in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation: CDF review of TA578

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)

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Date completed 09/02/2022

Source of funding: This report was commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme as project number NIHR135354.

Declared competing interests of the authors
None.

Acknowledgements
None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout 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 HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Armstrong N, Grim S, Witlox W, Westwood M, Danopoulos E, Duffy S, Joore MA, Kleijnen J. Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation: CDF review of TA578. York: Kleijnen Systematic Reviews Ltd, 2022.

Contributions of authors
Nigel Armstrong acted as project lead as well as a systematic reviewer and health economist on this assessment, critiqued the clinical effectiveness methods and evidence as well as the company's economic evaluation and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Marie Westwood and Evan Danopoulos acted as systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy acted as information specialist and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	adverse event
AiC	academic in confidence
AUCss	area under the curve at steady state
BICR	Blinded Independent Central Review
BSC	best supportive care
CDF	Cancer Drugs Fund
CI	confidence interval
CiC	commercial in confidence
CRT	chemoradiation therapy
CS	company submission
CSR	clinical study report
DCO	data cut-off
DOR	duration of response
DoT	duration of treatment
DSA	deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost effectiveness ratio
KSR	Kleijnen Systematic Reviews
LY	life-year
LYG	life-year gained
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSCLC	non-small-cell lung cancer
OS	overall survival
PAS	Patient Access Scheme
PD	progressed disease
PD-L1	programmed death ligand 1
PF	progression-free
PFS	progression-free survival
PHE	Public Health England
PPS	post-progression survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q2W	every two weeks
Q4W	every four weeks
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
SACT	systemic anti-cancer therapy
SoC	standard of care
ToE	Terms of Engagement
TPS	tumour proportion score

TTP	time-to-progression
UK	United Kingdom
UMC+	University Medical Centre
US	United States
WHO PS	World Health Organisation Performance Score
WTP	willingness to pay

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1. EXECUTIVE SUMMARY

1.1 Critique of the adherence to committees preferred assumptions from the Terms of Engagement in the company's submission

The following is a list of the key committee assumptions (preferences) according to the Terms of Engagement (ToE) for the Cancer Drugs Fund (CDF) review, each one followed by a statement as to the Evidence Review Group's (ERG's) finding of the extent to which the company submission (CS) has adhered to the committee preferences.[1, 2]

Assumption 0: Durvalumab administered as a fixed dose of 1,500 mg every four weeks (Q4W). This was not specified in the ToE, but was implemented as an option in the economic model, and has been used in the company's base-case. The ERG notes that the clinical effectiveness evidence, from the PACIFIC trial, is for the weight-based dose regimen of 10 mg/kg every two weeks (Q2W). The ERG questions the validity of the conclusion by the company that there will be no clinically meaningful difference between a weight-based dose and the specific flat dose of 1,500 mg every four weeks (Q4W), in terms of effectiveness and safety. More specifically, this might lead to an overestimation of the survival that would be observed in clinical practice (see Section 2 for details).

Assumption 1: Population: Adults with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based chemoradiation therapy (CRT) only if they had concurrent chemoradiation are the relevant population for the CDF review. The ERG can confirm that data presented from the PACIFIC trial are for the specified population. With respect to the generalisability of the PACIFIC trial data to the real-world United Kingdom (UK) setting, the ERG notes that there is a discrepancy between this population and those patients treated with durvalumab from whom the systemic anti-cancer therapy (SACT) data were obtained in that 12% of the SACT patients had unknown PD-L1 status. Whilst this did not affect the summary statistics for overall survival (OS) very much, it is unclear to the ERG why these patients received durvalumab given the risk of treating patients with PD-L1<1%, which is outside of scope (see Sections 2 and 3 for further details).

Assumption 2: Comparator: The company should present clinical and cost-effective evidence for durvalumab compared to standard care. The ERG considers that this assumption was adhered to in the CS.

Assumption 3: Survival outcomes: The company should use updated survival data from the PACIFIC trial and fully explore the most appropriate method to extrapolate survival outcomes. The ERG considers that this assumption was not adequately adhered to in the CS given the ERG criticism of model structure. Notwithstanding the ToE appearing to preclude any change in model structure, exploring an overall survival (OS)/ progression-free survival (PFS) modelling approach might resolve some of the uncertainty (see Sections 2 and 4 for further details).

Assumption 4: Assumption of cure: The company should use updated survival data from the PACIFIC trial to inform the appropriateness of a cure assumption. The ERG considers that this assumption was not adhered to in the CS. However, the ERG, like the company, considers it preferable to use extrapolations based on the available data to model survival, rather than relying on additional assumptions about cure.

Assumption 5: Treatment effect duration: The company should use updated survival data from the PACIFIC trial and fully explore the treatment effect after stopping treatment. The ERG considers that this assumption was partly adhered to in the CS (see Section 4 for further details).

Assumption 6: Utility values: The company should use more mature quality of life data from PACIFIC to inform the progression free and progressed health states in the economic model. The CS states that: *'As more mature data on health-related quality of life has not been collected in further data cuts, the utility values applied in this cost-effectiveness analysis have remained unchanged.'* The ERG notes that this assumption was not adhered to in the CS (see Sections 2 and 4 for further details).

Assumption 7: Economic model: The economic model's name '*[ID1175] durvalumab CEM to support AZ technical engagement response 220119 LB (ACIC)*' should be used be used as the basis for the CDF review. It should include the committee's preferred assumptions as stated above. The following functionality should be available within the model at CDF review:

- Replication of the key cost effectiveness results used in the committee's decision-making at the point of CDF entry.
- Cost effectiveness results that incorporate data collected during the CDF data collection period, with the assumptions used in the committee's decision-making at the point of CDF entry.
- Cost effectiveness results that incorporate data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions.
- Capacity to run the key sensitivity and scenario analyses presented in the original CS.

The ERG considers that this assumption was adhered to in the CS.

Assumption 8: Durvalumab does not meet the end-of-life criteria. The ERG can confirm that this assumption was adhered to in the CS.

1.2 Summary of key issues in the clinical effectiveness evidence

1) Update of survival data from the PACIFIC trial, according to the ToE: The ERG can confirm that this has been done with the latest data cut-off (DCO) being 11th January 2021, i.e., five years follow-up. The ERG can confirm that updated survival analyses have been undertaken and that the survival advantage of durvalumab over placebo was maintained, in terms of hazard ratio (HR) and median survival, at five years. The progression-free survival (PFS) advantage of durvalumab over placebo was also maintained, in terms of HR and median survival, at five years.

2) SACT dataset to assess the generalisability of the PACIFIC trial, according to the ToE: The ERG notes two further key differences between the durvalumab treated PACIFIC PD-L1 ≥1% group and the SACT cohort:

- All patients in the durvalumab treated PACIFIC subgroup had tumours which expressed PD-L1 in ≥1% of tumour cells, whereas PD-L1 status could not be determined for 12% of patients in the SACT cohort.

However, the ERG notes that an analysis of the SACT cohort excluding the patients without PD-L1 status did not affect the summary statistics for OS very much and therefore the conclusion that the survival benefit for durvalumab treated patients, observed at the 22nd March 2018 DCO is maintained at the 11th January 2021 DCO (five years).

- All patients in the durvalumab treated PACIFIC PD-L1 ≥1% group were treated with a weight-based dose regimen (10 mg/kg Q2W), whereas an unreported number of patients in the SACT cohort were treated with a fixed dose regimen (1,500 mg Q4W).

