inputs!A7:A33” and “Survival Inputs AC7:AC33” were updated to ensure that all options were linked to “Nivo_PFS” and “Doc_PFS” sheets.

Update of 5-year TTD data

All of the 5-year Kaplan-Meier curves for OS, PFS, and TTD were added to “Response and Survival!DX36:EF369”. The TTD curves were linked to “Patient flow – 1!CL19:CM1059” such that the selection dropdown in “Dashboard!C18” could be used to toggle between the ERG 2-year hybrid exponential TTD and the updated 5-year KM data.

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!C32” allowing the user to toggle between weight-based dosing and fixed dosing approaches. [redacted].

Removal of redundant elements of the model

The selection of PD-L1 subgroups and survival analysis parameters related to these analyses were removed, including programming related to selection of PD-L1 subgroup hybrid exponential models in "Response and survival!J39:Q1039".

The option to include a "melanoma and RCC rebate" was removed from the Dashboard.

B2. Priority request. Please provide the mean (± standard error) time from diagnosis of patients in the nivolumab arm and of those in the docetaxel arm of the CheckMate 017 trial.

The information on time from initial diagnosis to randomisation, for CheckMate-017 is presented in Table 1.

Table 1: Time from Initial Diagnosis to Randomisation (All Randomised Subjects)

	Nivolumab 3mg/kg Q2W (n=135)	Docetaxel 75mg/m2 Q3W (n=137)
Median (min – max), years	0.74 (0.1 - 10.0)	0.73 (0.1 - 4.6)
Mean (SE)	[redacted]	[redacted]
Time from initial diagnosis, n (%)		
<1 year	[redacted]	[redacted]
1 – <2 years	[redacted]	[redacted]
2 – <3 years	[redacted]	[redacted]
3 – <4 years	[redacted]	[redacted]
4 – <5 years	[redacted]	[redacted]
≥ 5 years	[redacted]	[redacted]

Source: Bristol-Myers Squibb data on file (2015)[1]; Bristol Myers-Squibb Data on File (2019)[2]

B2. Priority request. Please provide time to death from any cause (overall survival) Kaplan-Meier analysis to the following specifications:

Trial data set: CheckMate 017

Data cut: 5-year May 2019 database lock

Format: Please present analysis outputs using the format used in the sample table below

Trial arms: (i) Nivolumab 3mg/kg Q2W (n=135)

(ii) Docetaxel 75mg/m^2 Q3W (n=137)

Censoring: (i) Standard censoring methods

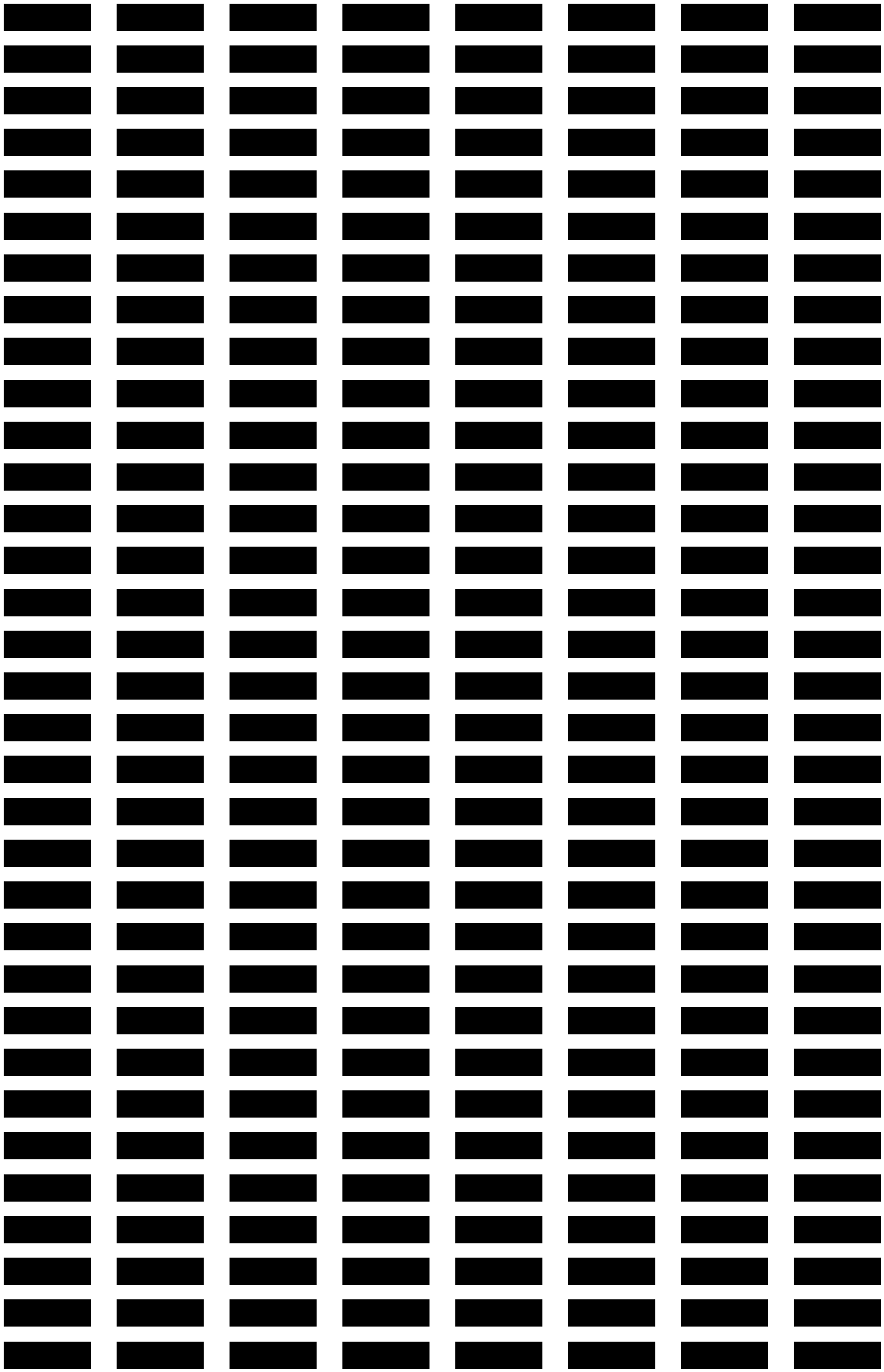
(ii) Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off censored at the date of data cut-off, not when last known to be alive.

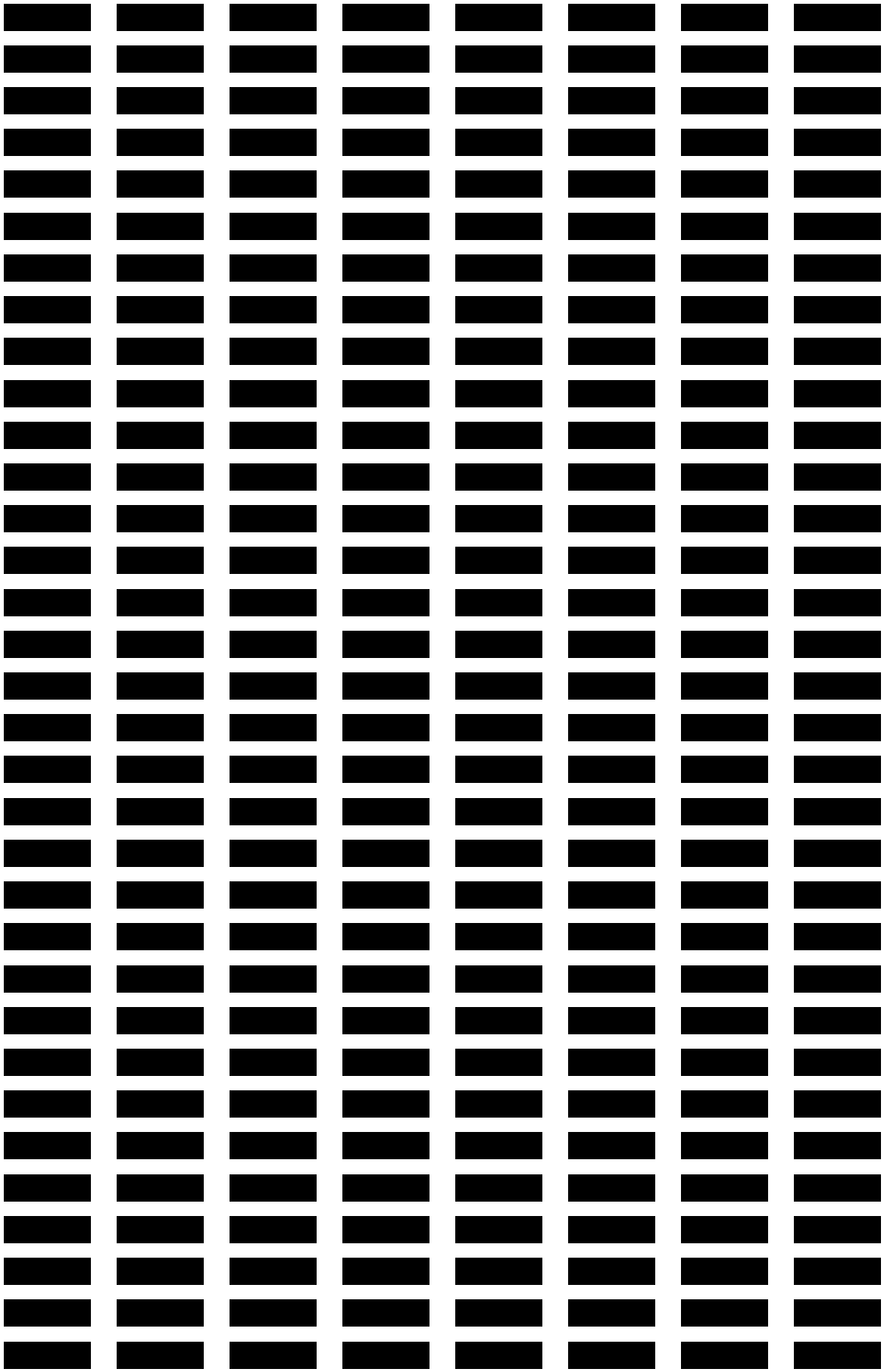
Time to death from any cause (overall survival) in CheckMate 017 at 5-year database lock is presented using standard censoring methods for nivolumab (Table 2) and docetaxel (Table 3), as well as censoring lost to follow-up and withdrawn patients at 60 months for nivolumab (Table 4) and docetaxel (Source: Bristol Myers-Squibb Data on File (2019)[4]

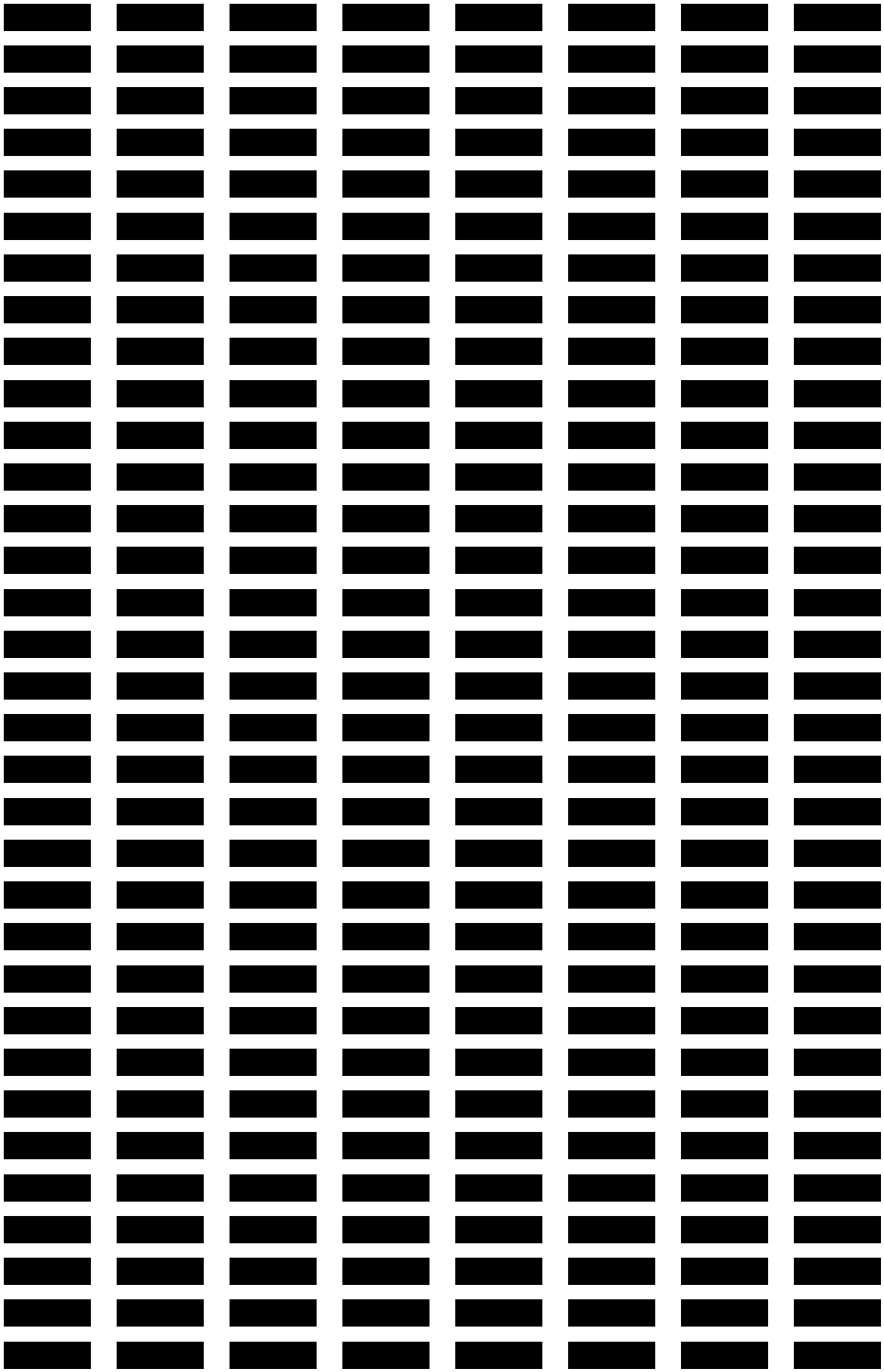
Table 5).

