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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Cancer Drugs Fund update of TA483

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

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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

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