Evidence from a report by the European Medicines Agency (EMA) shows that [redacted].

3) Update of quality-of-life data from the PACIFIC trial, according to the ToE: The ERG notes that no additional quality of life data has been collected and that this issue remains outstanding.

1.3 Summary of the key issues in the cost effectiveness evidence

1) The ERG considers that the most appropriate method to extrapolate survival outcomes (as stipulated in the ToE) was not explored by the company. The company continue to use their original PFS/TTP/PPS modelling approach. The ERG is not completely satisfied with the company's PFS/TTP/PPS approach, as it requires more assumptions than an OS/PFS approach (for example that PPS is equal for both treatment arms). Internal consistency between the model and the evidence used for it is lacking (perhaps as a consequence of the modelling approach) and it appears that the company's modelling approach induces bias in favour of durvalumab. If no updated model structure can be provided, survival models should be chosen such that internal consistency between the model and the trial is achieved. Furthermore, full details should be provided for all extrapolated quantities (i.e., TTP and PPS) and should include expert opinion on the most appropriate models.

2) It appears clear from the company's provided information that treatment effectiveness wanes at some time point after three years (this occurs later for OS than PFS). The company claim that this was reflected in their chosen survival distributions. The ERG would like to see this supported with evidence, both for the company's and for the ERG's preferred PFS distributions.

3) In order to perform an unbiased assessment of the impact of excluding subsequent treatments that are not routinely used in National Health Service (NHS) clinical practice from the model, the company could perform an analysis adjusting for treatment switching.

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG made one change to the company's base-case:

- PFS durvalumab modelled using lognormal instead of generalised gamma

In addition, one scenario analysis was performed.

- PFS durvalumab modelled using the Gompertz

Table 1.1: Summary of exploratory and sensitivity analyses undertaken by the ERG

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company's new base-case							
Durvalumab	[redacted]	8.082	[redacted]	[redacted]	3.064	[redacted]	11,719
SoC	[redacted]	5.018	[redacted]				
ERG base-case: change PFS durvalumab to lognormal from generalised gamma							
Durvalumab	[redacted]	7.003	[redacted]	[redacted]	1.985	[redacted]	22,441
SoC	[redacted]	5.018	[redacted]				
ERG scenario: change PFS durvalumab to Gompertz							
Durvalumab	[redacted]	7.905	[redacted]	[redacted]	2.887	[redacted]	12,830
SoC	[redacted]	5.018	[redacted]				

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; LYs = life-year; PFS = progression-free survival; QALYs = quality-adjusted life year; SoC = standard of care

2. INTRODUCTION AND BACKGROUND

2.1 Background

The Terms of Engagement (ToE) for the Cancer Drugs Fund (CDF) review states the following:[1] *'Durvalumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced unresectable non-small-cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after platinum-based chemoradiation therapy (CRT) only if they have had concurrent platinum-based chemoradiation and the conditions in the managed access agreement are followed.'*

Incremental cost effectiveness ratios (ICERs) presented to the committee included a Patient Access Scheme (PAS) discount of [redacted]. The committee concluded that the cost effectiveness estimates were uncertain but that some scenarios were in the range considered a cost-effective use of National Health Service (NHS) resource. The committee therefore accepted that durvalumab demonstrated plausible potential to be cost-effective.

The committee's key uncertainties were the long-term survival outcomes including PFS, OS and the duration of any treatment effect.

Durvalumab was accepted in the CDF on the basis that the key trial, PACIFIC was ongoing, and the committee agreed that additional survival data would reduce these uncertainties and provide additional information on the treatment effect duration and cure rates. The data collection arrangement included the following statements:[3]

- *'The following outcome data that will be collected during the data collection arrangement is described below:*
    - *5-year PFS and OS data from PACIFIC - This will provide an additional 3 years of follow-up relative to the evidence presented in the NICE appraisal 1175 (22 March 2018 data cut-off) and should resolve the clinical uncertainty regarding the longer-term survival benefit of durvalumab versus standard-of-care (active follow-up) in the patient population covered by this managed access arrangement.*
    - *In addition, data on subsequent therapies will also be collected. These data will be used to update the frequency, duration, and cost of subsequent therapies in the economic model.'*

- *'Data will be collected via Public Health England's routine population-wide datasets, including the SACT dataset. This collection will support data collected in the clinical trial. During the managed access agreement period, Public Health England will collect data to provide information on overall survival, duration of therapy, unless it is determined by the SACT Operational Group that no meaningful data will be captured in during the period of data collection.'*

2.2 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

Table 2.1 summarises the key committee assumptions (preferences) according to the ToE for CDF review.[1] It also summarises the extent to which the company submission (CS) has adhered to the committee preferences.[2] In addition, the ToE state that the end-of-life criteria have not been met.

ERG comments:

Assumption 0: Durvalumab dosing

Durvalumab administered as a fixed dose of 1,500 mg every four weeks (Q4W). This was not specified in the ToE, but was implemented as an option in the economic model, by the company, following the introduction of this dose regimen as part of COVID-19 interim guidance in April 2020.[4] Section A4 of the CS states that the 4-weekly fixed dose is now standard in United Kingdom (UK) clinical practice and this dose has been used in the company's base-case.[2] The ERG notes that the clinical effectiveness evidence, from the PACIFIC trial, is for the weight-based dose regimen of 10 mg/kg every two weeks (Q2W).

The ERG therefore asked the following questions in the clarification letter:[5]

'The CS reports that standard UK clinical practice for durvalumab is now a fixed dose of 1500mg administered every 4 weeks (Q4W) and this is the dose used in the company base-case. Please confirm that the durvalumab regimen evaluated in the PACIFIC trial remained 10mg/kg administered every 2 weeks (Q2W) throughout the trial.

Please provide evidence of the relationship between the clinical effectiveness and safety of durvalumab between the different dosing regimens (fixed dose of 1500mg administered Q4W and 10mg/kg Q2W).'

The company confirmed that the dose in the PACIFIC trial remained weight based.[5] The company also stated that the EMA accepted there were no clinically significant differences in efficacy and safety between the 10 mg/kg Q2W dose and the 1,500 mg Q4W dose. [redacted]

[redacted]

It goes on to conclude the following:

[redacted]

[redacted]

[redacted] This is reflected in a statement in the conclusions of the EMA report:

[redacted]

The ERG therefore questions the validity of the conclusion by the company that there will be no clinically meaningful difference between a weight-based dose and the flat dose of 1,500 mg Q4W, in terms of effectiveness. An analysis of the SACT data by dosing regimen might provide an idea of the effect of dosing in clinical practice.

Assumption 1: Trial population

Adults with locally advanced, unresectable non-small-cell lung cancer (NSCLC) whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based chemoradiation therapy (CRT) only if they had concurrent chemoradiation are the relevant population for the CDF review.

The ERG can confirm that data presented from the PACIFIC trial are for the specified population. With respect to the generalisability of the PACIFIC trial data to the real-world UK setting, the ERG notes that there is a discrepancy in PD-L1 status between the PACIFIC trial population and patients in the SACT cohort; 12% of patients in the SACT cohort had unknown PD-L1 status. The ERG therefore requested the following additional information, in the clarification letter:[5]

'Would the company expect that if there was a positive recommendation by NICE then such patients (those with unknown PD-L1 status) would be expected to receive durvalumab?'