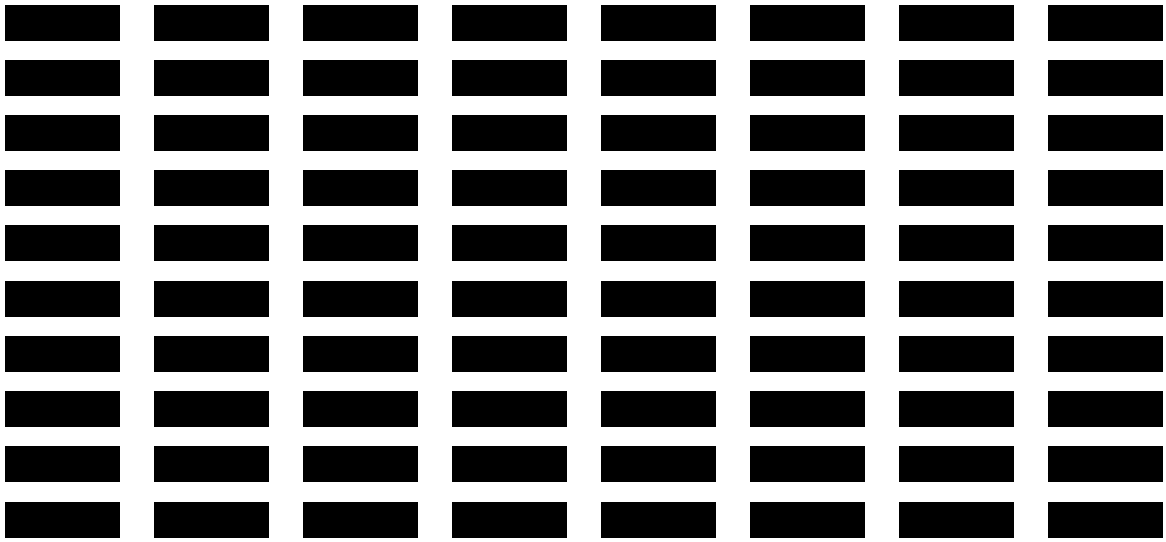
Table 2: Output for time to death from any cause (overall survival) Kaplan-Meier analysis – Standard Censoring, Nivolumab 3mg/kg Q2W (n=135)

Product-Limit Survival Estimates							
Time (months)	n.risk	n.event	n.censor	Survival	Standard error	Lower	Upper
[redacted]							









Source: Bristol Myers-Squibb Data on File (2019)[3]

Table 3: Output) for time to death from any cause (overall survival) Kaplan-Meier analysis – Standard Censoring, Docetaxel 75mg/m2 Q3W (n=137)

Product-Limit Survival Estimates							
Time (months)	n.risk	n.event	n.censor	Survival	Standard error	Lower	Upper

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

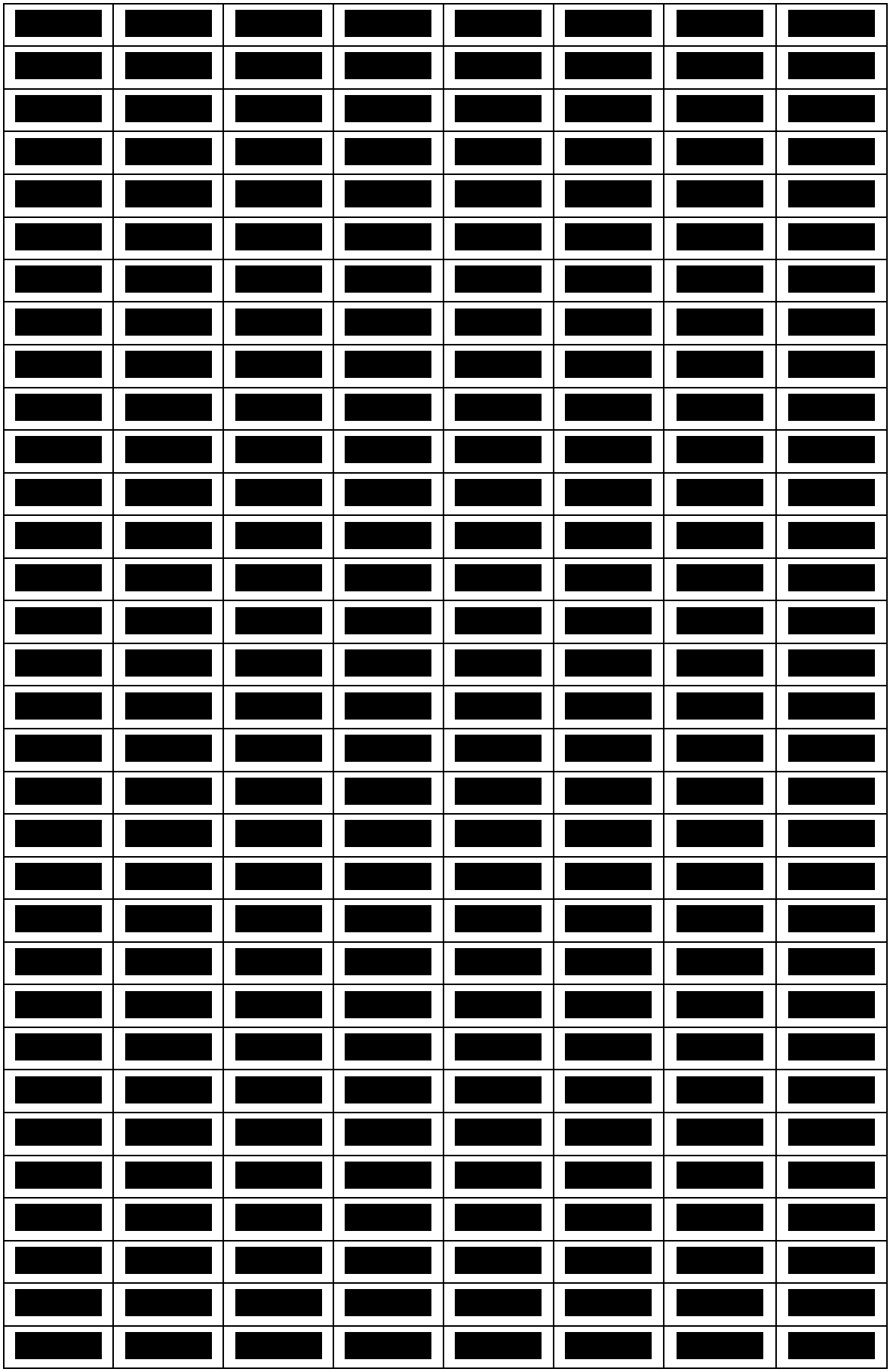
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]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

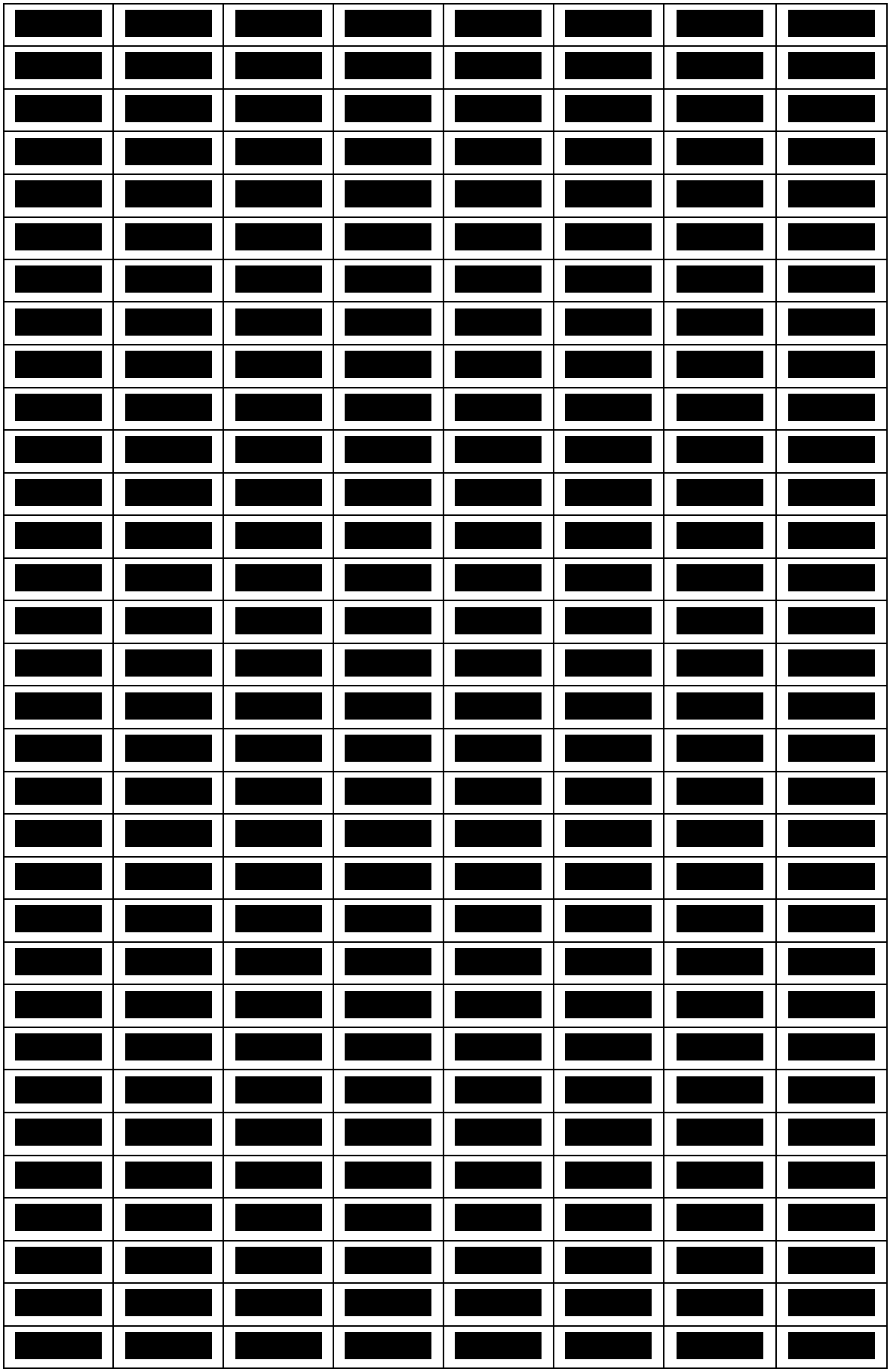
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]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

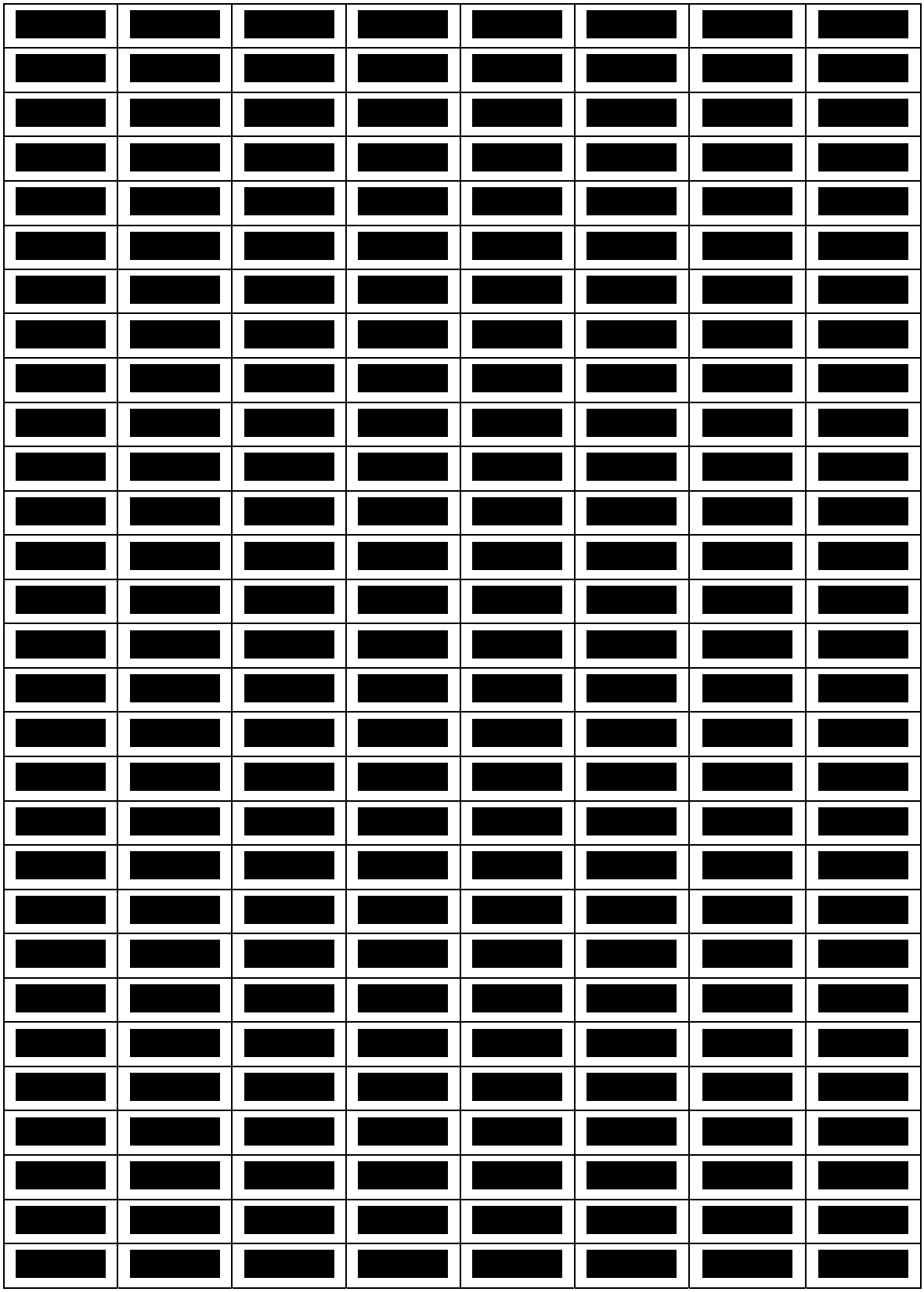
Source: Bristol Myers-Squibb Data on File (2019)[3]

Table 4: Output for time to death from any cause (overall survival) Kaplan-Meier analysis – Censor lost to follow-up and withdrawn patients at 60 months, Nivolumab 3mg/kg Q2W (n=135)

Product-Limit Survival Estimates							
Time (months)	n.risk	n.event	n.censor	Survival	Standard error	Lower	Upper



