Cancer Drugs Fund Review

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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

Completed 21 January 2020

DOES CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title:	Nivolumab for previously treated non-squamous non-small cell lung cancer [ID1572] (Cancer Drugs Fund update of TA484)
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 Tosin Lambe, Health Economic Modeller, LR*i*G, University of Liverpool
Correspondence to:	Angela Boland, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB
Date completed:	21 January 2020

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number NIHR 129536.

Declared competing interests of the authors: None.

Acknowledgements: The authors would like to thank Dr John Green, Consultant in Medical Oncology, The Clatterbridge NHS Foundation Trust, Liverpool who provided feedback on the final version of the report.

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, Mahon J and Lambe T. Nivolumab for previously treated non-squamous non-small cell lung cancer [ID1572]: Cancer Drugs Fund update of TA484. 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
Tosin Lambe	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
ALK	Anaplastic lymphoma kinase
AUC	Area Under the Curve
BIC	Bayesian Information Criterion
BSA	Body surface area
BSC	Best supportive care
CAA	Commercial Access Agreement
CDF	Cancer Drugs Fund
CI	Confidence interval
CS	Company submission
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions Questionnaire
ERG	Evidence Review Group
FAD	Final Appraisal Determination
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
K-M	Kaplan-Meier
MAA	Managed Access Agreement
NICE	National Institute of Health and Care Excellence
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PHE	Public Health England
PS	Performance status
QALY	Quality adjusted life year
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
ToE	Terms of Engagement

EXECUTIVE SUMMARY

1.1 Background

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

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

1.1.1 Available evidence

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

1.2 Summary of key clinical effectiveness issues

Population

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

Comparators

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

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

Clinical effectiveness

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

Generalisability

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

1.3 Summary of key issues in cost effectiveness evidence

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

Model structure

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

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

Population and subgroups

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

Extrapolation of OS and PFS

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

Utilities

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

Stopping rule

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

Treatment waning

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

Treatment costs

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

1.4 Exploratory cost effectiveness estimates

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

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

Results from these analyses are provided in the table below.

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

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

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

1.5 End of life

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

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

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

1.6 ERG conclusions

1.6.1 Clinical effectiveness

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

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

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

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

1.6.2 Cost effectiveness

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

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

2 EVIDENCE REVIEW GROUP REPORT

2.1 Introduction

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

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

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

2.2 Nivolumab

Key facts about nivolumab:

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

2.3 Effectiveness of nivolumab and comparators

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

Box 1 Clinical effectiveness issues

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

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

3 CLINICAL DECISION PROBLEM

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

Table 1 NICE Appraisal Committee's preferred clinical assumptions

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

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

3.1 Population and subgroups

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

Population

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

Subgroups

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

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

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

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

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

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

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

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

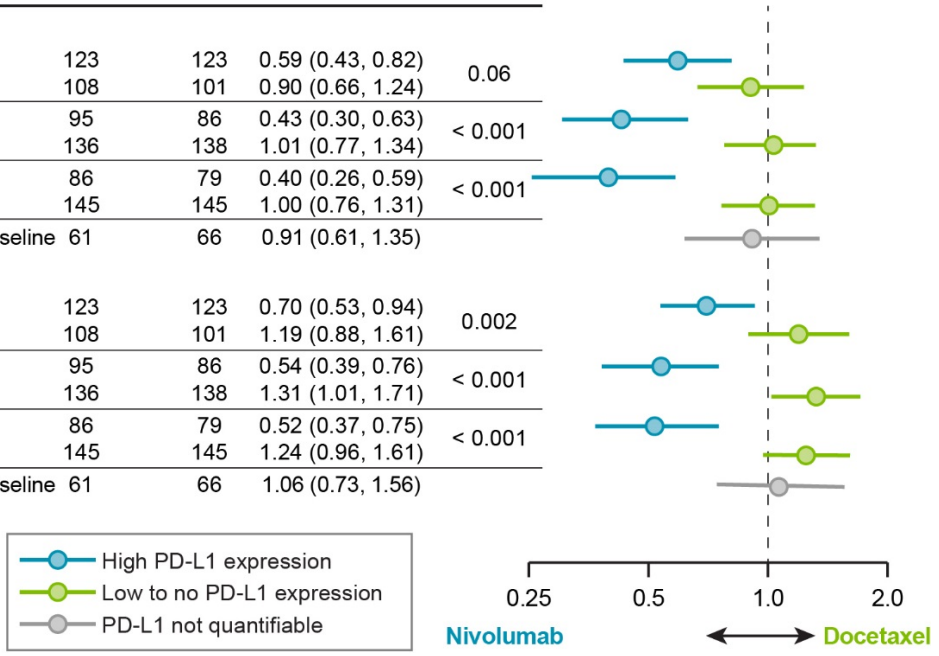

Figure 1 CheckMate-057 trial OS and PFS by level of PD-L1 expression: 1-year analysis

Source: CDF Review CS, Figure 6

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

Source: CDF Review CS, Figure 7

3.2 Comparators

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

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

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

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

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

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

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

3.3 Generalisability

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

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

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

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

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

3.4 SACT database outcomes

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

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

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

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

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

Table 3 SACT database: patient summary characteristics

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

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

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

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

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

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

Table 4 SACT database: overall survival data

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

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

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

3.4.1 ERG comments on SACT analyses

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

3.4.2 Conclusions of the clinical effectiveness section

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

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

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

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

4 COST EFFECTIVENESS DECISION PROBLEM

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

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

Table 5 NICE Appraisal Committee's preferred economic assumptions

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

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

4.1 Model structure

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

The company's model structure was accepted

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

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

4.2 Subgroups

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

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

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

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

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

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

4.3 Extrapolation of overall survival

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

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

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

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

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

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

4.4 Extrapolation of progression-free survival

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

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

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

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

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

4.5 Utilities

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

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

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

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

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

4.6 Stopping rule and continued treatment effect

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

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

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

Treatment stopping rule

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

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

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

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

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

Treatment waning effect

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

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

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

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

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

4.7 Dose intensity reduction

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

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

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

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

4.8 Treatment costs

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

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

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

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

4.9 End of life

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

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

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

The NICE end of life criteria[9] are:

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

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

Table 7 End of life estimates

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

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

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

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

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

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

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

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

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

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

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

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

** [redacted]

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

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

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

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

6 ERG COST EFFECTIVENESS ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

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

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

6.2 Conclusions of cost effectiveness section

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

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

7 REFERENCES

1. NICE. Final appraisal determination: nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer. Technology appraisal guidance [TA484]. 2017; Available from: https://www.nice.org.uk/guidance/ta484/documents/final-appraisal-determination-document. Accessed.
2. NICE. Cancer Drugs Fund Managed Access Agreement: nivolumab for previously treated non-squamous non-small-cell lung cancer. 2017; Available from: https://www.nice.org.uk/guidance/ta484/resources/managed-access-agreement-november-2017-pdf-4659629293. Accessed.
3. NICE. Nivolumab for preciously treated non-squamous non-small cell lung cancer. TA484. 2017; Available from: https://www.nice.org.uk/guidance/ta484. Accessed 2020 December.
4. EMA. Opdivo: summary of product characteristics. European Medicines Agency; 2019; Available from: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf. Accessed.
5. NICE. Terms of engagement for CDF review of TA484: Nivolumab for previously treated non-squamous non-small-cell lung cancer. 2019; Accessed.
6. NICE. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. TA428. 2020; Available from: https://www.nice.org.uk/guidance/ta428. Accessed 2020 January.
7. NICE. TA520. Final Appraisal Determination. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. 2018; Available from: https://www.nice.org.uk/guidance/ta520/documents/final-appraisal-determination-document. Accessed.
8. Public Health England. Nivolumab for treating locally advanced or metastatic non-squamous non-small cell lung cancer - data review [TA484]2019.
9. NICE. Appraising life-extending end of life treatments. 2009; Available from: https://www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2. Accessed 2019 12 December.