'If so, then could the company perform all analyses for participants of the PACIFIC Trial including those for whom PD-L1 status could not be determined as well as those with PD-L1 ≥1%'

'Could the company also obtain an analysis of the SACT data excluding those patients with unknown PD-L1 status.'

The company refused to perform the analysis including unknown PD-L1 status on the basis that this would be outside the scope of the CDF review and that the trial did not mandate PD-L1 testing.[5] The ERG would accept this as a valid reason given that there will be a greater proportion of unknown and thus potentially PD-L1 <1% patients in the trial. It should also be noted that the company did provide an analysis of the SACT OS data excluding patients with unknown PD-L1 status, referred to as the "Overall survival secondary sensitivity analysis", and subsequent to submission of the clarification letter, the ERG received an analysis of the SACT data, following the removal of unknown PD-L1 scores, PD-L1 testing not possible and PD-L1 result unquantifiable. It should also be noted that the results for 12 months and 24 months excluding patients whose PD-L1 status was unknown were almost identical to those including these patients (see Section 3.2.1).[7] Nevertheless, this might be because, by chance, most or even all patients with unknown PD-L1 status had PD-L1≥1%.

Assumption 2: Comparator

The committee agreed that standard care (which involves surveillance every six months for two years, and a volume chest CT scan at least every year) was the appropriate comparator for this appraisal.

As established in the original 2018 appraisal, the comparator was *'active follow-up'*, defined as *'surveillance every six months for two years with a visit including history, physical examination and—preferably contrast-enhanced—volume chest CT scan at least at 12 and 24 months is recommended, and thereafter an annual visit including history, physical examination and chest CT scan in order to detect second primary tumours.'*

The ERG considers that this assumption was adhered to in the CS.

Assumption 3: Survival outcomes:

The company did not fully explore the most appropriate method to extrapolate survival outcomes (as detailed in Section 4). However, the ToE stated: "*The company should not…make further alterations to the model during the CDF review period unless NICE requests or agrees to this in advance*." (p.6)[1]

Assumption 4: Cure

The company did not use the survival data or any evidence other than clinical expert opinion, which was already available before entry to the CDF, to test the validity of the claim that some patients might be cured.[2] However, the ERG, like the company, considers it preferable to use extrapolations based on the available data to model survival, rather than relying on additional assumptions about cure.

Assumption 5: Treatment effect duration

The company did not fully explore the treatment effect after stopping treatment (as detailed in Section 4).

Assumption 6: Utility values

Section A.7.4 of the CS states that: *'As more mature data on health-related quality of life has not been collected in further data cuts, the utility values applied in this cost-effectiveness analysis have remained unchanged.'*[2]

The ToE stated that: *'The company should use more mature quality of life data from PACIFIC to inform the progression free and progressed health states in the economic model.'*[1] The ERG therefore requested confirmation, in the clarification letter, that no additional quality of life data had been collected, which was provided by the company.[5]

The ERG notes that this assumption was not adhered to in the CS (as detailed in Section 4).

Assumption 7: Economic model

The extent of adherence to the assumptions specified for the economic model is discussed in detail in Chapter 4.

Assumption 8: End-of-life criteria

The ERG can confirm that durvalumab does not meet the end-of-life criteria.

Table 2.1: Preferred assumptions from Terms of Engagement

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	ERG comment
Assumption 1	Population: Adults with locally advanced, unresectable non-small-cell lung cancer whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based CRT only if they had concurrent chemoradiation are the relevant population for the CDF review.	Yes, for PACIFIC trial data. Inconsistent for SACT data.	None given	See chapter 3 for details.
Assumption 2	The company should present clinical and cost-effective evidence for durvalumab compared to standard care. The committee agreed that standard care (which involves surveillance every six months for two years, and a volume chest CT scan at least every year) was the appropriate comparator for this appraisal.	Yes	Not applicable	See chapter 3 for details.
Assumption 3	Survival outcomes: The company should use updated survival data from the PACIFIC trial and fully explore the most appropriate method to extrapolate survival outcomes.	Partly	The company stated in the clarification letter response: "*Based on the discussion at the kick-off meeting, it was the Company's understanding that for a CDF review submission, the model approach and structure should remain unchanged compared with the original submission.*"[5]	The ToE stated: "*The company should not…make further alterations to the model during the CDF review period unless NICE requests or agrees to this in advance.*" (p.6)[1] See chapter 4 for details.
Assumption 4	Assumption of cure: The company should use updated survival data from the PACIFIC trial to inform the appropriateness of a cure assumption. Clinical experts expected people on standard care who did not have	No	None given	See Section 2.2 for details.

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	ERG comment
	progressed disease at five years would have low risk of future progression.			
Assumption 5	Treatment effect duration: The company should use updated survival data from the PACIFIC trial and fully explore the treatment effect after stopping treatment.	Yes	Not applicable	See chapter 4 for details.
Assumption 6	Utility values: The company should use more mature quality of life data from PACIFIC to inform the progression free and progressed health states in the economic model.	No	None given	See chapters 3 and 4 for details.
Assumption 7	Economic model: The economic model's name '*[ID1175] durvalumab CEM to support AZ technical engagement response 220119 LB (ACIC)*' should be used as the basis for the CDF review. It should include committee's preferred assumptions as stated above. The following functionality should be available within the model at CDF review: • Replication of the key cost effectiveness results used in committee's decision-making at the point of CDF entry • Cost effectiveness results that incorporate data collected during the CDF data collection period with the assumptions used in committee's decision-making at the point of CDF entry • Cost effectiveness results that incorporate data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions	Yes	Not applicable	See chapter 4 for details.

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	ERG comment
	• Capacity to run the key sensitivity and scenario analyses presented in the original company submission			
Assumption 8	Durvalumab does not meet the end-of-life criteria	Yes	Not applicable	None

Source: Based on table of key committee assumptions as reported in the Terms of Engagement (ToE) for CDF review.[1] and the CS[2]
CDF = Cancer Drugs Fund; CRT = chemoradiation therapy; CS = company submission; ERG = Evidence Review Group; ToE = Terms of Engagement

3. CLINICAL EFFECTIVENESS

3.1 Overview of the new clinical evidence

3.1.1 Sources of evidence

The clinical efficacy of durvalumab for the treatment of locally-advanced, unresectable, stage III non-small-cell lung cancer (NSCLC), in patients whose disease has not progressed following two or more overlapping cycles of definitive, platinum-based chemoradiation therapy (CRT), has been investigated in one randomised controlled trial (RCT), PACIFIC.[2] PACIFIC is a phase III, multicentre, double-blind placebo-controlled randomised trial comparing the efficacy and safety of durvalumab 10 mg Q2W versus active follow-up. Its main methodological features are summarised in Table 3.1. As noted in the company submission (CS),[2] entry to PACIFIC was not restricted with respect to PD-L1 expression. However, in line with the population specified in the Terms of Engagement (ToE),[1] only results for the subgroup of patients whose tumours expressed PD-L1 on ≥1% of tumour cells were presented in the CS and are summarised in the following sections.