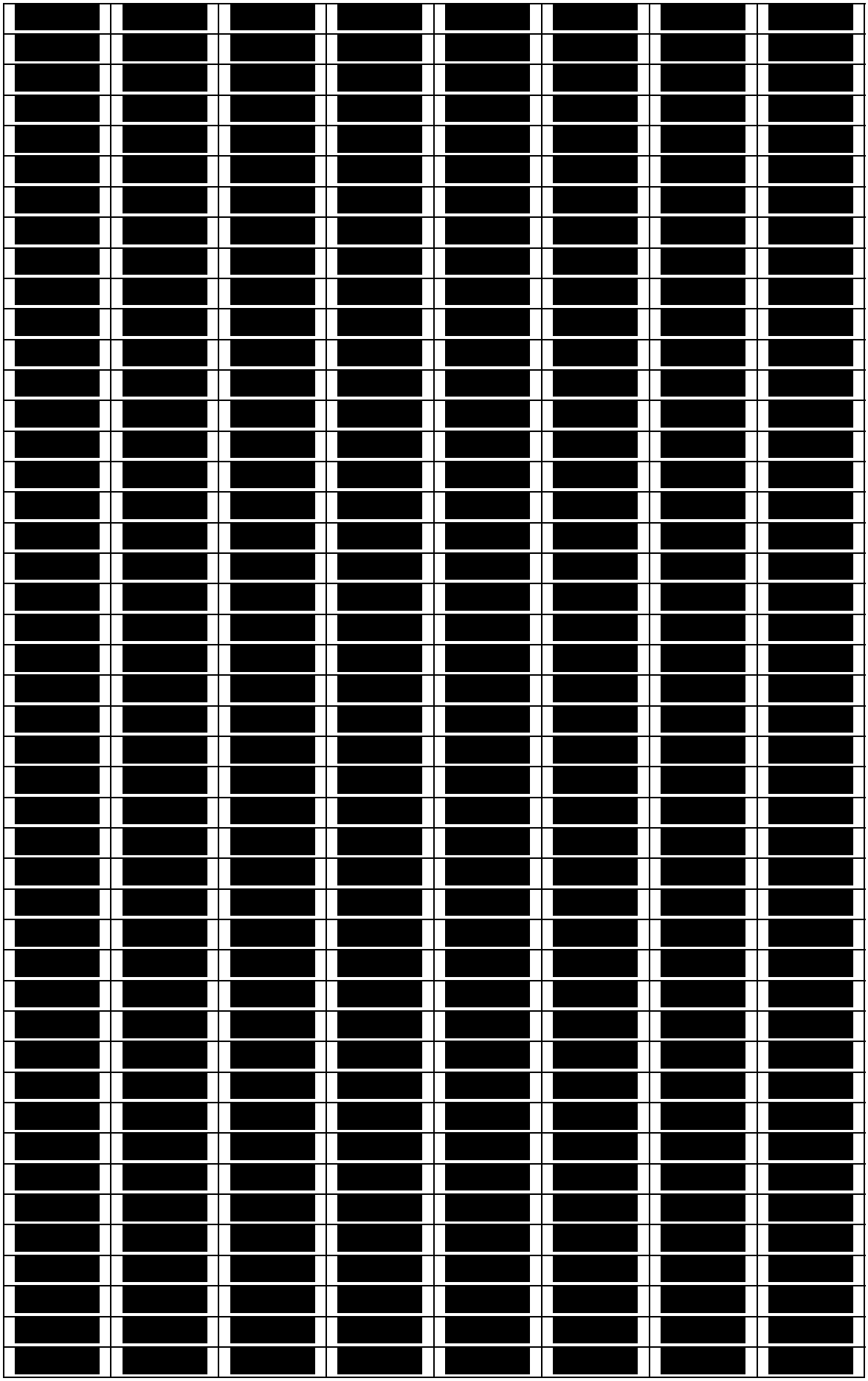


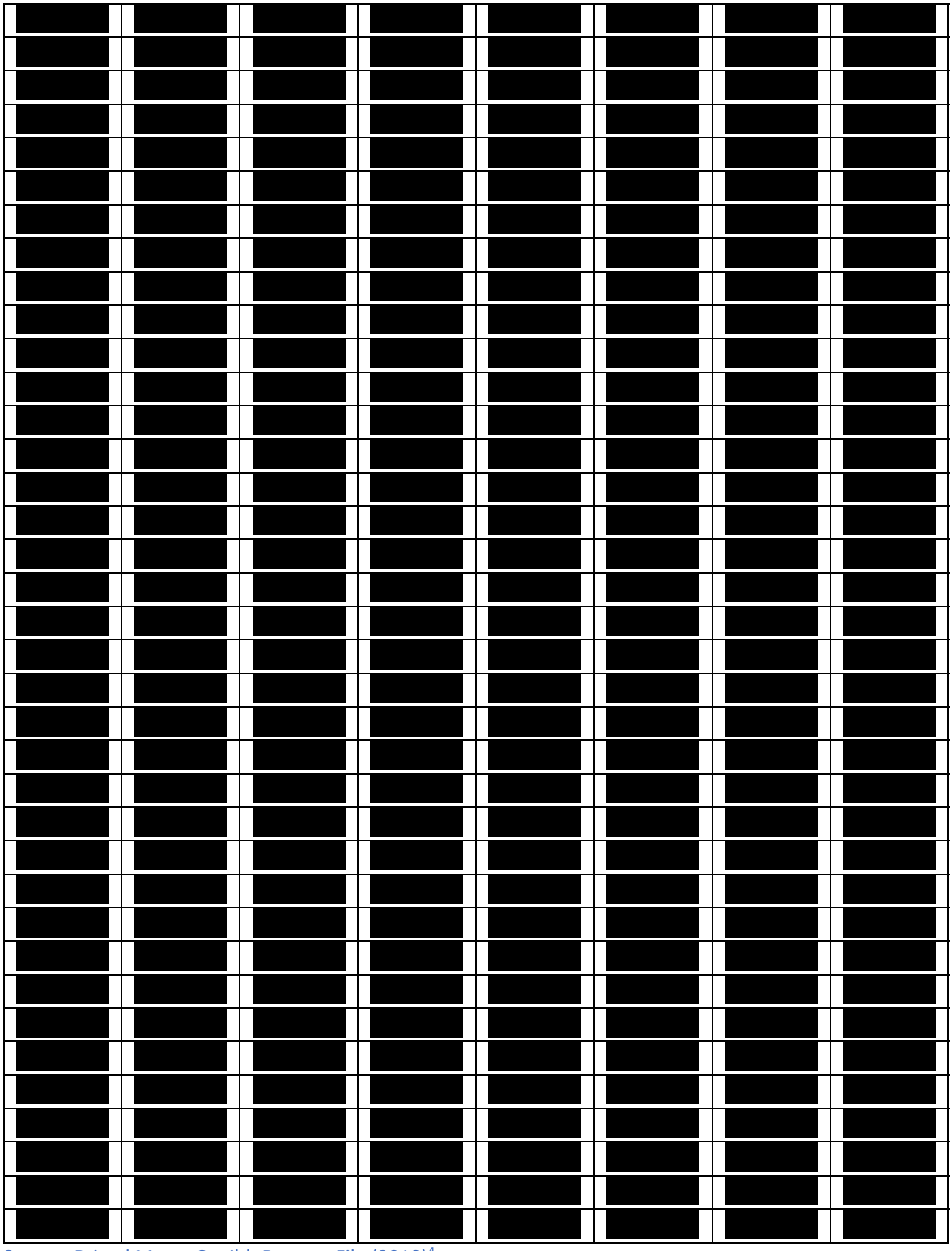


Source: Bristol Myers-Squibb Data on File (2019)[4]

Table 5: Output for time to death from any cause (overall survival) Kaplan-Meier analysis – Censor lost to follow-up and withdrawn patients at 60 months, Docetaxel 75mg/m2 Q3W (n=137)

Product-Limit Survival Estimates							
Time (months)	n.risk	n.event	n.censor	Survival	Standard error	Lower	Upper
[redacted]							





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

Section C: Textual clarification and additional points

No ERG questions

References

1. Bristol-Myers Squibb data on file. Final Clinical Study Report for Study CA209017. 2015.
2. Bristol Myers-Squibb Data on File. Time from diagnosis to randomisation in CheckMate 017. 2019.
3. Bristol Myers-Squibb Data on File. CheckMate 017. Time to death from any cause (overall survival) Kaplan-Meier analysis, Standard Censoring Methods. 2019.
4. Bristol Myers-Squibb Data on File. CheckMate 017. Time to death from any cause (overall survival) Kaplan-Meier analysis, Censor lost to follow-up and withdrawn patients at 60 months. 2019.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Non-small cell lung cancer (squamous) - nivolumab (CDF review TA483) [ID1559]

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.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

Public Health England

Protecting and improving the nation's health

Nivolumab for treating locally advanced or metastatic 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, 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.

Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

Prepared by: [this line can be deleted if not required]
For queries relating to this document, please contact: [this line can be deleted if not required]

Published Month 20XX
PHE publications
gateway number: 201XXXX

PHE supports the UN
Sustainable Development Goals

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 locally advanced or metastatic 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 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, 389 applications for nivolumab were identified in the NHS England's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 348 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 348 (100%) unique patients with CDF applications were reported in the SACT dataset.

Median treatment duration for the analysis cohort was 3.5 months (106 days) [95% CI: 3.0, 4.1]. 30% [95% CI: 25%, 35%] of patients were receiving treatment at 6 months and 16% [95% CI: 12%, 21%] of patients were receiving treatment at 12 months.

At data cut off, 80% (278) of patients were identified as no longer being on treatment; 60% (N=168) of patients had stopped treatment due to disease progression, 9% (N=24) of patients had stopped treatment due to toxicity, 4% (N=10) of patients chose to end their treatment, 21% (N=57) of patients died (not on treatment), 6% (N=18) of patients died on treatment and <1% of patients (N=1) ended treatment on account of unrelated comorbidity.

The median overall survival (OS) was 8.4 months (255 days) [95% CI: 7.2, 9.7]. OS at 6 months was 57% [95% CI: 51%, 62%], OS at 12 months was 35% [95% CI: 30%, 41%].

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 expression levels.

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].

Nivolumab is recommended as a treatment option for locally advanced or metastatic (stage IIIB or IV) squamous NSCLC for a maximum of 2 years, or earlier if the patient progresses[6].

Background to this report

The Public Health England 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[7]. 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[8].

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 appraisal of nivolumab treating locally advanced or metastatic squamous non-small-cell lung cancer (NSCLC) [TA483]

The NICE Appraisal Committee reviewed the evidence for the clinical and cost effectiveness of nivolumab in treating locally advanced or metastatic squamous NSCLC [TA483] and NICE published the guidance for this indication in November 2017[9].

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 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 the CheckMate 003 and CheckMate 017 clinical trials. Data collected from the CheckMate 017 clinical trial will be 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 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 017 clinical trials[10,11].

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

- **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) squamous non-small cell lung cancer

- 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 all other criteria are met
- Patient has had PD-L1 testing with an approved and validated test to determine the tumour proportion score
- 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 the treatment of locally advanced or metastatic 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 the treatment of locally advanced or metastatic 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 did not match the SACT treating trust.

If two applications are submitted for nivolumab for the treatment of locally advanced or metastatic 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 cohorts

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.

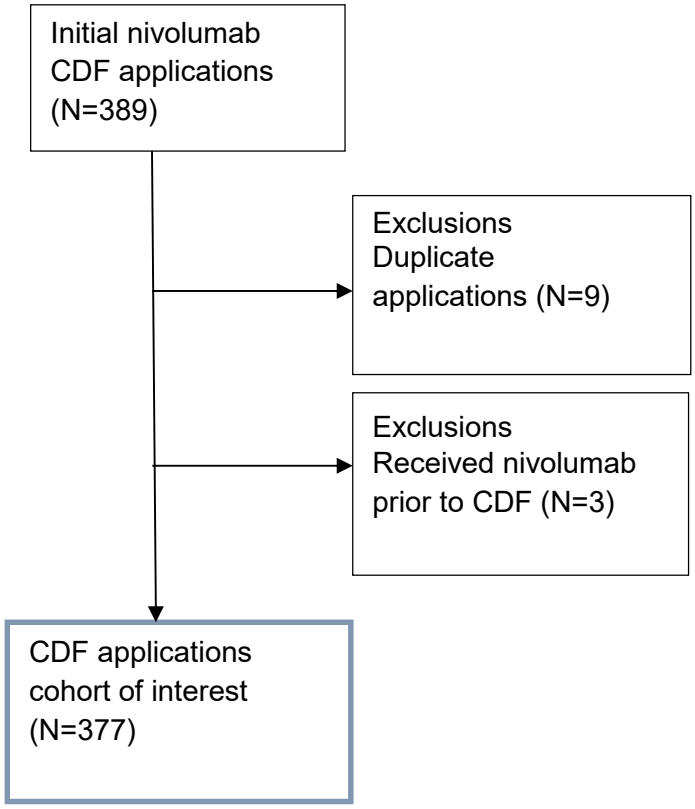
The CDF applications included in these analyses are from 20 September 2017 to 19 December 2018. A snapshot of SACT data was taken on 4 May 2019 and made available

for analysis on the 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 389 applications for CDF funding for nivolumab for treating locally advanced or metastatic squamous NSCLC between 20 September 2017 to 19 December 2018 in the NHS England Blueteq database. Following de-duplication this relates to 380 unique patients.

An additional three 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 nivolumab for previously treated 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 is provided below:

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, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st 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 1st and 8th 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 generally 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 or 27-days has been added to final treatment date for all patients, this represents the duration from a patients last cycle to their next and will depend whether a patient is receiving a split dose on 2 days/cycle or a single dose once/cycle[12].

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 one of the following:

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 three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

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.

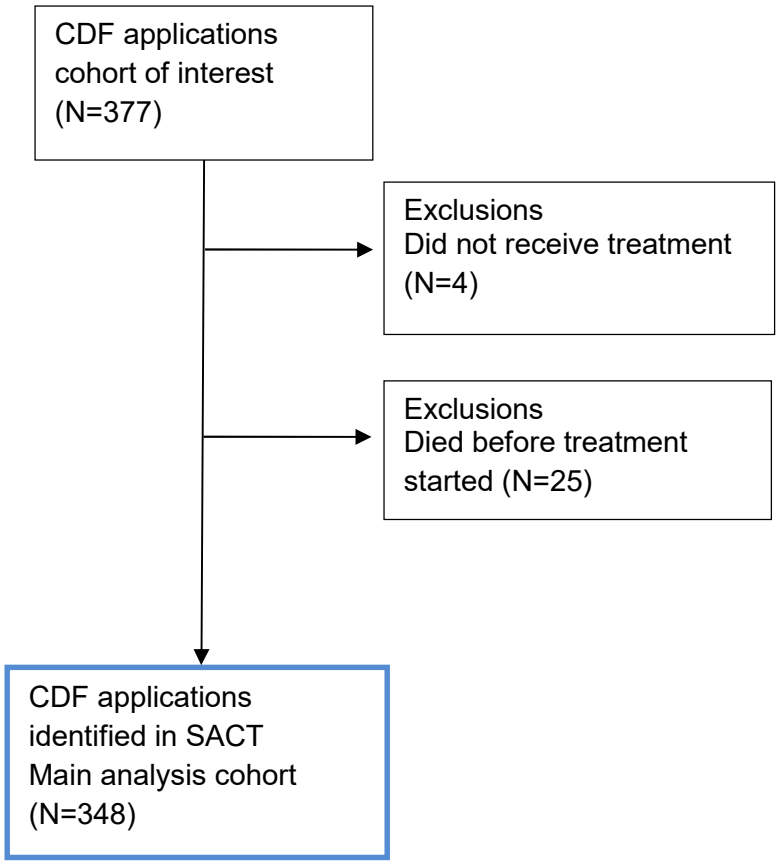
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 377 new applications for CDF funding for nivolumab for locally advanced or metastatic squamous NSCLC, four patients did not receive treatment and 25 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 squamous NSCLC between 20 September 2017 and 19 December 2018.



A maximum of 348 nivolumab records are expected in SACT for patients who were alive and eligible to commence treatment (Figure 2). 100% (348/348) of these applicants for CDF funding have a treatment record in SACT.

[1] The 25 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 >90% 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=348)

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 278 patients. Of these, 278 have an outcome summary recorded in the SACT dataset 100% (278/278).

Table 2: Completeness of outcome summary for patients that have ended treatment (N=278)

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 99% (345/348) 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=348)

Variable	Completeness (%)
PD-L1 score	99%

Patient characteristics

The median age of the 348 patients receiving nivolumab for squamous NSCLC was 70 years; and was consistent for both genders.

Table 4: Patient characteristics (N=348)

Patient characteristics[2]			
		Frequency (N)	**Percentage (%)**
Sex	Male	230	66%
	Female	118	34%
Age	<40	3	1%
	40-49	5	1%
	50-59	45	13%
	60-69	117	34%
	70-79	148	43%
	80+	30	9%
Performance status	0	59	17%
	1	247	71%
	2	9	3%
	3	1	<1%
	4	0	0%
	Missing	32	9%

PD-L1 distribution

The distribution of PD-L1 score in table 5 shows that 69% of patients have a score <1%, 16% of patients did not have enough tissue, and as such, no PD-L1 score was available, 10% of patients have a score ≥10.

Table 5: Distribution of PD-L1 score in Blueteq (N=348)

PD-L1 TPS score (%)	**Frequency (N)**	**Percentage (%)**
<1	241	69%
≥1 to <5	11	3%
≥5 to <10	3	1%
≥10	35	10%
TPS cannot be quantified	55	16%
Not captured	3	1%
Total	**348**	**100%**

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

Treatment duration

Of the 348 patients with CDF applications, 278 (80%) 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 97 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.

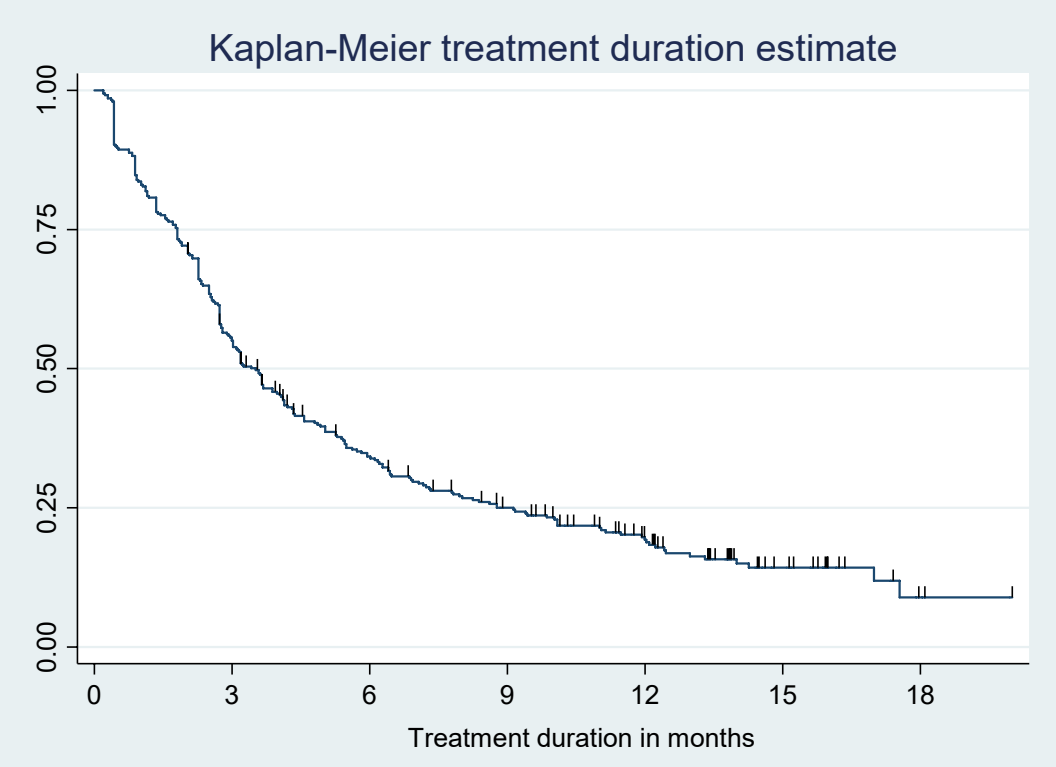
Table 6: Breakdown by patients' treatment status[3,4,5]

Patient status	Frequency (N)	Percentage (%)
Patient died - on treatment	18	5%
Patient died - not on treatment	219	63%
Treatment stopped	41	12%
Treatment ongoing	70	20%
Total	**348**	

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 3.5 months (106 days) [95% CI: 3.0, 4.1] (N=348). 30% of patients were still receiving treatment at 6 months [95% CI: 25%,35%], 16% of patients were still receiving treatment at 12 months [95% CI: 12%, 21%].