The other source of evidence is the SACT dataset.[8] This was specified in the ToE and created, at the behest of National Health Service (NHS) England and NHS Improvement, by Public Health England (PHE), with the purpose of evaluating the real-world treatment effectiveness of durvalumab in the Cancer Drugs Fund (CDF) population during the managed access period.[3] It provides evidence on overall survival (OS) and treatment duration for all patients treated with durvalumab for unresectable NSCLC, in the CDF, during the managed access period (28th March 2019 to 1st February 2021).[8]

ERG comment: The SACT dataset permits, to some degree, a test of the generalisability of the outcomes observed in the PACIFIC trial. For this reason, throughout the following sections the Evidence Review Group (ERG) will compare these two data sources both to establish comparability of outcomes in terms of design and baseline characteristics and in terms of the outcomes, OS and treatment duration. However, it should be noted that the inclusion criteria for the real world SACT cohort study allowed the inclusion of patients whose PD-L1 status could not be determined, although the company did provide an analysis excluding those patients in the form of the "Overall survival secondary sensitivity analysis".

3.1.2 Patient characteristics in the PACIFIC trial and SACT cohort study

The baseline characteristics appear comparable, between the durvalumab group and the placebo group, for patients in the PD-L1 ≥1% subgroup of the pacific trial.[9] The CS noted differences in baseline patient characteristics between the SACT cohort and the durvalumab treated PACIFIC PD-L1 ≥1% group, with respect to age and performance status.[2] The median age of patients in the SACT cohort (67 years)[8] was three years older than the durvalumab treated PACIFIC PD-L1 ≥1% cohort (64 years).[9] The SACT cohort also had a worse performance status (27% PS0; 59% PS1; 1% PS2; 14% missing PS)[8] compared with the durvalumab treated PACIFIC PD-L1 ≥1% group (49.5% PS0; 50.0% PS1; 0.5% PS not reported).[9]

The CS concluded that differences in baseline characteristics, between the durvalumab treated PACIFIC PD-L1 ≥1% group and the SACT cohort suggest that the patients included in the SACT cohort were generally older with worse performance status and hence may experience less optimal clinical outcomes than the durvalumab treated PACIFIC PD-L1 ≥1% group.

A comparison of the baseline characteristics, between the durvalumab treated and placebo groups in the PACIFIC trial (PD-L1 ≥1% subgroup) **and** the SACT cohort study, is provided in Table 3.2.

ERG comment: The ERG considers that the differences in age and performance status, between the durvalumab treated PACIFIC PD-L1 ≥1% group and the SACT cohort are unclear; the age range is not reported for the SACT cohort, but the distribution across age groups appears similar to that for the durvalumab treated PACIFIC PD-L1 ≥1% group, and the difference in performance status is mainly with respect a higher proportion of patients with missing data in the SACT cohort.

The ERG notes two further key differences between the durvalumab treated PACIFIC PD-L1 ≥1% group and the SACT cohort: All patients in the durvalumab treated PACIFIC subgroup had tumours which expressed PD-L1 in ≥1% of tumour cells, whereas PD-L1 status could not be determined for 12% of patients in the SACT cohort; all patients in the durvalumab treated PACIFIC PD-L1 ≥1% group were treated with a weight-based dose regimen (10 mg/kg Q2W), where as an unreported number of patients in the SACT cohort were treated with a fixed dose regimen (1,500 mg Q4W). The ERG therefore requested the following additional information, in the clarification letter:[5]

'Would the company expect that if there was a positive recommendation by NICE then such patients (those with unknown PD-L1 status) would be expected to receive durvalumab?'

'If so, then could the company perform all analyses for participants of the PACIFIC Trial including those for whom PD-L1 status could not be determined as well as those with PD-L1 ≥1%'

'Could the company also obtain an analysis of the SACT data excluding those patients with unknown PD-L1 status.'

'Please provide evidence of the relationship between the clinical effectiveness and safety of durvalumab between the different dosing regimens (fixed dose of 1500mg administered Q4W and 10mg/kg Q2W).'

It should also be noted that the company did provide an analysis of the SACT OS data excluding patients with unknown PD-L1 status, referred to as the "Overall survival secondary sensitivity analysis. Subsequent to submission of the clarification letter, the ERG also received an analysis of the SACT data, following the removal of unknown PD-L1 scores, PD-L1 testing not possible and PD-L1 result unquantifiable.[7]

Table 3.1: Summary of methodology of the PACIFIC trial and SACT cohort study

Trial name	***PACIFIC***	***SACT dataset***
Location	235 study centres in 26 countries: • Australia, Belgium, Canada, Chile, France, Germany, Greece, Hungary, Israel, Italy, Japan, Mexico, Netherlands, Peru, Poland, Singapore, Slovakia, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, United States, and Vietnam	United Kingdom
Design	Multicentre, double-blind, phase III RCT	Observational study
Eligibility criteria for participants	*Key inclusion criteria:* • Patients with locally-advanced, unresectable stage III NSCLC, who have not progressed following ≥2 cycles of definitive, overlapping platinum-based CRT • 18 years or older • WHO PS score 0 or 1 • Estimated life expectancy ≥12 weeks *'All comers'* population, i.e., any PD-L1 status	*Key inclusion criteria:* • Application has been made by and the first cycle of SACT with durvalumab will be prescribed by a consultant specialist specifically trained and accredited in the use of SACT • The prescribing clinician is fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to anti-PD-L1 treatments including pneumonitis, colitis, nephritis, endocrinopathies and hepatitis • Patient has a histologically- or cytologically-confirmed diagnosis of NSCLC • Patient has locally advanced and unresectable NSCLC which is either stage IIIA or stage IIIB or stage IIIC at the time of commencing concurrent chemoradiotherapy • PD-L1 testing with an approved and validated test to determine the PD-L1 TPS has been done prior to this application and the result either demonstrates a PD-L1 score of ≥1% or the PD-L1 TPS cannot be ascertained despite an intent and a reasonable attempt to do so • Patient has completed treatment with two or more cycles (defined according to local practice) of platinum-based combination chemotherapy given concurrently with definitive radical radiotherapy which must have been at a

Trial name	*PACIFIC*	*SACT dataset*
		dose of 54-66 Gy (or a biologically equivalent dose of 54-66 Gy) • Patient has been re-staged since chemoradiotherapy was completed and does not have any evidence of disease progression or metastatic spread • Patient will start his/her first treatment with durvalumab within 42 days of the last active treatment date of chemoradiotherapy • Patient has an ECOG PS 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 antibody unless durvalumab has been received as part of AstraZeneca's early access program for durvalumab after concurrent chemoradiotherapy
Trial drugs and method of administration	*Durvalumab group* Durvalumab 10 mg/kg Q2W, administered intravenously for up to 12 months *Active follow-up group* Placebo Q2W, administered intravenously for up to 12 months	*Durvalumab only* Durvalumab, either 10 mg/kg Q2W or 1,500 mg Q4W for up to 12 months
Outcomes collected for the CDF review	• PFS • OS • Subsequent therapies (frequency and duration)	• OS • Treatment duration
Subgroups	Patients whose tumour expressed PD-L1 on ≥1% of tumour cells*	Patients whose tumour expressed PD-L1 on ≥1% of tumour cells i.e. excluding patients with unknown PD-L1 status, referred to as the "Overall survival secondary sensitivity analysis"
Duration of study and follow-up	Five years	21 months
Source: Section B.2.3 and Figure 6, 2018 CS,[9] and SACT dataset report.[8]		

Trial name	*PACIFIC*	*SACT dataset*
[*]Only data for this patient subgroup are reported in subsequent sections CRT: chemoradiation therapy; ECOG: Eastern Cooperative Oncology Group; NA: not applicable; NSCLC: non-small-cell lung cancer; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; PS = performance status; Q2W: every 2 weeks; RCT = randomised controlled trial; SACT = systemic anti-cancer therapy; TPS: tumour proportion score; WHO PS: World Health Organisation Performance Score		