[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=348)



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	348	189	107	72	42	15	2

Table 8 shows that for all patients who received treatment, 70 were still on treatment (censored) at the date of follow-up and 278 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	70	67	53	46	31	13	2
Events	278	122	54	26	11	2	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. 80% (N=278) of patients had ended treatment at 31 January 2019.

Table 9: Treatment outcomes for patients that have ended treatment (N=278)[6,7]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	168	60%
Stopped treatment – acute chemotherapy toxicity	24	9%
Stopped treatment – patient choice	10	4%
Stopped treatment – died not on treatment	57	21%
Stopped treatment – died on treatment	18	6%
Stopped on account of unrelated comorbidity[8]	1	<1%
Total	**278**	

Table 10: Treatment outcomes and treatment status for patients that have ended treatment (N=278)

Outcome[9]	Patient died [10] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	137	31	
Stopped treatment – acute chemotherapy toxicity	18	6	
Stopped treatment – patient choice	7	3	
Stopped treatment – died not on treatment	57		
Stopped treatment – died on treatment			18
Stopped on account of unrelated comorbidity		1	
Total	**219**	**41**	**18**

[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] Stopped on account of unrelated comorbidity is not an outcome collected in SACT. This was discussed and agreed with a consultant.
[9] Relates to outcomes submitted by the trust in table 9.
[10] Relates to treatment status in table 6 for those that have ended treatment.

Overall survival

Of the 348 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 8.4 months (255 days) [95% CI: 7.2, 9.7] (N=348). Survival at 6 months was 57% [95% CI: 51%, 62%], 12 months survival was 35% [95% CI: 30%, 41%].

Figure 4: Kaplan-Meier survival plot (N=348)

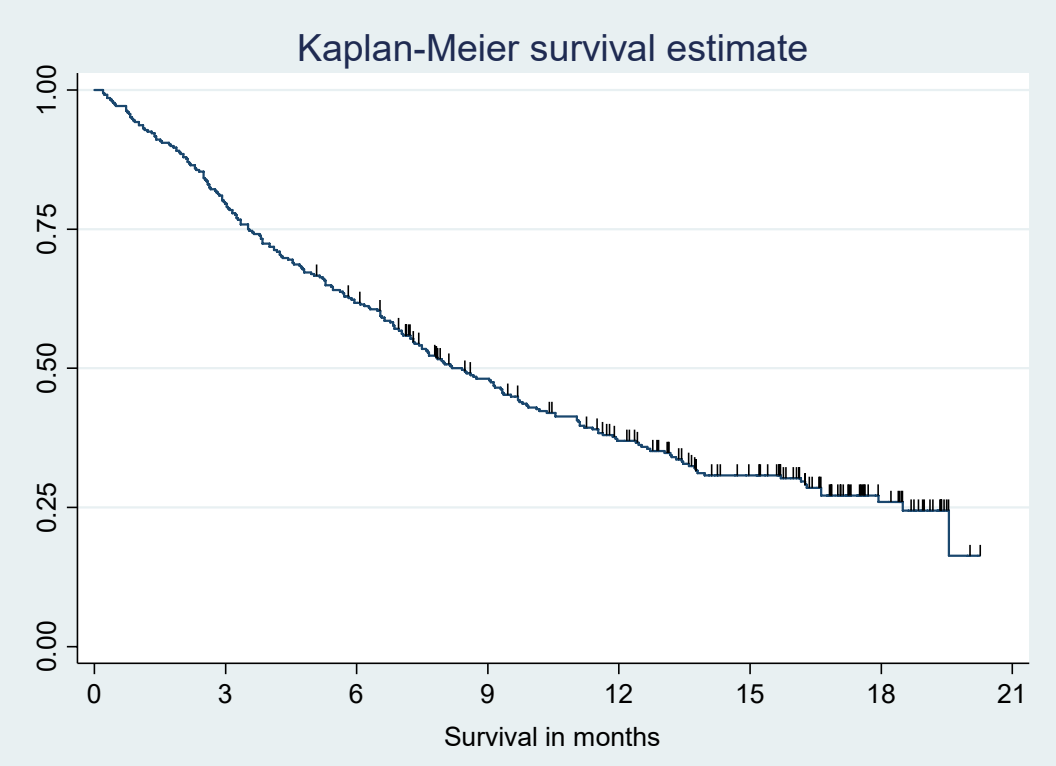


Table 11 and 12 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 20 months (608 days), all patients were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

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

Time intervals (months)	0-21	3-21	6 -21	9-21	12-21	15-21	18-21
Number at risk	348	277	213	150	106	67	22

Table 12 shows that for all patients who received treatment, 111 were still alive (censored) at the date of follow-up and 237 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)	0-21	3-21	6 -21	9-21	12-21	15-21	18-21
Censored	111	111	119	91	81	58	20
Events	237	166	104	59	25	9	2

Sensitivity analyses

Treatment duration

Sensitivity analyses was carried out on a cohort with at least 6 months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 20 September 2017 to 31 July 2018 and SACT activity was followed up to the 31 January 2019. 312 patients (90%) were included in these analyses. The median follow-up time in SACT was 98 days.

The Kaplan-Meier curve for ongoing treatment is shown in figure 5. The median treatment duration for patients in this cohort was 3.3 months (100 days) [95% CI: 2.9, 4.0] (N=312).

Figure 5: Kaplan-Meier treatment duration (N=312)

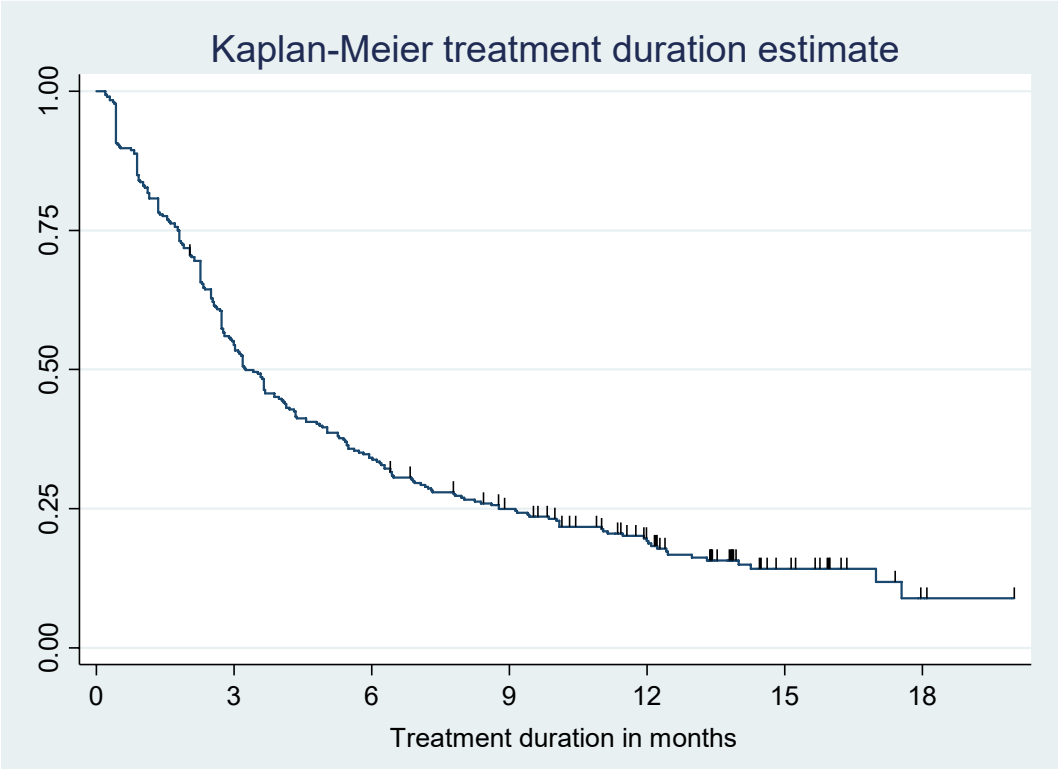


Table 13 and 14 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for treatment duration was 16 months. The minimum follow-up was 6 months.

Table 13: 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	312	169	106	72	42	15	2

Table 14 shows that for all patients who received treatment, 53 were still on treatment (censored) at the date of follow-up and 259 had ended treatment (events).

Table 14: 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	53	52	52	46	31	13	2
Events	259	117	54	26	11	2	0

Overall survival

Sensitivity analyses was also carried out for overall survival on a cohort with at least 6 months follow-up in SACT. To identify the cohort, CDF applications were limited from 20 September 2017 to 5 December 2018. 345 patients (99%) were included in the survival analyses with all patients having a minimum follow-up of 6 months. Follow up continued from treatment start date to date of tracing for vital status (5 June 2019).

Figure 6 provides the Kaplan-Meier curve for overall survival, censored at 5 June 2019. The median survival was 8.4 months [95% CI: 7.3, 9.7] (N=345).

Figure 6: Kaplan-Meier survival plot (N=345)

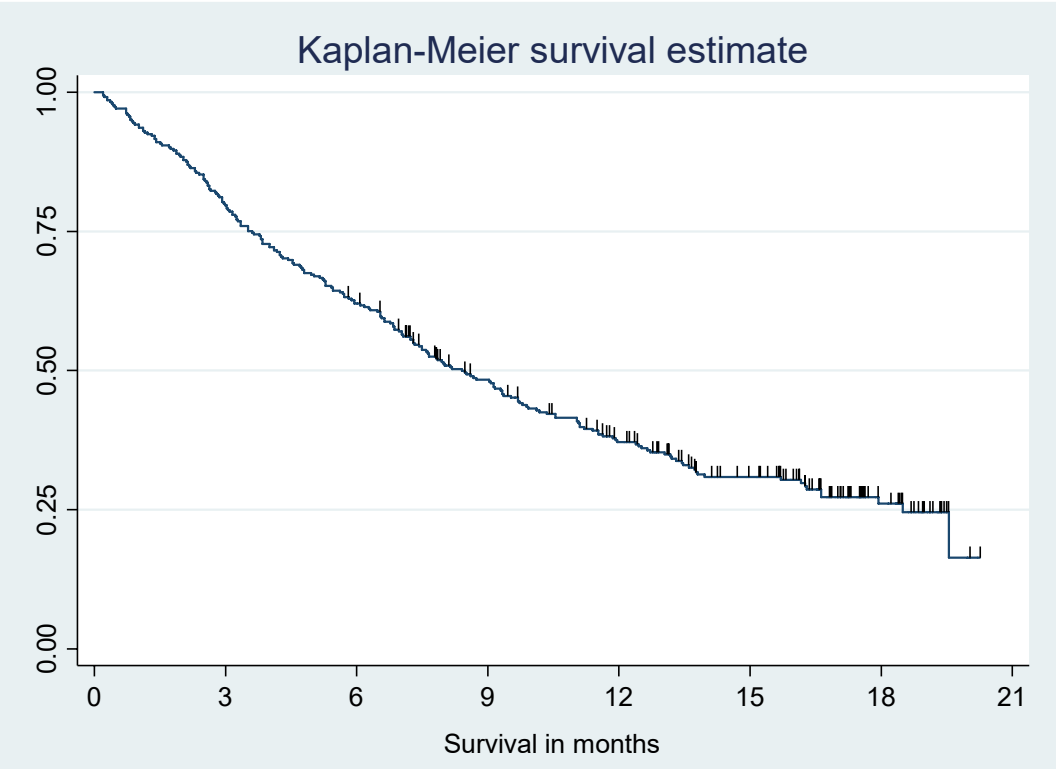


Table 15 and 16 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 20 months (608 days), all patients were traced on 5 June 2019.

Table 15: **Includes the number of patients at risk, by quarterly breakpoints.**

Time intervals (months)	**0-21**	**3-21**	**6 -21**	**9-21**	**12-21**	**15-21**	**18-21**
Number at risk	345	275	213	150	106	67	22

Table 16 shows that for all patients who received treatment, 110 were still alive (censored) at the date of follow-up and 235 had died (events).

Table 16: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-21	3-21	6 -21	9-21	12-21	15-21	18-21
Censored	110	110	109	91	81	58	20
Events	235	165	104	59	25	9	2

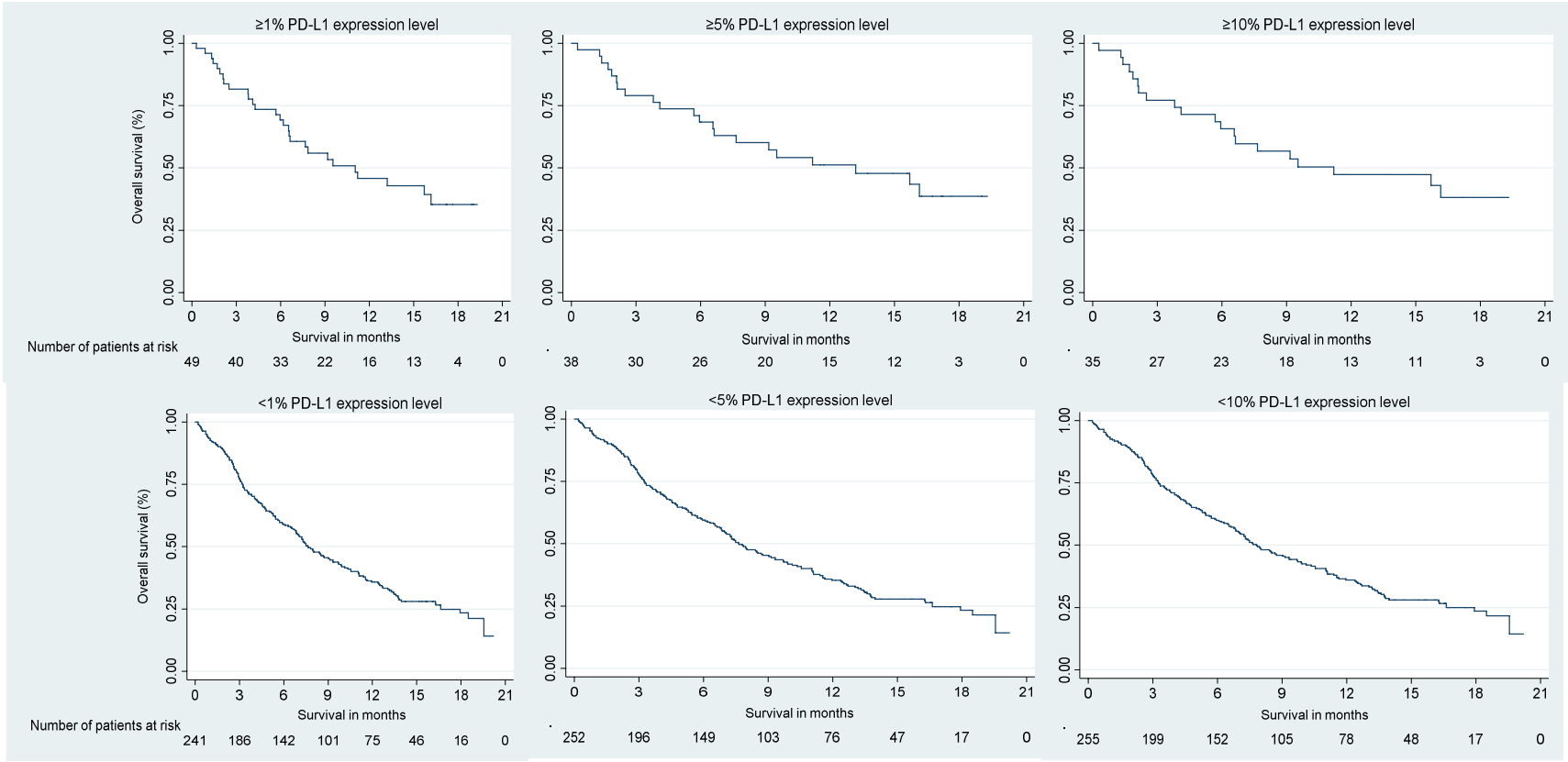
Table 17: Median treatment duration, full cohort and sensitivity analysis.

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort
N	348	312 (treatment duration) 345 (OS)
Median treatment duration	3.5 months (106 days) [95% CI: 3.0, 4.1]	3.3 months (100 days) [95% CI: 2.9, 4.0]
OS	8.4 months (255 days) [95% CI: 7.2, 9.7]	8.4 months (255 days) [95% CI: 7.3, 9.7]

Overall survival by PD-L1 expression level

Figure 7 provides the Kaplan-Meier curves for overall survival by PD-L1 expression level, censored at 5 June 2019.

Figure 7: Kaplan-Meier curves by PD-L1 expression level



Conclusions

348 patients received nivolumab for the treatment of locally advanced or metastatic squamous NSCLC [TA483] through the CDF in the reporting period (20 September 2017 and 19 December 2018). All patients were reported to the SACT dataset. For an additional 29 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 348 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 (66% male, 34% female). Most of the cohort was aged between 60 and 79 years (76%) 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, 278 patients were identified as no longer receiving treatment, of these, 100% (N=278) of patients had an outcome submitted by the treating trust to the SACT dataset which detailed the reason why a patient ended their treatment. 60% (N=168) of patients had stopped treatment due to disease progression, 9% (N=24) had stopped treatment due to toxicity, 4% (N=10) of patients chose to end their treatment, 21% (N=57) of patients died (not on treatment), 6% (N=18) of patients died on treatment and <1% of patients (N=1) ended treatment on account of unrelated comorbidity.

The median treatment duration was 3.5 months (106 days) [95% CI: 3.0, 4.1]. The median follow-up was 97 days and the maximum follow-up was 16 months (487 days).

The median overall survival was 8.4 months (255 days) [95% CI: 7.2, 9.7]. 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 very little difference in treatment duration (full cohort = 3.5 months; sensitivity analysis cohort = 3.3 months), this difference was not statistically significant. There was no difference in overall survival.

References

1. The Personal Demographics Service (PDS) [Internet]. NHS Digital: 2018 [cited 2019 May]. Available from: https://digital.nhs.uk/Demographics

2. Office for National Statistics. Cancer Registration Statistics, England: 2017. 2019 [cited 2019 May]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland

3. National Cancer Registration and Analysis Service (NCRAS). Cancer Survival in England: 2011 and 2015 and followed up to 2016. 2018 (Unpublished)

4. National Cancer Registration and Analysis Service (NCRAS). http://www.ncin.org.uk/about_ncin/

5. National Cancer Registration and Analysis Service (NCRAS). Cancer breakdown by stage, England: 2017: 2019 [cited 2019 May]. Available from: http://www.ncin.org.uk/publications/survival_by_stage

6. National Institute for Health and Care Excellence: 2016 [cited 2019 Jun]. Available from: https://www.nice.org.uk/guidance/TA483/chapter/1-Recommendations

7. Cancer Drugs Fund. [Internet]. NHS England: 2017 [cited 2019 Jun]. Available from: https://www.england.nhs.uk/cancer/cdf/

8. Appraisal and funding of Cancer Drugs. NHS England: 2016 [cited 2019 Jun]. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf

9. National Institute for Health and Care Excellence: 2016 [cited 2019 Jun]. Available from: https://www.nice.org.uk/guidance/ta483/resources/managed-access-agreement-november-2017-pdf-4659350653

10. CheckMate 003 clinical trial: 2018 [cited 2019 Jun] Available from: https://clinicaltrials.gov/ct2/show/NCT00730639

11. CheckMate 017 clinical trial: 2018 [cited 2019 Jun] Available from: https://clinicaltrials.gov/ct2/show/NCT01642004

12. CDF analytical methods. [Internet]. PHE: 2019 [cited 2019 Jun]. Available from: http://www.chemodataset.nhs.uk/nhse_partnership/

NICE National Institute for Health and Care Excellence

Clinical expert statement

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483) ID1559

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	
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 squamous NSCLC, TA483), 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 paclitaxel and carboplatin chemotherapy, TA600) 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 paclitaxel and carboplatin chemotherapy, as per TA600, and as indicated in NICE Lung Cancer Treatment Pathway "Advanced squamous (stages IIIB and IV) non-small-cell lung cancer: PD-L1 under 50% (no gene mutation, fusion protein or biomarker)" or "Advanced 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 across the NHS? (Please state if your experience is from outside England.)	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
• 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 technology? (For example, for facilities, equipment, or training.)	No additional investment
12. Do you expect the technology to provide clinically meaningful benefits compared	Yes, this class of therapy is a step change over standard chemotherapy

with current care?	
• 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 modest differential activity by PDL1 status, as demonstrated in the CM017 trial for PFS and modest differential activity for overall survival by PDL1 status
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current	No. Using immune checkpoint inhibitors is now clinically routine in the NHS.

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.)	
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	No

(QALY) calculation?	
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 particular unmet need of the patient population?	Yes, for those that were unable to access a first-line immune checkpoint inhibitor, it addresses poor survival, otherwise
18. How do any side effects or adverse effects of the technology affect the management of the condition	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

and the patient's quality of life?	
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 CM017
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	A number of secondary endpoints were used, including PFS and response rate, all improved compared to 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. 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 CM017 trial
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

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

- Nivolumab for relapsed squamous NSCLC is an important step-change in therapy over docetaxel chemotherapy
- The majority of newly diagnosed advanced 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
- PDL1 status has modest impact if any on survival benefit

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.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NHS England submission on the NICE re-appraisal of nivolumab monotherapy for the treatment of locally advanced/metastatic squamous (S) non small cell lung cancer (NSCLC) in patients who have been treated with prior platinum-based chemotherapy (ID1559)

1. 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..
2. NHS England notes the sustained 5 year overall survival (OS) rate of [redacted]% with nivolumab in Checkmate 017. 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.
3. NHS England notes the continued nivolumab treatment rate of [redacted]% and [redacted]% at 2 and 5 years in Checkmate 017. 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.
4. 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 but now to have 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 017 study and in some NSCLC patients in Checkmate 003 who discontinued treatment at 96 weeks.
5. NHS England supports the company conclusion that PD-L1 status is not predictive of PFS and OS.
6. BMS claims that the outcomes of Checkmate 017 can be generalised into the NHS given that [redacted]. What really matters is where the long term tail plateaus in the OS KM curve in the NHS and the SACT data is not mature enough to give any indications as to this.

7. 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.
8. Use of 2nd line immunotherapy in S NSCLC is falling now that 1st line immunotherapy in combination with chemotherapy is in practice via a CDF recommendation.

Prof Peter Clark

National Clinical lead for the Cancer Drugs Fund

NHS England

March 2020

Cancer Drugs Fund

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated squamous non-small cell lung cancer [ID1559]

Cancer Drugs Fund update of TA483

This report was commissioned by the NIHR Systematic Reviews Programme as project number 129534

Completed 08 January 2020

Confidential information redacted

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title:	Nivolumab for previously treated squamous non-small cell lung cancer [ID1559] (Cancer Drugs Fund update of TA483)
Produced by:	Liverpool Reviews & Implementation Group (LR*i*G)
Authors:	Sophie Beale, Research Associate, LR*i*G, University of Liverpool Angela Boland, Director, LR*i*G, University of Liverpool James Mahon, Director, Coldingham Analytical Services, Berwickshire
Correspondence to:	Angela Boland, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB
Date completed:	08 January 2020

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number NIHR 129534.

Declared competing interests of the authors: None.

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.

This report should be referenced as follows: Beale S, Boland A and Mahon J. Nivolumab for previously treated squamous non-small cell lung cancer [ID1559]: Cancer Drugs Fund update of TA483. Liverpool Reviews and Implementation Group, University of Liverpool, 2020.

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

Table of contents

List of tables

List of figures

LIST OF ABBREVIATIONS

AC	Appraisal Committee
AE	Adverse event
AIC	Akaike information criterion
AUC	Area Under the Curve
BIC	Bayesian information criterion
BSA	Body surface area
CDF	Cancer Drugs Fund
CI	Confidence interval
CS	Company submission
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions Questionnaire
ERG	Evidence Review Group
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
K-M	Kaplan-Meier
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 TA483 was to recommend nivolumab as an option for use within the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) in adults after chemotherapy. Terms of Engagement, although not binding, outline NICE's expectations for the company submission (CS) for the CDF review. This Evidence Review Group (ERG) report focuses on the key issues outlined in the final Terms of Engagement document issued by NICE.

To inform TA483, the company provided evidence from the CheckMate-017 trial. The CheckMate-017 trial is a randomised, open-label, international, phase III study evaluating the efficacy and safety of nivolumab versus docetaxel in patients with advanced squamous NSCLC whose disease has progressed during or after first-line chemotherapy. This CDF review is taking place as 5-year follow-up data (May 2019 database lock) are now available from this trial. In addition to CheckMate-017 trial data, observational data, collected during the period that nivolumab was available via the CDF, were collected and have been extracted (by NHS England) from the systemic anti-cancer therapy (SACT) dataset.

1.2 Summary of key issues in clinical effectiveness evidence

As set out in the Terms of Engagement document, the company has provided evidence for patients with previously treated locally advanced or metastatic squamous NSCLC who have received prior chemotherapy.

The company, as expected by the NICE Appraisal Committee (AC), has submitted clinical evidence for the full population, as well as by level of tumour PD-L1 expression (1%, 5% and 10%). For the full population, median overall survival (OS) calculated using data from the CheckMate-017 trial (May 2019 database lock), was [redacted]months (95% 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 ERG highlights that the 5-year OS rate for patients randomised to receive nivolumab ([redacted]%; 95% CI: [redacted]% to [redacted]%) was at least [redacted] times that of patients randomised to receive docetaxel ([redacted]%; 95%CI: [redacted]% to [redacted]%), despite the fact that, at this time point, patients randomised to the docetaxel arm of the trial were also likely to be receiving immunotherapy (IO) (after switching to nivolumab at 2 years or receiving IO as a subsequent therapy).

CheckMate-017 trial results provided by the company to inform TA483 showed no statistically significant differences between treatment with nivolumab and treatment with docetaxel in terms of OS by level of tumour PD-L1 expression. The OS results by level of tumour PD-L1 expression generated from analyses of data from the 5-year database lock, confirm these original results.

CheckMate-017 trial results suggests that the difference between arms in terms of median progression-free survival (PFS) is [redacted] (nivolumab: [redacted] months [95% CI: [redacted] to [redacted] months], docetaxel: [redacted] months [95% CI: [redacted] to [redacted] months]).

The comparator described in the Terms of Engagement document is docetaxel. Clinical advice to the ERG supports the view that this is the relevant comparator for this appraisal. The AC considered that results from the CheckMate-017 trial were generalisable to clinical practice in England. The OS and time on treatment data from the CheckMate-017 trial and the SACT database are similar, which support this conclusion.

1.3 Summary of key issues in cost effectiveness evidence

Results from the CheckMate-017 trial show that the variation in median OS, by level of tumour PD-L1 expression, is not statistically significantly different. The ERG, therefore, supports the company's decision not to generate cost effectiveness results by level of tumour PD-L1 expression.

The company implemented approaches to modelling OS and PFS that differed from the approaches outlined in the Terms of Engagement document; the AC's preferred approaches did not provide good statistical or visual fits to updated CheckMate-017 trial Kaplan-Meier (K-M) data. The ERG considers that the company's preferred distributions that were used to model OS and PFS are, for the purpose of decision making, adequate.

A treatment stopping rule was not included in the CheckMate-017 trial protocol. However, in line with AC preference, the company's CDF review base case analysis included a 2-year stopping rule. If treatment with nivolumab is continued up until 5 years, then the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained that is generated using the company base case assumptions, for the comparison of the cost effectiveness of nivolumab versus docetaxel, is £48,717.

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 the modelling of treatment waning would have little effect on estimates of the relative cost effectiveness of treatment with nivolumab versus docetaxel.

The updated company ICER per QALY gained for the comparison of the cost effectiveness of nivolumab versus docetaxel is £35,657. The ERG does not consider that any amendments could be made to the company model or company parameter choices that would result in a more accurate estimate of cost effectiveness.

1.4 End of life

As life expectancy under standard of care is less than 2 years and the gain in life extension with nivolumab versus docetaxel is greater than 3 months, the ERG considers that the NICE end of life criteria have been met for nivolumab in people with previously treated squamous NSCLC.

2 EVIDENCE REVIEW GROUP REPORT

2.1 Introduction

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

- nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression
- the conditions in the Managed Access Agreement (MAA) are followed.[2]

This recommendation followed a lengthy appraisal process which 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, the Evidence Review Group (ERG) and the NICE Decision Support Group (DSU). The key trial used by the company to provide evidence to support treatment with nivolumab was the CheckMate-017 trial.[3] The CheckMate-017 trial is a randomised, open-label, international, phase III study evaluating the efficacy and safety of nivolumab versus docetaxel in patients with advanced squamous NSCLC whose disease has progressed during or after first-line chemotherapy. At the time of the original company submission (CS) to NICE, overall survival (OS) data from this trial were very immature; however, 5-year follow-up data are now available (May 2019 database lock). The company has provided updated clinical and cost effectiveness results based on the 5-year follow-up data.

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, and approval by the European Medicines Agency was granted in July 2017[4]
- nivolumab is administered by intravenous infusion
- at the time of the original CS,[5] dosing was based on weight but the dosing regime was changed to a flat dose of 240mg every 2 weeks (Q2W) in 2018

- A Patient Access Scheme (PAS) means that nivolumab is available at a (confidential) discounted price to the NHS.

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 TA483,[5] and which remain relevant to this CDF review, are summarised in Box 1.

Box 1 Clinical effectiveness issues

Population

- There are some patients who may be seen in clinical practice who are not covered by the clinical effectiveness data in the CheckMate-017 trial. These include patients with ECOG PS>1 and patients using higher-dose corticosteroids
- Due to the limited number of patients aged ≥75 years participating in the CheckMate-017 trial (8% in the nivolumab arm and 13% in the docetaxel arm), the relative efficacy of nivolumab versus docetaxel in this age group is unknown
- Nivolumab is a PD-1 inhibitor which blocks the interaction of PD-1 with PD-L1. However, there is no evidence from the CheckMate-017 trial to suggest that treatment with nivolumab should be targeted based on tumour PD-L1 status.

Intervention

- One fifth of patients randomised to the nivolumab arm of the CheckMate-017 trial carried on receiving nivolumab after disease progression. This was permitted when the investigator suspected that a patient had experienced a 'pseudo-progression' and one third of these patients (i.e., 6.7% of all patients treated with nivolumab) continued to benefit (in terms of tumour response). The ERG is unsure how these 'non-conventional benefitters' (as the company describes such patients) would be identified and treated in routine clinical practice in England.

Comparators

- [redacted]% of patients randomised to the docetaxel arm of the CheckMate-017 trial discontinued treatment with docetaxel within the first week of starting treatment; this rate of discontinuation appears to be higher than would be expected in clinical practice
- The company carried out ITCs to allow treatment with nivolumab to be compared with treatment with erlotinib and BSC. There was heterogeneity, in terms of patient characteristics, across the included trials and insufficient data to determine whether the assumption that survival hazards were proportional. These issues meant that the ERG was not confident that the ITC results were credible.

BSC=best supportive care; ECOG=European Cooperative Oncology Group; ERG= Evidence Review Group; ITC=indirect treatment comparison; PD-1=programmed death-1; PD-L1= programmed death-ligand 1; PS=performance status
Source: ERG report[5] (nivolumab for previously treated squamous patients)

3 CLINICAL DECISION PROBLEM

The NICE AC's preferred clinical assumptions (as set out in the Terms of Engagement document[6]) are presented in Table 1. The Terms of Engagement, although not binding, outline NICE's expectations relating to the content of the CDF review CS. The extent to which the information provided in the CDF Review CS meets the terms of engagement is considered in Sections 3.1 to 3.4.

Table 1 NICE Appraisal Committee's preferred clinical assumptions

Area	Summary of NICE AC's preferred clinical assumptions
Population	*People with previously treated locally advanced or metastatic squamous NSCLC after prior chemotherapy*
Comparators	*Docetaxel*
Generalisability	*Results of CheckMate-017 are generalisable to clinical practice in England*
Subgroups	*The company are expected to submit evidence for the full population, as well as by PD-L1 expression level (1%, 5% and 10%)*

AC=Appraisal Committee; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1
Source: NICE Terms of Engagement document 2019[6]

3.1 Population and subgroups

Box 1 NICE Appraisal Committee's preferred clinical assumption: population and subgroups

Population

The NICE AC considered that the population should be patients with previously treated locally advanced or metastatic squamous NSCLC after prior chemotherapy

Subgroup

The company are expected to submit evidence for the full population, as well as by PD-L1 expression level (1%, 5% and 10%)

Source: NICE Terms of Engagement document 2019[6]

Population

The company has submitted clinical evidence for the population described in the Terms of Engagement document,[6] i.e., those with previously treated locally advanced or metastatic squamous NSCLC after prior chemotherapy. Key clinical effectiveness results (OS, progression-free survival [PFS] and time to treatment discontinuation [TTD]) from the Checkmate-017 trial (May 2019 database lock) for this population are provided in Table 2. The 5-year OS rate for patients receiving nivolumab ([redacted]%; 95% CI: [redacted]% to [redacted]%) was at least [redacted] times that for the docetaxel group ([redacted]%; 95%CI: [redacted]% to [redacted]%). The company highlights that this continued benefit from treatment with nivolumab was seen despite the fact that, at

this time point, patients randomised to the docetaxel arm of the trial were also likely to be receiving immunotherapy (IO) (after switching to nivolumab at 2 years or receiving IO as a subsequent therapy).