Table 3.2: Baseline characteristics of patients in the PACIFIC trial compared to the SACT cohort study

Characteristic	PACIFIC (PD-L1 ≥1% subgroup)			SACT
	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)	Durvalumab (n=591)
Demographics				
Age, mean (SD)	63.0 (8.4)	63.1 (8.8)	63.1 (8.5)	NR
Age, median (range) [years]	64 (36−83)	64 (41−90)	64 (36−90)	67 (NR)
Age groups PACIFIC (years), n (%)				
<50	12 (5.7)	6 (6.6)	18 (5.9)	-
≥50−<65	104 (49.1)	45 (49.5)	149 (49.2)	-
≥65−<75	81 (38.2)	34 (37.4)	115 (38.0)	-
≥75	15 (7.1)	6 (6.6)	21 (6.9)	-
Age groups SACT (years), n (%)				
<40	-	-	-	7 (1)
40−49	-	-	-	29 (5)
50-59	-	-	-	105 (18)
60-69	-	-	-	216 (37)
70-79	-	-	-	219 (37)
≥80	-	-	-	15 (3)
Sex, n (%)				
Male	144 (67.9)	65 (71.4)	209 (69.0)	346 (59)
Female	68 (32.1)	26 (28.6)	94 (31.0)	245 (41)

Characteristic	PACIFIC (PD-L1 ≥1% subgroup)			SACT
	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)	Durvalumab (n=591)
Race, n (%)				
White	146 (68.9)	60 (65.9)	206 (68.0)	NR
Black/African American	8 (3.8)	1 (1.1)	9 (3.0)	NR
Asian	58 (27.4)	27 (29.7)	85 (28.1)	NR
Native Hawaiian or other	0	1 (1.1)	1 (0.3)	NR
American Indian or Alaska	0	2 (2.2)	2 (0.7)	NR
Other	0	0	0	NR
Weight, mean (SD) [kg]	72.6 (17.88)	67.4 (15.4)	71.1 (17.3)	NR
Weight, median (range)	69 (34−133)	65 (43−128)	69 (34−133)	NR
Weight group (kg), n (%)				
<70	107 (50.5)	54 (59.3)	161 (53.1)	NR
≥70-≤90	77 (36.3)	31 (34.1)	108 (35.6)	NR
>90	28 (13.2)	6 (6.6)	34 (11.2)	NR
Smoking status, n (%)				
Current smoker	39 (18.4)	13 (14.3)	52 (17.2)	NR
Former smoker	153 (72.2)	71 (78.0)	224 (73.9)	NR
Never smoked	20 (9.4)	7 (7.7)	27 (8.9)	NR
Disease characteristics				
Disease Stage, n (%)				
IIIA	118 (55.7)	48 (52.7)	166 (54.8)	284 (48)
IIIB	89 (42.0)	42 (46.2)	131 (43.2)	246 (42)
IIIC	NR	NR	NR	61 (10)
Other[a]	5 (2.3)	1 (1.1)	6 (2.0)	0 (0)

Characteristic	PACIFIC (PD-L1 ≥1% subgroup)			SACT
	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)	Durvalumab (n=591)
WHO PS score, n (%)[b]				
0	105 (49.5)	45 (49.5)	150 (49.5)	157 (27)
1	106 (50.0)	46 (50.5)	152 (50.2)	346 (59)
2	0 (0)	0 (0)	0 (0)	3 (1)
Missing	1 (0.5)	0	1 (0.3)	85 (14)
Tumour histological type, n (%)				
Squamous	109 (51.4)	41 (45.1)	150 (49.5)	NR
Non-squamous	103 (48.6)	50 (54.9)	153 (50.5)	NR
PD-L1 status, n (%)[c]				
TC ≥1%	212 (100)	91 (100)	303 (100)	522 (88)
TC <25%	97 (45.8)	47 (51.6)	144 (47.5)	NR
TC ≥25%	115 (54.2)	44 (48.4)	159 (52.5)	NR
Unknown[d]	N/A	N/A	N/A	69 (12)
EGFR mutation status, n (%)				
Positive	17 (8.0)	4 (4.4)	21 (6.9)	NR
Negative	180 (84.9)	84 (92.3)	264 (87.1)	NR
Unknown[d]	15 (7.1)	3 (3.3)	18 (5.9)	NR
Prior anti-cancer therapy				
Previous radiotherapy, n (%)[e]				
<54 Gy	2 (0.9)	0	2 (0.7)	NR
≥54 to ≤66 Gy	193 (91.0)	86 (94.5)	279 (92.1)	NR
>66 to ≤74 Gy	17 (8.0)	5 (5.5)	22 (7.3)	NR
Previous chemotherapy, n (%)[f]				

Characteristic	PACIFIC (PD-L1 ≥1% subgroup)			SACT
	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)	Durvalumab (n=591)
Adjuvant	2 (0.9)	0	2 (0.7)	NR
Induction	49 (23.1)	21 (23.1)	70 (23.1)	NR
Concurrent with radiation therapy	211 (99.5)	91 (100.0)	302 (99.7)	NR
Best response to previous CRT, n (%)[g]				
Complete response	3 (1.4)	2 (2.2)	5 (1.7)	NR
Partial response	106 (50.0)	45 (49.5)	151 (49.8)	NR
Stable disease	100 (47.2)	43 (47.3)	143 (47.2)	NR
Progression	1 (0.5)	0	1 (0.3)	NR
Non-evaluable	2 (0.9)	1 (1.1)	3 (1.0)	NR

Sources: Based on Table 4 of the 2018 CS[9]

[a]Patients with other disease stages included 12 patients in the durvalumab group (four with Stage IV, four with Stage IIB, three with Stage IIA, and one with Stage IA) and five patients in the placebo group (two with Stage IIB, one with Stage IIA, and two with Stage IB)

[b]WHO PS scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increased disability

[c]PD-L1 status was collected before patients received CRT

[d]No sample collected or no valid test result. The *EGFR* status for two patients in the durvalumab group changed from unknown to negative between the 13th February 2017 and 22nd March 2018 DCOs, as the results for these two patients were analysed after the previous DCO

[e]The decision regarding the actual dose was based on investigator or radiologist assessment of each individual patient, resulting in doses that differed from the inclusion criteria. All radiation therapy was administered concurrently with chemotherapy

[f]Patients may have received previous chemotherapy in more than one context

[g]Best response to prior therapy is based on the last therapy prior to entering the study

CRT = chemoradiation therapy; CS = company submission; CSR = clinical study report; DCO = data cut-off; EGFR = epidermal growth factor receptor; N/A = not applicable; NR = not reached; PD-L1 = programmed cell death ligand 1; PS = performance status; SACT = systemic anti-cancer therapy; SD = standard deviation; TC = tumour cell; WHO = World Health Organisation

3.2 Results of the new clinical evidence

3.2.1 Overall survival

An overview of OS in the previous DCO (22nd March 2018**)** and new DCO (11th January 2021**)** of the PACIFIC trial (PD-L1 ≥1% subgroup**)** and the overall survival secondary sensitivity analysis of the SACT data is provided in Table 3.3

At the time of the final analysis (11th January 2021 DCO), the overall data maturity for the OS endpoint in the PD-L1 ≥1% group had increased to 52.5%, compared with 38.0% at the time of the original submission (22nd March 2018 DCO).[2]

The OS benefit indicated by the HR for durvalumab treated patients relative to placebo treated patients at the 22nd March 2018 DCO was maintained at the 5-year follow-up, (Table 3.3).