Table 2 CheckMate-017 trial results for key outcomes (May 2019 database lock)

	Nivolumab N=135	**Docetaxel N=137**
Overall survival, median (95% CI)	[redacted]m ([redacted] to [redacted])	[redacted]m ([redacted] to [redacted]m)
Progression-free survival, median (95% CI)	[redacted]m ([redacted] to [redacted]m)	[redacted]m ([redacted] to [redacted]m)
Time to treatment discontinuation, median (95% CI)	[redacted] ([redacted] to [redacted]m)	[redacted] ([redacted] to [redacted]m)

CI=confidence interval; m=months
Source: CDF Review CS, Section D.6.1

Tumour PD-L1 expression subgroups

At the time of the original CS, the company provided clinical evidence to support the assumption that PD-L1 subgroup status was not predictive of clinical outcomes for patients with squamous disease. These data have been reproduced in the CDF Review CS (Figure 6). The company has also provided effectiveness results, by level of tumour PD-L1 expression, generated from analyses of data from the 5-year database lock (see Figure 1), which confirm the results from the original analysis. The ERG notes that the European Medicines Agency (EMA) marketing authorisation does not restrict use of nivolumab for the treatment of advanced or metastatic NSCLC after prior chemotherapy by tumour PD-L1 mutation expression.[4]

Figure 1 Checkmate-017 trial overall survival by PD-L1 subgroup: 5-year update

Source: CDF Review CS, Figure 7

3.2 Comparators

Box 2 NICE Appraisal Committee's preferred clinical assumption: comparator

The NICE AC considered that docetaxel was the most appropriate comparator

Source: NICE Terms of Engagement document (2019)[6]

The comparator in the results presented in the CDF Review CS is docetaxel. At the time of the original CS, the NICE AC considered, and then dismissed, best supportive care (BSC) and erlotinib as possible comparators to nivolumab. Docetaxel is the treatment provided to patients randomised to the comparator arm of the CheckMate-017 trial and thus direct evidence is available for the comparison of treatment with nivolumab versus docetaxel.

3.3 Generalisability

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

Results of CheckMate-017 are generalisable to clinical practice in England

Source: NICE Terms of Engagement document (2019)[6]

The NICE AC concluded that the results from the CheckMate-017 trial were generalisable to clinical practice in England, despite the fact that only patients with European Cooperative Oncology Group (ECOG) Performance Status (PS) scores ≤1 were included in the trial and the trial only included a limited number of patients aged ≥75 years. The ERG and the company's interpretation of the systemic anti-Cancer therapy (SACT) data (see Section 3.5) support this view.

3.4 SACT database outcomes

Public Health England (PHE) provided a report[7] for NHS England which includes results from analyses of data collected from patients who received nivolumab via the CDF (application from 20 September 2017 to 19 December 2018). Patients were followed up until 31 January 2019. Summary characteristics of the 348 unique patients included in the analyses are described in

Table 3. The OS data from analyses of SACT data are presented in Table 4.

Table 3 SACT data: summary of characteristics of patients receiving nivolumab via the CDF

Characteristic	Patients with CDF application (n=348)
Male	230 (66%)
Age, median	70 years
PS 0 or 1	59 (17%) or 301 (71%)*
PD-L1<1%	241 (69%)
PD-L1≥1%	49 (14%)
PD-L1 not reported	58 (17%)
Patents who had completed tx by Jan 2019	278 (80%)
Median follow up time in SACT (Range: minimum to maximum)	487 days (5 months to 20 months)
Median treatment duration	3.5 months (95% CI: 3.0 to 4.1 months)
Proportion of patients receiving tx at 6 months	30% (95% CI: 25% to 35%)
Proportion of patients receiving tx at 12 months	16% (95% CI: 12% to 21%)

CDF=Cancer Drugs Fund; CI=confidence interval; PS=performance status; treatment=tx
* PS of remaining patients is not reported
Source: CDF Review CS, Section D.6.6

Table 4 SACT data: overall survival data of patients receiving nivolumab via the CDF

Survival	Estimate
Median OS	8.4 months (95% CI: 7.2 to 9.7 months)
Survival at 6 months	57% (95% CI: 51% to 62%)
Survival at 12 months	35% (95% CI: 30% to 41%)
Alive/dead at date of follow up	111/237

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

The company suggests that TTD data from the CheckMate-017 trial are generalisable to the real world because the median treatment durations of patients randomised to the nivolumab arm of the CheckMate-017 trial and those treated with nivolumab who provided data recorded in the SACT database were similar, and the TTD Kaplan-Meier (K-M) curves for these two populations are similar (Figure 2).

Figure 2 SACT database and CheckMate-017 trial treatment duration data

Source: CDF Review CS, Figure 10

The company suggests that OS data from the CheckMate-017 trial are generalisable to the real world because median OS calculated using SACT data from patients treated with nivolumab was similar to the median OS for the population randomised to the nivolumab arm of the CheckMate-017 trial (months), and the OS K-M curves for these two populations are similar (Figure 3).

Figure 3 SACT database and CheckMate-017 trial overall survival data

Source: CDF Review CS, Figure 11

In the CDF Review CS (p25), the company also provides SACT database OS K-M data by level of tumour PD-L1 expression, censored at 5 June 2019, from patients treated with nivolumab. These data support the assumptions that (i) nivolumab is effective across all tumour PD-L1 expression levels and (ii) that tumour PD-L1 expression is not a good predictor of outcome.

3.4.1 ERG comments on SACT analyses

The ERG notes that patients who received nivolumab via the CDF were older than patients in the CheckMate-017 trial (median: 70 years versus 63 years). It is difficult to make comparisons between SACT and CheckMate-017 trial patients in terms of ECOG PS and level of tumour PD-L1 expression as, for 12% and 17% of SACT patients respectively, there are no data relating to these baseline characteristics.

3.5 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[6]).

Key outcomes from the CheckMate-017 trial (nivolumab versus docetaxel) are presented for a population with previously treated locally advanced or metastatic squamous NSCLC. The company has presented clinical effectiveness evidence for the full population as well as by tumour PD-L1 expression level. These data support the assumptions that (i) nivolumab is effective across all tumour PD-L1 expression levels and (ii) that tumour PD-L1 expression is not a good predictor of outcome. The ERG highlights that the EMA marketing authorisation does not restrict use of nivolumab by level of tumour PD-L1 expression.[6]

Clinical advice to the ERG is that docetaxel is the most appropriate comparator and that results from the CheckMate-017 trial are generalisable to clinical practice in England. This view is supported by SACT data.

4 COST EFFECTIVENESS DECISION PROBLEM

The NICE AC's preferred economic assumptions, as set out in the Terms of Engagement[6] document, are presented in Table 5. Further information relating to each assumption is provided in the text following the table.

Table 5 NICE Appraisal Committee's preferred economic assumptions

Area	Summary of NICE AC's economic assumptions
Model structure	*Company's model structure was accepted. It was anticipated that the model structure would not change*
Subgroups	*The company are expected to submit evidence for the full population, as well as by PD-L1 expression level (1%, 5% and 10%)*
Extrapolation of OS*	*It is anticipated that the AC's preferred approach to extrapolation of OS (DSU: observed K-M followed by generalised gamma curve) would remain, unless the company can demonstrate that additional data from the trial and the SACT justify departure from this approach*
Extrapolation of PFS	*Observed K-M followed by exponential curve*
Utilities	*Utility value of 0.693 in the PF health state was appropriate* *Utility value of 0.509 in the PD health state was reasonable*
Treatment duration	*Not limiting docetaxel to a maximum of 4 cycles was appropriate*
Stopping rule	*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	*Nivolumab's treatment effect could last up to 3 years*
Treatment costs	*Use distributions for body weights and surface areas and the average NHS costs for generic medicines based on eMIT tool*
End of life	*Nivolumab met the criteria to be considered a life-extending, end-of-life treatment*

AC=Appraisal Committee; DSU=Decision Support Unit; eMIT=electronic Market Information Tool; K-M=Kaplan-Meier; PD-L1=programmed death-ligand 1; PD=progressed disease; PF=progression-free; PFS=progression-free survival; OS=overall survival; SACT=systemic anti-cancer therapy

* The AC's preferred approach (as put forward by the DSU) was a generalised gamma distribution for the whole period, not the hybrid model described in the NICE Terms of Engagement document 2019[6]

Source: NICE Terms of Engagement document (2019)[6]

4.1 Model structure

Box 4 NICE Appraisal Committee's preferred economic assumption: model structure

The NICE AC accepted the company's model structure. It was anticipated that the model structure would not change

Source: NICE Terms of Engagement document (2019)[6]

The ERG has been able to use the company model to replicate the cost effectiveness results that are reported in the NICE Final Appraisal Determination (FAD) document.[1]

4.2 Subgroups

Box 5 NICE Appraisal Committee's preferred clinical assumption: subgroups

The company are expected to submit evidence for the full population, as well as by PD-L1 expression level (1%, 5% and 10%)

Source: NICE Terms of Engagement document (2019)[6]

Median OS results, by level of tumour PD-L1 expression, from the CheckMate-017 trial are not statistically significantly different. The ERG considers that if effectiveness results are not statistically significant, then a difference should not be modelled when estimating cost effectiveness. The ERG, therefore, supports the company's decision not to generate cost effectiveness results by level of tumour PD-L1 expression.

4.3 Extrapolation of overall survival

Box 6 NICE Appraisal Committee's preferred economic assumption: extrapolation of overall survival

It is anticipated that the AC's preferred approach to extrapolation of OS (DSU: observed K-M followed by generalised gamma curve) would remain, unless the company can demonstrate that additional data from the trial and the SACT justify departure from this approach

Source: NICE Terms of Engagement document (2019)[6]

The ERG highlights that the AC's preferred approach (as put forward by the NICE Decision Support Unit [DSU] was a generalised gamma distribution used for the whole time period) not as described in the NICE Terms of Engagement document 2019[6] (K-M data followed by a generalised gamma distribution).

The company concluded, based on visual inspection, that the generalised gamma distribution was not a good fit to the 5-year CheckMate-017 trial OS K-M data and carried out a curve fitting exercise to identify the best fitting extrapolations. The company concluded that the OS hazards for patients treated with nivolumab and docetaxel were proportional (except during the early stages of the trial) and thus fitted survival distributions to the CheckMate-017 trial data with treatment as a covariate. The 14 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-017 trial OS K-M data. Based on these assessments, the company's preferred distribution was the spline hazard 2 knots distribution.

The maturity of the OS data from the CheckMate-017 trial means that the distribution choice makes little difference to cost effectiveness results. For the comparison of treatment with nivolumab versus docetaxel, the majority of good fitting distributions generated incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained that were between £34,000 and £37,000. The ERG, therefore, considers that, for the purpose of decision making, the company's preferred extrapolations are adequate.

4.4 Extrapolation of progression-free survival

Box 7 NICE Appraisal Committee's preferred economic assumption: extrapolation of progression-free survival

Observed K-M followed by exponential curve

Source: NICE Terms of Engagement document (2019)[6]

The company concluded, based on visual inspection, that the AC's preferred distribution (CheckMate-017 trial PFS K-M data followed by an exponential distribution) was not a good fit to the 5-year CheckMate-017 trial PFS K-M data and carried out a curve fitting exercise to identify the best fitting extrapolations. The company concluded that the PFS hazards for patients treated with nivolumab and docetaxel were not proportional and thus fitted independent survival distributions to the CheckMate-017 trial data. The 13 different curves fitted by the company were assessed statistically (using the AIC and the BIC statistics) and by assessing visual fit to the CheckMate-017 trial PFS K-M data. The company concluded that the best distribution to use to model PFS for patients treated with nivolumab and for those treated with docetaxel was the spline hazard 1 knot.

Due to the maturity of the CheckMate-017 PFS K-M data, the choice of distribution used to extrapolate the trial data makes little difference to cost effectiveness results. For the comparison of treatment with nivolumab versus docetaxel, the majority of good fitting distributions generated ICERs per QALY gained that were between £33,500 and £37,500. The ERG considers that, for the purpose of decision making, the company's preferred extrapolations are adequate.

The CheckMate-017 trial PFS K-M data and the plausible extrapolations considered by the company suggest that, after 5 years, patients receiving nivolumab effectively do not experience disease progression (almost all progression events are deaths). The clinical plausibility of a lifetime zero hazard rate for disease progression in a population that had previously been diagnosed with locally advanced or metastatic NSCLC is uncertain.

4.5 Utilities

Box 8 NICE Appraisal Committee's preferred economic assumption: utilities

Utility value of 0.693 in the PF health state was appropriate *Utility value of 0.509 in the PD health state was reasonable*

Source: NICE Terms of Engagement document (2019)[6]

The ERG confirms that the company has used the AC's preferred utility values to generate the base case cost effectiveness results.

4.6 Treatment duration

Box 9 NICE Appraisal Committee's preferred economic assumption: treatment duration

Not limiting docetaxel to a maximum of 4 cycles was appropriate

Source: NICE Terms of Engagement document (2019)[6]

The ERG confirms that, in line with the AC's preference, in the company base case analysis, treatment with docetaxel has not been limited to a maximum of four cycles.

4.7 Stopping rule and continued treatment effect

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

Stopping rule *A 2-year stopping rule was included in the recommendations given current available evidence but should be reviewed in light of any evidence* ***Treatment waning*** *Nivolumab's treatment effect could last up to 3 years*

Source: NICE Terms of Engagement document (2019)[6]

Treatment stopping rule

A treatment stopping rule was not included in the CheckMate-017 trial protocol. However, in line with AC preference, the company's CDF review base case analysis included a 2-year stopping rule. The ERG highlights that the CheckMate-017 trial TTD data used in the company model show that, at 2 years, [redacted]% of patients were still receiving nivolumab and it is reported in the CDF Review CS that, at 3 and 5 years, [redacted]% and [redacted]% of patients, respectively, were still receiving nivolumab. If treatment with nivolumab is continued up until 5 years, then the ICER per QALY gained, generated using the company base case assumptions, for the comparison of the cost effectiveness of nivolumab versus docetaxel is £48,717.

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:

- most patients who were randomised to the nivolumab arm of the CheckMate-017 trial received treatment for less than 2 years
- in the CheckMate-003 trial, 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 patients randomised to the nivolumab arm of the CheckMate-017 trial.

The trial evidence presented by the company (CheckMate-017 and CheckMate-003) does not fully discount the possibility of a treatment waning effect occurring. However, the length of time that any treatment effect might continue is not known. In addition, as patients randomised to the docetaxel arm of the CheckMate-017 trial crossed 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.

4.8 Treatment costs

Box 11 NICE Appraisal Committee's preferred economic assumption: treatment costs

Use distributions for body weights and surface areas and the average NHS costs for generic medicines based on eMIT tool

Source: NICE Terms of Engagement document (2019)[6]

The company has estimated treatment costs using the 5-year CheckMate-017 trial TTD K-M data. These data are virtually complete (see CDF Review CS, Figure 18) and have been used directly in the company model, without extrapolation. The ERG considers that this is appropriate.

At the time of TA483,[5] the dose of nivolumab that patients received depended on their weight. In 2018, the dose of nivolumab changed to 240mg every 2 weeks (Q2W). The company has, therefore, generated cost effectiveness results using this new flat dose.

4.9 End of life

Box 12 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[6]

NICE end of life criteria 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.

The company's base case model estimate of mean OS for patients treated with docetaxel is [redacted] months and median OS is [redacted] months (CheckMate-017 trial). The ERG, therefore, considers that the short life expectancy criterion is met.

The company's base case model estimate of mean OS for patients treated with nivolumab is [redacted] months and median OS is [redacted] months (CheckMate-017 trial). The ERG, therefore, considers that the life extension criterion (i.e., OS gain greater than 3 months) is also met.

5 COMPANY 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 16). Different combinations of study data, survival extrapolations and nivolumab doses have been used to generate cost effectiveness results. The cost effectiveness estimates from each of the company's analyses are shown in Table 6. The company's new base case with new PAS price and nivolumab flat dose (cost effectiveness analysis 3) generated an ICER per QALY gained of £35,657.

The impact on the ICER per QALY gained of individual parameter changes to the NICE AC's preferred economic assumptions is shown in Table 7.