At the time of the final analysis, the increase in median OS for patients treated with durvalumab compared to placebo in the PACIFIC trial (PD-L1 ≥1% subgroup) was 33.5 months,[2] and 5-year survival rates were 50.1% (95% confidence interval (CI): 43.0, 56.8) for durvalumab treated patients compared to 36.9% (95% CI: 26.8, 47.1) for the placebo treated patients (Table 3.3). At the latest comparable time point (24-months), survival rates appeared slightly lower in the SACT cohort 68% (95% CI: 62, 74) than in durvalumab treated patients from the PACIFIC trial (PD-L1 ≥1% subgroup) 72.9% (95% CI: 66.2, 78.4), (Table 3.3).

ERG comment: The ERG agrees that the survival benefit, for durvalumab treated patients, observed at the 22nd March 2018 DCO is maintained at the 11th January 2021 DCO (5-years). It notes that the SACT data appear to indicate that the survival benefits observed in the PACIFIC trial may not be fully achieved in, but are plausibly applicable to the real world, UK setting. It should also be noted that the SACT results for 12 months and 24 months including patients whose PD-L1 status was unknown were almost identical to those in Table 3.3, i.e. 84% (81%, 87%) and 67% (61%, 72%) for 12 and 24 months respectively .[7]

Table 3.3: Overall survival for the PD-L1 ≥1% subgroup in the PACIFIC trial and the SACT cohort study

Outcome	PACIFIC (PD-L1 ≥1% subgroup) 22nd March 2018		PACIFIC (PD-L1 ≥1% subgroup) 11th January 2021		Overall survival secondary sensitivity analysis of SACT 30th July 2021
	Durvalumab (n=212)	Placebo (n=91)	Durvalumab (n=212)	Placebo (n=91)	Durvalumab (n=522)
Death, n (%)	70 (33.0)	45 (49.5)	103 (48.6)	56 (61.5)	115 (22)
Censored patients, n (%)	142 (67.0)	46 (50.5)	109 (51.4)	35 (38.5)	407 (78)
Median OS, months (95% CI)[a]	NR (NR, NR)	29.1 (17.7, NR)	63.1 (43.7, NE)	29.6 (17.7, 44.7)	NA
Hazard ratio (95% CI)[b,c]	0.54 (0.35, 0.81)		0.61 (0.44, 0.85)		NA
12-month survival rate, % (95% CI)	86.5 (81.1, 90.5)	74.7 (64.2, 82.6)	86.5 (81.1, 90.5)	74.7 (64.2, 82.6)	85 (82, 88)
24-month survival rate, % (95% CI)	72.8 (66.2, 78.4)	53.6 (42.5, 63.4)	72.9 (66.2, 78.4)	53.7 (42.6, 63.5)	68 (62, 74)
36-month survival rate, % (95% CI)	NA	NA	61.9 (54.8, 68.2)	45.3 (34.6, 55.5)	NA
48-month survival rate, % (95% CI)	NA	NA	54.9 (47.8, 61.4)	38.1 (27.9, 48.3)	NA
60-month survival rate, % (95% CI)	NA	NA	50.1 (43.0, 56.8)	36.9 (26.8, 47.1)	NA

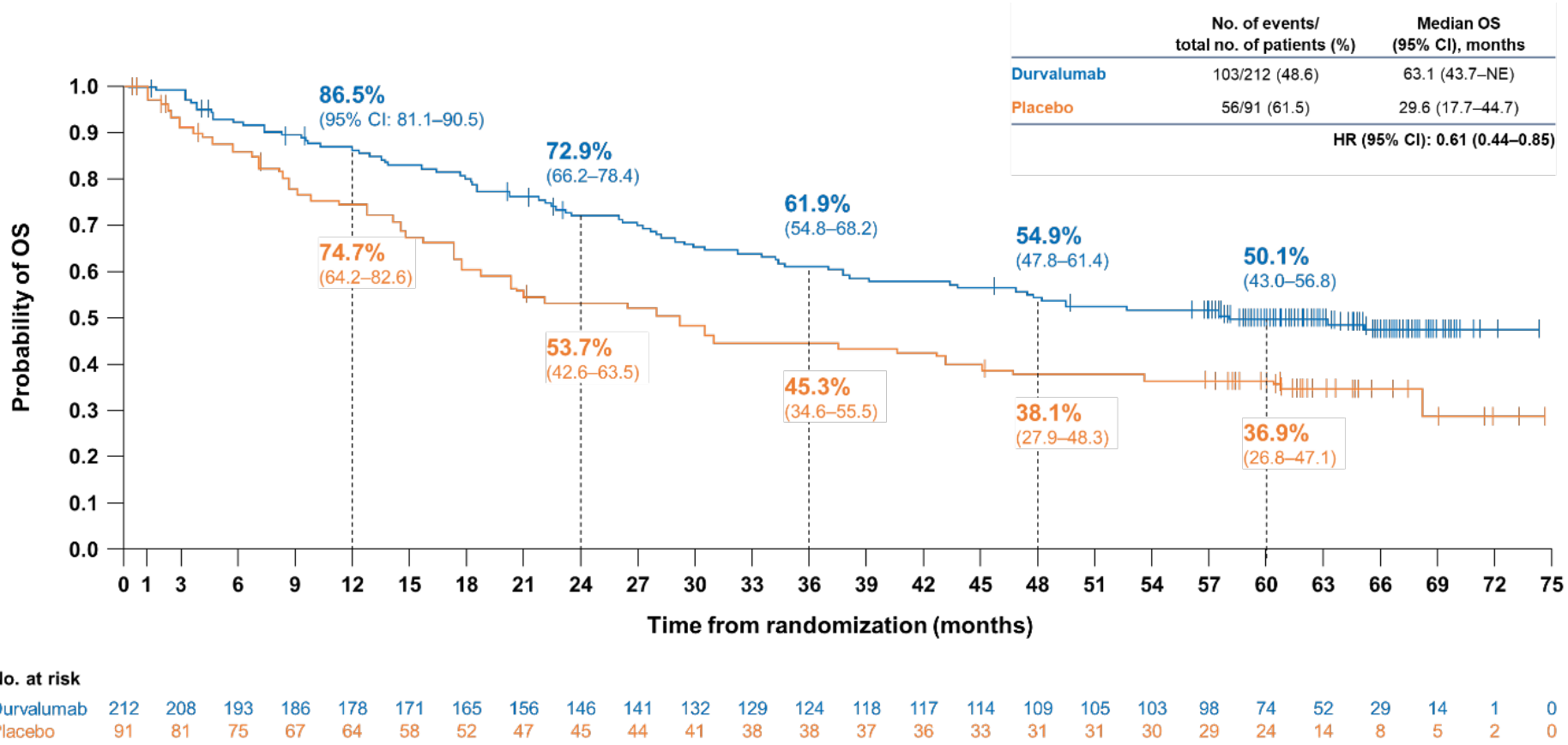
Sources: Table 6, CS[2] Appendix A, CS[10], Appendix C, CS[11] and Table 14, 2018 CS[9]

[a]Calculated using the Kaplan–Meier technique

[b]22nd March 2018 DCO: The analysis was performed using a stratified log rank test adjusting for age at randomisation (<65 versus ≥65), sex (male versus female), and smoking history (smoker versus non-smoker), with ties handled using the Breslow approach. A hazard ratio < 1 favours durvalumab

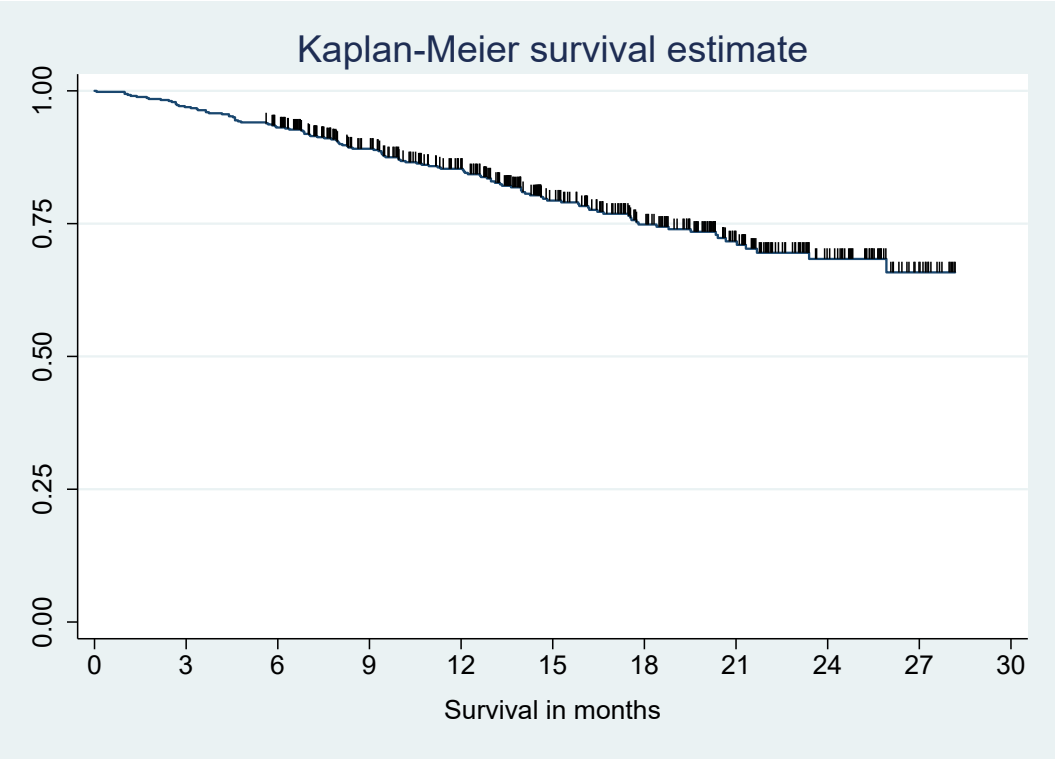
[c]The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties
CI: confidence interval; DCO: data cut-off; PD-L1: programmed death-ligand 1; NA; not applicable; NE: not estimable; NR: not reached; OS: overall survival

Figure 3.1: Kaplan-Meier plot for overall survival in PACIFIC (PD-L1 ≥1% subgroup)



Data cut-off: 11th January 2021
NE: not estimable; OS: overall survival
Source: company submission, Figure 2.[2]

Figure 3.2: Kaplan-Meier plot for overall survival, censored at 30th July 2021, in the SACT overall survival secondary sensitivity analysis of patients with PD-L1 ≥1%



Source: company submission, Appendix C, Figure 1[11].

3.2.2 Progression-free survival

An overview of PFS in the previous DCO (22nd March 2018**)** and new DCO (11th January 2021**)** of the PACIFIC trial (PD-L1 ≥1% subgroup**)** is provided in Table 3.4.

At the time of the 5-year follow-up analysis (11th January 2021 DCO), based on the Blinded Independent Central Review (BICR) assessments of PFS according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 in the PD-L1 ≥1% patients, since the 22nd March 2018 DCO an additional [redacted] events had occurred in the durvalumab group and an additional [redacted] events in the placebo group. Overall, the PFS data maturity increased from 54.5% at the 22nd March 2018 DCO to 59.4% at the 11th January 2021 DCO.[10, 12]

The PFS benefit indicated by the hazard ratio for durvalumab treated patients relative to placebo treated patients at the 22nd March 2018 DCO was maintained at the 5-year follow-up, (Table 3.4).

At the time of the final analysis, Kaplan-Meier estimate of median PFS was 24.9 months (95% CI: 16.9, 38.7) in the durvalumab group compared to 5.5 months (95% CI: 3.6, 10.3) in the placebo group,[2] and 5-year PFS rates were 35.8% (95% CI: 28.0, 43.7) for durvalumab treated patients compared to 17.6% (95% CI: 9.8, 27.3) for the placebo treated patients (Table 3.4).

ERG comment: The ERG agrees that the PFS benefit, for durvalumab treated patients, observed at the 22nd March 2018 DCO is maintained at the 11th January 2021 DCO (5-years).

Table 3.4: Progression Free Survival for the PD-L1 ≥1% subgroup in the PACIFIC trial

Outcome	PACIFIC (PD-L1 ≥1% subgroup) 22nd March 2018		PACIFIC (PD-L1 ≥1% subgroup) 11th January 2021	
	Durvalumab (n=212)	Placebo (n=91)	Durvalumab (n=212)	Placebo (n=91)
Events, n (%)[a]	[redacted]	[redacted]	111 (52.4)	69 (75.8)
Censored patients, n (%)	[redacted]	[redacted]	101 (47.6)	22 (24.2)
Median PFS, months (95% CI)[b]	23.9 (17.2, NR)	5.6 (3.6, 11.0)	24.9 (16.9, 38.7)	5.5 (3.6, 10.3)
Hazard ratio (95% CI)[c,d]	0.44 (0.31, 0.63)		0.47 (0.35, 0.64)	
12-month PFS rate, % (95% CI)	62.7 (55.4, 69.1)	37.1 (26.7, 47.6)	62.2 (55.0, 68.6)	35.5 (25.4, 45.7)
18-month PFS rate, % (95% CI)	49.8 (40.1, 58.6)	30.7 (20.1, 41.8)	55.2 (47.8, 62.1)	27.1 (17.9, 37.2)
24-month PFS rate, % (95% CI)	NA	NA	50.3 (42.7, 57.4)	24.2 (15.3, 34.1)
36-month PFS rate, % (95% CI)	NA	NA	43.3 (35.5, 50.8)	17.6 (9.8, 27.3)
48-month PFS rate, % (95% CI)	NA	NA	37.9 (30.2, 45.7)	17.6 (9.8, 27.3)

60-month PFS rate, % (95% CI)	NA	NA	35.8 (28.0, 43.7)	17.6 (9.8, 27.3)

Sources: Table 5 CS[2] Appendix A, CS[10], and Table 7, 2018 CS[9]

[a]Patients who have not progressed or died, or who progress or die after two or more missed visits, are censored at the latest non-missing RECIST assessment, or day 1 if there are no non-missing visits. Patients who have no non-missing visits or do not have baseline data will be censored at study day one unless they die within two visits of baseline