Table 6 Company's cost effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Inc. 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							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£23,076	0.80	0.46	£49,826[a]
Cost-effectiveness analysis 1b: replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry with CDF PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£23,153	0.80	0.46	£49,992
Cost-effectiveness analysis 1c: replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry with new PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£31,881	0.80	0.46	£68,838
Cost-effectiveness analysis 2: analysis that demonstrated plausible potential for cost effectiveness at CDF entry, with new PAS and incorporating updated OS (generalised gamma) and PFS (hybrid exponential) fitted to 5-year CheckMate-017 K-M data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£29,683	0.66	0.43	£69,647
Cost-effectiveness analysis 3: new company base case with new PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£31,281	1.49	0.88	£35,657

[a] Revised ICER after a programming error was corrected during preparation of current submission (ICER at CDF entry was £49,982[1])
CDF=Cancer Drugs Fund; ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; LYG=life years gained; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year
Source: CDF Review CS, Table 16

Table 7 Impact on the ICER per QALY gained

Scenario and cross-reference	Scenario detail	Impact on ICER per QALY gained
Committee preferred assumptions: replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry with PAS and nivolumab flat dose (analysis 1c)		**£68,838**
OS extrapolation	OS modelled with updated base case: spline hazards 2 knots extrapolation (5-year May 2019 CheckMate-017 database lock).	-£11,486
PFS extrapolation	PFS modelled with updated base case: spline hazards 1 knot extrapolation (5-year May 2019 CheckMate-017 database lock).	-£33,464
Time to treatment discontinuation	Time to treatment discontinuation modelled with KM data (5-year May 2019 CheckMate-017 database lock), with 2-year stopping rule	£891
Duration of effect	Duration of treatment effect modelled with no waning of effect.	-£5,576

CDF=Cancer Drugs Fund; ICER=incremental cost effectiveness ratio; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year
Source: CDF Review CS, Table 17

5.1.1 Model validation and face validity check

The company states (CDF Review CS, p13) that SACT data have been used to validate the company's preferred survival extrapolations and to assess the duration of treatment effect in routine NHS clinical practice.

5.2 ERG amendments to company model

The ERG has made no amendments to the company model. The maturity of the CheckMate-017 trial data means that that choice of method used to extrapolate available OS and PFS data has little impact on cost effectiveness results. The ERG does not consider that any amendments could be made to the company model or company parameter choices that would result in a more accurate estimate of cost effectiveness.

6 REFERENCES

1. National Institute for Health and Care Excellence (NICE). Final appraisal determination: nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483] National Institute for Health and Care Excellence. 2017; Available from: https://www.nice.org.uk/guidance/ta483/documents/final-appraisal-determination-document. Accessed 2019 12 December.
2. Bristol Myers-Squibb. Managed access agreement. Nivolumab for previously treated squamous NSCLC. Available from: https://www.nice.org.uk/guidance/ta483/resources/managed-access-agreement-november-2017-pdf-4659350653. Accessed 2019 12 December.
3. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, *et al.* Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015; 373:123-35.
4. European Medicines Agency. Opdivo: summary of product characteristics. European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf. Accessed 2019 12 December.
5. National Institute for Health and Care Excellence (NICE). Nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal guidance [TA483]. 2017; Available from: https://www.nice.org.uk/guidance/ta483. Accessed 2019 December.
6. National Institute for Health and Care Excellence (NICE). Terms of engagement for CDF review of TA483: nivolumab for previously treated squamous non-small-cell lung cancer. 2019; Accessed.
7. Public Health England. Nivolumab for treating locally advanced or metastatic squamous non-small cell lung cancer - data review [TA483]. 2019.
8. National Institute for Health and Care Excellence (NICE). Appraising life-extending, end of life treatments. Available from: https://www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2 Accessed 6 January 2020.

Updated Addendum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated squamous non-small cell lung cancer [ID1559]

Cancer Drugs Fund update of TA483

This report was commissioned by the NIHR Systematic Reviews Programme as project number 129534

Completed 24 January 2020

DOES CONTAIN ***

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Cost effectiveness results, requested by NICE (email dated 17 January 2020), following correction of a company model error, are provided in Table 1.

Table 1 Cost effectiveness results following correction of company model error (nivolumab PAS price)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Corrected company cost effectiveness analysis 2: analysis that demonstrated plausible potential for cost effectiveness at CDF entry, with [redacted] PAS and incorporating updated OS (generalised gamma) and PFS (hybrid exponential) fitted to 5-year CheckMate-017 K-M data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£29,683	0.66	0.43	£69,649
Corrected company cost effectiveness analysis 3: new company base case with [redacted] PAS and nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£31,275	1.48	0.88	£35,710
NICE requested analysis: analysis incorporating [redacted] PAS, updated OS (AC's preferred generalised gamma) and PFS (company preferred spline 1-knot-hazard) fitted to 5-year CheckMate-017 K-M data with nivolumab flat dose							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	£27,920	0.70	0.52	£53,881

CDF=Cancer Drugs Fund; ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; LYG=life years gained; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; QALYs=quality adjusted life year

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483)

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

This document is the 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 terms of engagement for the CDF review
- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

Issue date: January 2020

1. Topic background

1.1 Appraisal background

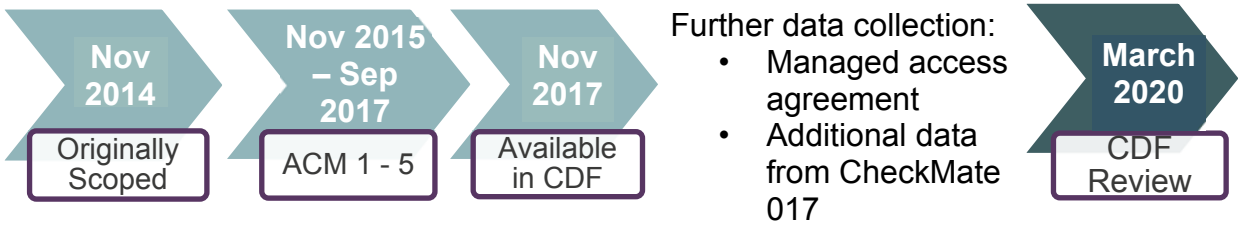
Nivolumab (Opdivo), Bristol-Myers Squibb

NICE TA483: Nivolumab is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic squamous non-small-cell lung cancer in adults after chemotherapy, only if:

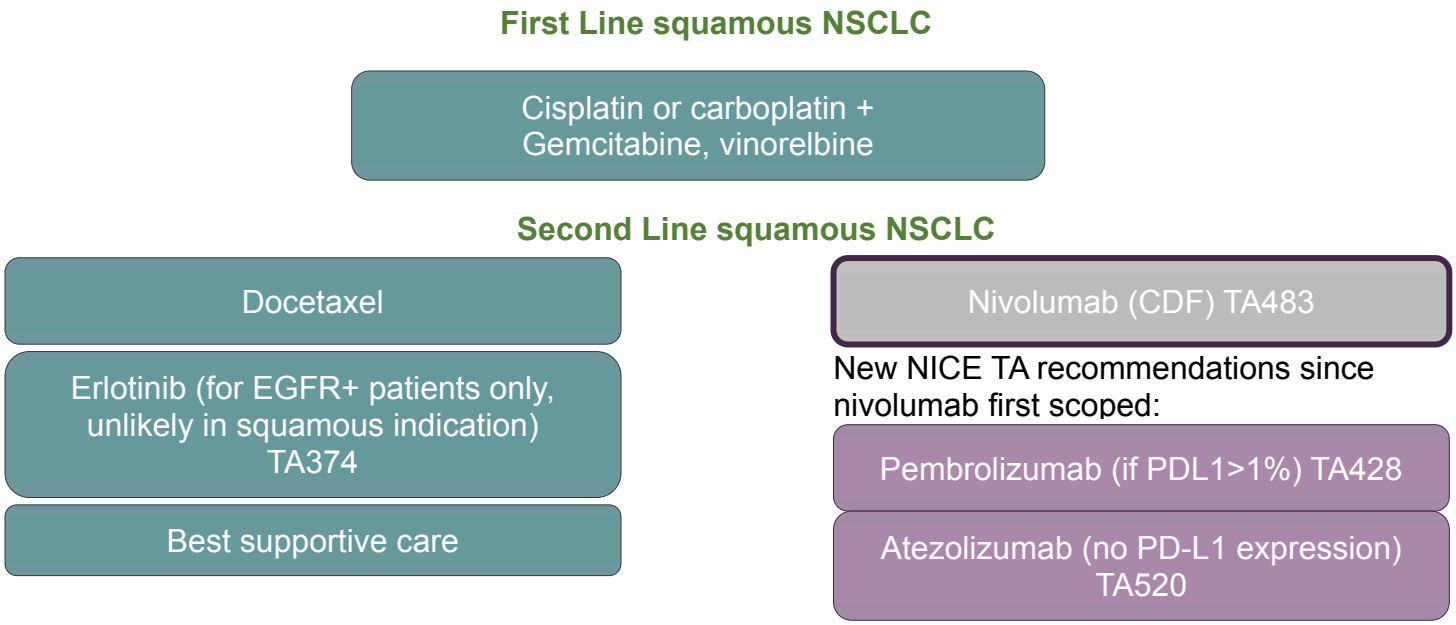
- nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression

Marketing Authorisation (MA): Nivolumab as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

	TA483 and CDF review scope
Population	People with previously treated locally advanced or metastatic (stage IIIB or IV) squamous NSCLC
Comparator	Docetaxel (BSC and erlotinib considered)
Outcomes	Overall survival, progression free survival, response rates, adverse events, health related quality of life



1.2 Treatment pathway



1.3 Key assumptions from TA483 appraisal

Published guidance	Topic	Committee consideration from original appraisal
4.2-4.3	Comparators	Erlotinib is rarely used in clinical practice, docetaxel would be used in preference to best supportive care – docetaxel is the most appropriate comparator
4.6	PD-L1 expression subgroups	Potential that PD-L1 expression has an effect on overall survival with nivolumab. Deemed not to be a clinically significant difference.
4.7	Generalisability	ECOG >1 excluded from the trial. However, CheckMate 017 generalisable to clinical practice in England
4.10	PFS extrapolation	Trial data + extrapolation with exponential distribution to avoid giving statistical weight to early progression data

4.11	OS extrapolation	Highly uncertain tail of overall survival extrapolations. Generalised gamma chosen to account for continued treatment effect
4.20	2-year stopping rule	Optimum treatment duration with immunotherapeutic treatments is uncertain, stopping treatment after 2 years improves cost-effectiveness and would be implemented by clinicians.
4.21	Continued treatment effect	Mechanism of nivolumab action means it continues to have an effect after stopping treatment, limited evidence to support this but it could last up to 3 years
4.25	End of life considerations	People with squamous NSCLC have a life expectancy of less than 24 months and nivolumab offers life extension greater than 3 months

1.4 Key new clinical evidence for CDF review of TA483

CheckMate 017 – pivotal trial	
Population	Adults with squamous NSCLC that had progressed during or after treatment with 1 platinum combination chemotherapy
Intervention (n=135)	Nivolumab 3mg/kg every 2 weeks until disease progression or unacceptable toxicity
Comparator (n=137)	Docetaxel
Outcomes	Overall survival, progression free survival, duration and time to response, health related quality of life, adverse events

	Original submission		Updated submission	
	Nivolumab	Docetaxel	Nivolumab	Docetaxel
Nominal follow-up period	2-years		5-years	
Median overall survival (months)	9.2	6.0	[redacted]	[redacted]
5-year overall survival	[redacted]	[redacted]	[redacted]	[redacted]

1.5 Systemic Anti-Cancer Therapy (SACT) data collection

Characteristics and overall survival estimates for the patients who received nivolumab within the CDF (application from 20 September 2017 to 19 December 2018) are shown below. Patients were followed up until January 2019. The full Public Health England report is included in the papers.

Characteristic	**Patients with CDF application (n=348)**
Male	230 (66%)
Age, median	70 years
PS 0 or 1	59 (17%) or 301 (71%)*
PD-L1<1%	241 (69%)
PD-L1≥1%	49 (14%)
PD-L1 not reported	58 (17%)
Patents who had completed tx by Jan 2019	278 (80%)
Median follow up time in SACT (Range: minimum to maximum)	487 days (5 months to 20 months)
Median treatment duration	3.5 months (95% CI: 3.0 to 4.1 months)
Survival	**Estimate**
Median OS	8.4 months (95% CI: 7.2 to 9.7 months)
Survival at 6 months	57% (95% CI: 51% to 62%)
Survival at 12 months	35% (95% CI: 30% to 41%)
Alive/dead at date of follow up	111/237

Figure 1 - Overall survival SACT data and CheckMate 017

2. Summary of the CDF review technical report

2.1 In summary, the technical team considered the following:

Issue 1 The 5-year overall survival and progression-free survival data confirm extended survival for a small number of patients; therefore it is appropriate to reconsider the choice of extrapolation. The company base case (2-knot-hazard spline distribution) and generalised gamma both provide plausible distributions for overall survival.

Issue 2 It is unclear if a 2-year stopping rule is appropriate and whether any continued treatment effect is appropriate.

Issue 3 The updated 5-year survival data confirm that PD-L1 subgroup expression status does not affect overall survival with nivolumab in this population.

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 include a commercial arrangement (patient access scheme) for nivolumab agreed by NHS England and the company effective in NHS routine practice. A confidential appendix includes a discount for erlotinib which is used as a subsequent treatment for some patients.

2.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of £52,300 per QALY gained (see table 1) by removing a 2-year treatment stopping rule and any continued treatment effect after discontinuation (see Issue 2).

2.5 Based on the modelling assumptions, the intervention is likely to meet the end-of-life criteria.

2.6 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Survival extrapolations

Questions for engagement	1. What is the most appropriate extrapolation for overall survival? 2. What is the most appropriate extrapolation for progression-free survival?
Background/description of issue	**TA483 (November 2017):** In the original appraisal (sections 4.10-4.14), progression-free survival and overall survival results were extrapolated from CheckMate 017 survival data, the latest of which was a 3-year data-cut. For progression-free survival, the committee considered that the most appropriate method of extrapolation was applying an exponential curve after the trial data split at 2.2 months (termed 'hybrid exponential'). This reduced the influence from data collected before the first radiological assessment on the long-term extrapolation. For overall survival, NICE commissioned the NICE Decision Support Unit (DSU) to create a report exploring goodness of fit to the observed data for overall survival extrapolations and to propose a preferred overall survival curve. The DSU considered the generalised gamma curve to be the most appropriate extrapolation because it featured slowly decreasing hazards. However, the DSU highlighted the uncertainty because of the small number of people still alive at 36 months. The committee agreed with the DSU and considered the generalised gamma curve to the most appropriate because the tail of the curve more closely reflected the likely continued treatment effect. **CDF review:** **The company** provide progression-free and overall survival data from the 5-year data-cut from CheckMate 017 for the CDF review. For progression-free survival, the company consider that the committee-preferred extrapolations (hybrid exponential) deviate from the long-term data in CheckMate 017. Therefore, the company refit the data with various distributions and selected the spline hazard 1 knot distribution to fit the progression-free survival data in both the nivolumab and docetaxel treatment arms.

	For overall survival, the company consider that the committee-preferred extrapolations (generalised gamma) underestimates long-term survival for nivolumab. Therefore, the company refit the data with various distributions and selected the spline hazard 2 knot distribution to fit the survival data in both the nivolumab and docetaxel treatment arms. **Figure 2 – progression-free survival extrapolation distributions**  **Figure 3 – overall survival extrapolation distributions**

	[redacted] **The ERG** consider that the maturity of the OS data means that the distribution choice makes little difference to the cost effectiveness results. Therefore, the ERG consider the company's preferred extrapolations are adequate. The ERG notes that almost all progression events are deaths after 5 years. The ERG notes that "the clinical plausibility of a lifetime zero hazard rate for disease progression in a population that had previously been diagnosed with locally advanced or metastatic NSCLC is uncertain." The ERG corrected an error within the model that limited overall survival by progression-free survival (see ERG addendum). **The technical team** noted the sensitivity of the ICER to overall survival distribution choice because a large proportion of life years gained occur in the tail of the extrapolation ([redacted] [calculated by NICE] of total life years gained after 5 years in the company base case). The technical team noted that some patients in the docetaxel treatment arm switched to nivolumab treatment after 2 years and

	this may affect survival extrapolation for the docetaxel group, although the company did not provide crossover analysis.
Why this issue is important	Using the committee assumptions from the original appraisal gives an ICER of **£68,761** per QALY gained compared to **£35,710** in the CDF review company base case (5-year 2-knot-hazard spline overall survival extrapolation and spline 1-knot hazard for progression-free survival). The generalised-gamma distribution for overall survival with spline 1-knot-hazard for progression-free survival gives an ICER of **£53,881** per QALY gained.
Technical team preliminary judgement and rationale	**The technical team** consider that the updated survival data show that a long-term survival benefit is plausible, and it is reasonable to update the extrapolation distributions based on new 5-year overall survival data. The progression-free survival curve using the hybrid exponential extrapolation consistently underestimates observed progression-free survival (see Figure 2), therefore the spline 1-knot-hazard provides a better fit. For overall survival, because the ICER is very sensitive to extrapolation choice and includes a modelled treatment benefit after discontinuation (see Issue 2), the technical team consider that both the generalised gamma and 2-knot-hazard spline provide plausible curve fits for overall survival.

Issue 2 – 2-year stopping rule and continued treatment effect

Questions for engagement	3 Is a 2-year stopping rule appropriate? 4 What is the continued effect of nivolumab after treatment is stopped?
Background/description of issue	**TA483 (November 2017):** In the original appraisal recommendations for inclusion in the CDF (sections 4.20 – 4.21), the committee agreed that a 2-year stopping rule should be applied in the economic model. However, CheckMate 017 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 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. The committee also considered that because of the mechanism of nivolumab, there was biological plausibility that the effect of nivolumab could continue after stopping treatment. But, because the there was a lack of evidence to support this and the exact effect was uncertain, the committee considered that the effect could last up to 3 years. **CDF review:** **The company's** CDF review base case analysis includes a 2-year stopping rule. The protocol for CheckMate 017 does not include a stopping rule, so [redacted] of patients continue to remain on nivolumab treatment at 5 years. The company consider that "continued follow-up of patients throughout data collection period shows no evidence of a waning of the treatment effect associated with nivolumab" and therefore model lifetime benefit of nivolumab. **The ERG** consider that the trial evidence presented by the company does not fully rule out the possibility of a treatment waning effect occurring. However, the length of time of any treatment effect is not known and some patients randomised to receive docetaxel crossed over to receive nivolumab in CheckMate 017, therefore it may not possible to determine the mortality and progression rates after treatment with nivolumab has ended.

	The technical team note that no further evidence for the stopping rule from CheckMate 153 has been submitted. The technical team also consider that continued treatment effect after discontinuation has not been explored with further data. Further justification for both these model assumptions is requested to justify a long-term effect. Additionally, the technical team request descriptive information and prognosis of patients that survive for up to 5 years in order to understand a potential long-term benefit.
Why this issue is important	The choice to remove the 2 year treatment stopping rule increases the company base case ICER from **£35,710** per QALY gained **to £49,284**. Reducing the continued treatment effect from a lifetime to 3-years increases the ICER from **£35,710** to **£40,168** per QALY gained. Using only evidence from the trial population in the company base case with neither of these modelling assumptions (observed treatment duration, no stopping rule and assuming treatment stops at 5 years) increases the company base case from **£35,710** to **£52,300** per QALY gained.
Technical team preliminary judgement and rationale	**The technical team** consider it is uncertain if the 2-year stopping rule remains appropriate in the absence of evidence of a continued treatment effect after discontinuation. The technical team consider the scenario with a continued treatment effect of 3-years or no continued treatment benefit to be more appropriate than a lifetime treatment benefit based on the available evidence, although further evidence is requested to justify any continued treatment effect.

Issue 3 – PD-L1 expression subgroups

Questions for engagement	5 Is it appropriate to consider the full population irrespective of PD-L1 expression, and not subgroups by PD-L1 expression?
Background/description of issue	**TA483 (November 2017):** In the original appraisal (sections 4.6 – 4.7), the company presented evidence that a PD-L1 expression level above 1% threshold had a higher median overall survival than those with a PD-L1 expression lower than the 1% threshold. The committee noted consultation comments that it was inappropriate to make a recommendation based on PD-L1 because it is a heterogeneous biological marker. Evidence from later data-cuts suggested that results did not suggest a clinically significant difference in overall survival according to PD-L1 expression. **CDF Review:** **The company** provide 5-year updated overall survival data by PD-L1 subgroup summarised in Figure 4 below **Figure 4 - Checkmate-017 trial median overall survival by PD-L1 subgroup: 5-year update**

	 **The ERG** consider these results confirm the results from the original analysis that PD-L1 subgroup status is not predictive of clinical outcomes for patients with squamous disease.
Why this issue is important	The effect of PD-L1 subgroup status on overall survival was an uncertainty specified in the terms of engagement and could affect optimisation of any recommendations if particular PD-L1 subgroups show different survival estimates.
Technical team preliminary judgement and rationale	**The technical team** consider that the 5-year updated data-cut results continue to suggest that there is no clinically significant difference in overall survival according to PD-L1 expression although it notes that CheckMate 017 was not powered to detect any difference.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	ICER	Change from base case
Company base case (PFS: spline hazard 1 knot, OS: spline hazard 2 knot, 2 year stopping rule, lifetime treatment effect)	–	**£35,657**	
ERG model correction of progression-free survival limiting overall survival	Technical team agree with ERG's corrections – see ERG addendum	**£35,710**	**+53**
Committee preferred assumptions with updated 5-year survival curves (PFS: hybrid exponential, OS: generalised gamma, 2 year stopping rule, 3-year treatment effect)	As defined in terms of engagement	**£69,649**	**+£33,992**
1. Corrected company base case with overall survival extrapolated using generalised gamma distribution	Technical team scenario	**£53,881**	**+£18,224**
2. Corrected company base case with 3-year continued treatment effect	Adjustment to terms of engagement scenario	**£40,168**	**+£4,511**
3. Corrected company base case without 2-year stopping rule (observed treatment duration)	Technical team scenario	**£49,284**	**+13,627**
2+3. Combined scenario	Technical team scenario	**£52,300**	**+16,643**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
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 base case ICER to £35,570 per QALY gained.
[redacted]	[redacted]	[redacted]

Table 3: Other issues for information

Issue	Comments
SACT data generalisability	In the original appraisal, the committee considered that the CheckMate 017 trial was likely to be generalisable to clinical practice in England, despite the fact only patients with European Cooperative Oncology Group (ECOG) Performance Status scores ≤1 were included in the trial and the trial only included a limited number of patients aged ≥75 years. The survival data for treatment duration and overall survival collected from the SACT database showed similarity to the CheckMate 017 trial data which confirmed that the results were generalisable to clinical practice in England.
End of life considerations	In the original appraisal, the committee considered nivolumab to meet the criteria to be an end-of-life treatment. The updated 5-year data confirm that the extension to life criterion is likely to be met.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

Authors

Professor Stephen O'Brien

Appraisal committee chair

Adam Brooke

Technical lead

Alexandra Filby

Technical adviser

Frances Sutcliffe

Associate director

With input from the lead team:

Paul Tappenden

Lead team member

Richard Nicholas

Lead team member

Stella O'Brien

Lead team member

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483) [ID1559]

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.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Wednesday 12 February 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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: Survival extrapolations	
What is the most appropriate extrapolation for overall survival?	• In the company submission, the standard parametric distributions were assessed for goodness of fit to the 5-year data. Based on AIC and BIC, spline hazard 2 knots and spline normal 2 knots were the best-fitting curves, and also provided the best visual fit to the data. • The generalised gamma distribution, preferred by the original appraisal committee, has clearly inferior visual fit to the 5-year data as well as AIC and BIC values much higher than those generally considered meaningful difference. (AIC > 15.8, BIC > 12.2) and should therefore be ruled out as an appropriate extrapolation. • The ERG considered that the maturity of the OS data means that the distribution choice makes little difference to the cost effectiveness results. Therefore, the ERG considered the company's preferred extrapolations are adequate. • It is important to note that all predictions from the original assessment underestimate the CDF results with regards to survival. o Once again, generalised gamma clearly underestimates the curve and has a poor statistical fit. It is clear already that this curve will not adequately capture long term survival. o Further, SACT data show that real world use of nivolumab follows trial data, thus as we see it no rationale for being overly conservative for extrapolations.
What is the most appropriate extrapolation for progression-free survival?	• In the company submission, the standard parametric distributions were assessed for goodness of fit to the 5-year data. The 1-knot hazard model is best fitting based

	on goodness-of-fit statistics and visual inspection based on the new data, for both treatment arms. • However, the maturity of the CheckMate-017 means the distribution makes little difference to cost effectiveness results. • The NICE technical judgement on page 11, seems to say they agree: "The progression-free survival curve using the hybrid exponential extrapolation consistently underestimates observed progression-free survival (see Figure 2), therefore the spline 1-knot-hazard provides a better fit."
Issue 2: 2-year stopping rule and continued treatment effect	
Is a 2-year stopping rule appropriate?	• Yes, a 2 year stop is in our opinion appropriate. • A two-year stopping rule has been consistently accepted in other Technology Appraisals for IO therapies, and was supported as implementable 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 CheckMate 017 after 2-years ([redacted]% on nivolumab treatment at 2-years). • In CheckMate 003, nivolumab treatment was stopped after 96 weeks (1.8 years). Long-term survival of nivolumab in CheckMate 017 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.
What is the continued effect of nivolumab after treatment is stopped?	• Based on the data now available, and the known mechanism of action of IO therapies, the assumption in the CS, that there is a sustained treatment effect of nivolumab, is the most plausible. • 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. • As shown in the submission, only [redacted]% of patients alive remain on treatment at 2 years in CheckMate 017 but there is still a clear benefit for the proportion of patients not on treatment. By 60 months only [redacted] of patients who are alive remain on treatment. The other [redacted] of patients continue to show long-term benefit from the earlier treatment with nivolumab. • As described in response to Question 3, in CheckMate 003, nivolumab treatment was stopped after 96 weeks, and six-year survival was comparable to that in CheckMate 017 (14.7% vs. [redacted]% 5-year survival), showing that a maximum of 1.8 year of nivolumab treatment contributes to a significant long-term survival. • Assuming all treatment effect stops 3-years after stopping treatment, appears to be an arbitrary cutoff and is not clinically plausible –we know that some patients continue to show a clear treatment effect at 5-years, without continued treatment.
Issue 3: PD-L1 expression subgroups	
Is it appropriate to consider the full population irrespective of PD-L1 expression, and not subgroups by PD-L1 expression?	• As presented in the company submission and confirmed by the ERG assessment report, the trial data shows that nivolumab is effective irrespective of PD-L1 expression and thus should not be limited to any subgroup.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483) [ID1559]

Technical Engagement Response

Appendix A

27 February 2020

File name	Version	Contains confidential information	Date
ID1559 Nivolumab SQ NSCLC Technical Engagement Response Appendix A	1	No	27th February 2020

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.

Treatment Waning Effect

Issue 2 in the Technical Engagement document queried the continued effect of nivolumab after treatment is stopped. The company base case assumes that treatment will continue for the lifetime of the patient. This is based on the outcome from the CheckMate-003 trial, where the protocol stipulated that treatment with nivolumab should be stopped at 2 years. Despite treatment being stopped OS rates for CheckMate-003 trial patients were similar to OS rates at for patients randomised to the nivolumab arm of the CheckMate-017 trial at 3 years and 5 years. Further, the 5-year TTD data from CheckMate 017 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 017 remain on treatment. In their report, the ERG stated 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".

The appraisal committee's original preference was that nivolumab treatment effect would continue for 3-years. Additional scenarios have been explored around the implementation of the waning of treatment effect in the model and are presented in this document.

As currently implemented in the model in the committee-preferred 3-year continued treatment effect scenario, 3-years after 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 been 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 017 and 003. Scenarios are included in Table 1 showing 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 is presented, potentially the most relevant being the scenario in which 49% 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-017 clinical trial (Brahmer et al., 2015). In all scenarios, the ICER remains below the £50,000 per QALY end-of-life threshold.

Table 1. Cost-effectiveness results: All-Comers Population

Proportion of patients who continue to benefit	**Duration of additional benefit after 3-years**			
	3-Years	5-Years	10-Years	20-Years
0%	£40,168	£40,168	£40,168	£40,168
25%	£39,554	£39,317	£39,058	£39,004
49%	£38,988	£38,527	£37,997	£37,883
75%	£38,400	£37,734	£36,894	£36,705
100%	£37,857	£37,024	£35,976	£35,710

References

Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015 Jul 9;373(2):123-35.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483) [ID1559]

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.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Wednesday 12 February 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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: Survival extrapolations	
What is the most appropriate extrapolation for overall survival?	We would defer to the statistical experts
What is the most appropriate extrapolation for progression-free survival?	We would defer to the statistical experts
Issue 2: 2-year stopping rule and continued treatment effect	
Is a 2-year stopping rule appropriate?	It is not an evidence based recommendation, we await the evidence from clinical trials addressing the optimal duration of these treatments.
What is the continued effect of nivolumab after treatment is stopped?	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.
Issue 3: PD-L1 expression subgroups	
Is it appropriate to consider the full population irrespective of PD-L1 expression, and not subgroups by PD-L1 expression?	We agree with the technical team judgement that the evidence 'suggests that there is no clinically significant difference in overall survival according to PD-L1 expression'.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for previously treated squamous non-small-cell lung cancer (CDF review TA483) [ID1559]

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.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Wednesday 12 February 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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: Survival extrapolations	
What is the most appropriate extrapolation for overall survival?	• In the company submission, the standard parametric distributions were assessed for goodness of fit to the 5-year data. Based on AIC and BIC, spline hazard 2 knots and spline normal 2 knots were the best-fitting curves, and also provided the best visual fit to the data. • The generalised gamma distribution, preferred by the original appraisal committee, has clearly inferior visual fit to the 5-year data as well as AIC and BIC values much higher than those generally considered meaningful difference. (AIC > 15.8, BIC > 12.2) and should therefore be ruled out as an appropriate extrapolation. • The ERG considered that the maturity of the OS data means that the distribution choice makes little difference to the cost effectiveness results. Therefore, the ERG considered the company's preferred extrapolations are adequate. • It is important to note that all predictions from the original assessment underestimate the CDF results with regards to survival. o Once again, generalised gamma clearly underestimates the curve and has a poor statistical fit. It is clear already that this curve will not adequately capture long term survival. o Further, SACT data show that real world use of nivolumab follows trial data, thus as we see it no rationale for being overly conservative for extrapolations.
ERG comment	• In the absence of long-term OS evidence to inform curve fitting it is difficult to choose between plausible options

What is the most appropriate extrapolation for progression-free survival?	• In the company submission, the standard parametric distributions were assessed for goodness of fit to the 5-year data. The 1-knot hazard model is best fitting based on goodness-of-fit statistics and visual inspection based on the new data, for both treatment arms. • However, the maturity of the CheckMate-017 means the distribution makes little difference to cost effectiveness results. • The NICE technical judgement on page 11, seems to say they agree: "The progression-free survival curve using the hybrid exponential extrapolation consistently underestimates observed progression-free survival (see Figure 2), therefore the spline 1-knot-hazard provides a better fit."
ERG comment	• The maturity of the CheckMate-017 trial PFS evidence means that the choice of distribution makes little difference to cost effectiveness results
Issue 2: 2-year stopping rule and continued treatment effect	
Is a 2-year stopping rule appropriate?	• Yes, a 2 year stop is in our opinion appropriate. • A two-year stopping rule has been consistently accepted in other Technology Appraisals for IO therapies, and was supported as implementable 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 CheckMate 017 after 2-years ([redacted] on nivolumab treatment at 2-years). • In CheckMate 003, nivolumab treatment was stopped after 96 weeks (1.8 years). Long-term survival of nivolumab in CheckMate 017 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.
ERG comment	• The optimal duration of treatment with nivolumab is unknown and, therefore, the implementation of a 2-year stopping rule would not be evidence based
What is the continued effect of nivolumab after treatment is stopped?	• Based on the data now available, and the known mechanism of action of IO therapies, the assumption in the CS, that there is a sustained treatment effect of nivolumab, is the most plausible. • 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. • As shown in the submission, only [redacted]% of patients alive remain on treatment at 2 years in CheckMate 017 but there is still a clear benefit for the proportion of patients not on treatment. By 60 months only [redacted] of patients who are alive remain on treatment. The other [redacted] of patients continue to show long-term benefit from the earlier treatment with nivolumab. • As described in response to Question 3, in CheckMate 003, nivolumab treatment was stopped after 96 weeks, and six-year survival was comparable to that in CheckMate 017 (14.7% vs. [redacted]% 5-year survival), showing that a maximum of 1.8 year of nivolumab treatment contributes to a significant long-term survival. • Assuming all treatment effect stops 3-years after stopping treatment, appears to be an arbitrary cutoff and is not clinically plausible –we know that some patients continue to show a clear treatment effect at 5-years, without continued treatment.

ERG comment	• There is no robust evidence to support any conclusions about the effect of nivolumab after treatment is stopped
Issue 3: PD-L1 expression subgroups	
Is it appropriate to consider the full population irrespective of PD-L1 expression, and not subgroups by PD-L1 expression?	• As presented in the company submission and confirmed by the ERG assessment report, the trial data shows that nivolumab is effective irrespective of PD-L1 expression and thus should not be limited to any subgroup.
ERG comment	• No comment