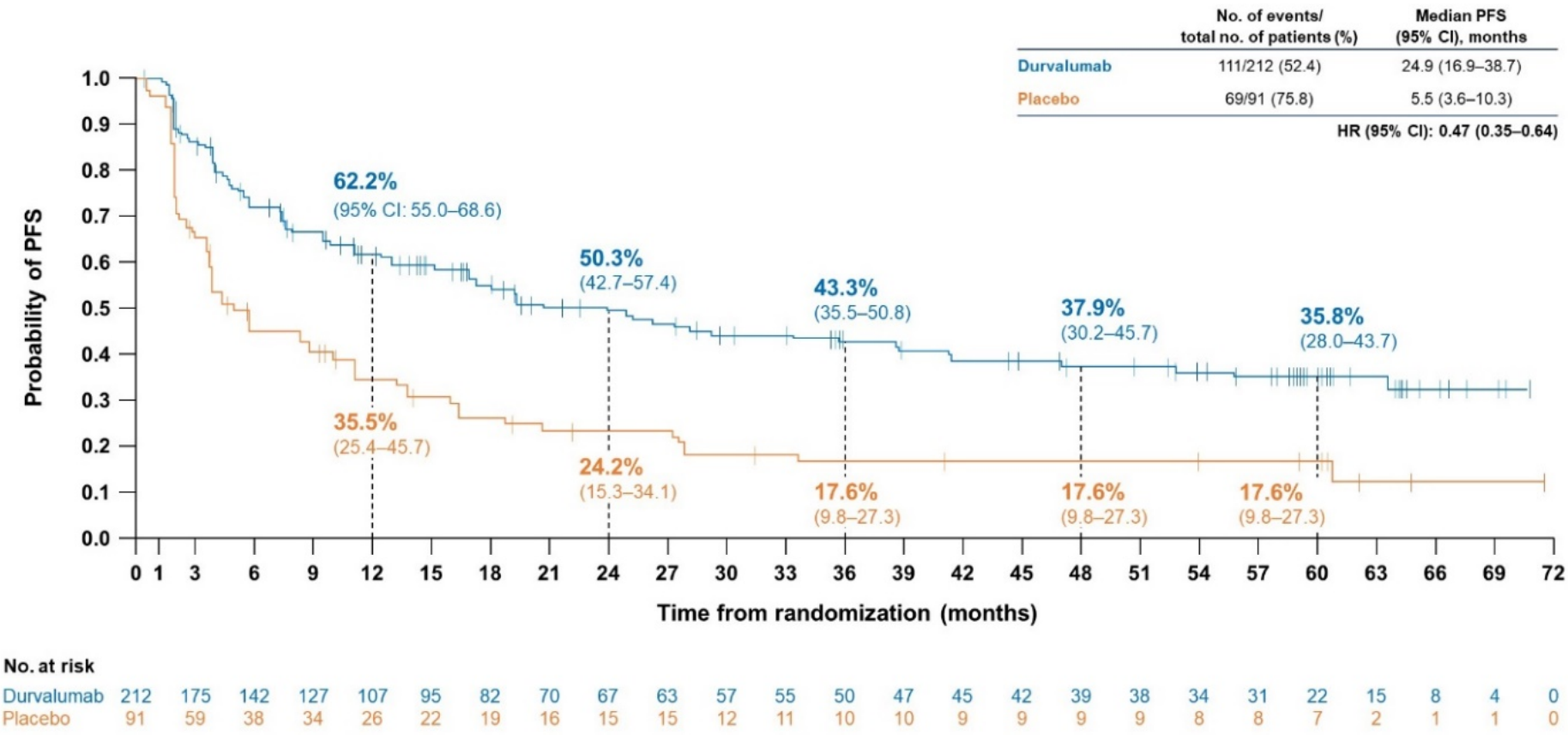
[b]calculated using the Kaplan-Meier technique

[c]22nd March 2018 DCO: analysed using a stratified log rank test adjusting for age at randomisation (<65 versus ≥65), sex (male versus female), and smoking history (smoker versus non-smoker), with ties handled using the Breslow approach

[d]11th January 2021 DCO: hazard ratio is estimated from unstratified Cox's proportional hazards model within each subgroup. Ties are handled by Efron approach. A hazard ratio < 1 favours durvalumab

CS = company submission; CI = confidence interval; DCO = data cut-off; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; NA = not applicable; NR = not reached; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1

Figure 3.3: Kaplan-Meier plot of BICR assessment of progression-free survival for the PD-L1 ≥1% subgroup in the PACIFIC trial



Data cut-off: 11th January 2021
BICR: Blinded Independent Central Review; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival
Source: company submission, Figure 1[2]

3.2.3 Treatment duration

As reported in Section B.2.10, Table 17 in the original CS,[9] the median actual time on treatment (total treatment duration – duration of dose days) for durvalumab treated patients in the PD-L1 ≥1% subgroup of the PACIFIC trial was 41.7 (range 2 to 53) weeks.

The median follow-up time for the 591 patients in the SACT dataset was 7.3 months and median treatment duration was 313 days, or 10.3 months (95% CI: 9.4, 11.1).[8] As noted in the CS,[2] treatment duration was not analysed by PD-L1 ≥1% expression, and therefore also includes data from patients with unknown PD-L1 expression. It was also noted that some patients in the SACT cohort received durvalumab treatment beyond the 12 months maximum treatment duration stipulated by the regulatory label and the CS suggested that this may be explained by some patients requiring treatment breaks due to toxicity (i.e. the total active treatment period, excluding breaks, did not exceed 12 months),[2] however, this information was not recorded in the PHE report of the SACT data.[8]

Table 3.5 provides a summary of outcomes for the 402 patents, in the SACT dataset, who were identified as having completed treatment by 31st March 2021 (latest follow up in SACT dataset).

Table 3.5: Treatment outcomes for patients in the SCAT cohort who have ended treatment

Outcome	Number (%)
Stopped treatment – progression of disease	84 (21)
Stopped treatment – acute toxicity	82 (20)
Stopped treatment – completed as prescribed	66 (16)
Stopped treatment – no treatment in at least three months	44 (11)
Stopped treatment – died not on treatment	39 (10)
Stopped treatment – palliative, patient did not benefit	32 (8)
Stopped treatment – palliative, patient did benefit	28 (7)
Stopped treatment – patient choice	14 (3)
Stopped treatment – COVID	7 (2)
Stopped treatment – died on treatment	6 (1)
Source: Table 10 Appendix B, company submission[8]	

ERG comment: The median treatment duration, for durvalumab, appeared similar when used in the trial setting (PACIFIC, PD-L1 ≥1% subgroup) compared to the real-world setting (SACT cohort), 10.4 months versus 10.3 months.

3.2.4 Subsequent therapies

A summary of post-discontinuation disease-related anti-cancer therapy use in the previous DCO (22nd March 2018**)** and new DCO (11th January 2021**)** of the PACIFIC trial (PD-L1 ≥1% subgroup**)** is provided in Table 3.6.

These data indicate that a greater proportion of patients in the placebo group received a subsequent therapy [redacted] compared with patients in the durvalumab group [redacted] at the 5-year follow-up.[10] The frequency of immunotherapy use was higher in the placebo group [redacted] than in the durvalumab group [redacted];[10] the CS[2] notes that, although some subsequent immunotherapy use was observed in durvalumab treated patients in the PACIFIC trial, this is not expected in UK clinical practice given the Blueteq criteria for PD-1/L1 inhibitors for use in locally advanced and metastatic NSCLC explicitly state that patients who have received previous PD-1/L1 therapy are not eligible for further PD-1/L1 treatment.[13]

Table 3.6: Post-discontinuation disease-related anti-cancer therapy use for the PD-L1 ≥1% subgroup in the PACIFIC trial

Therapy	PACIFIC (PD-L1 ≥1% subgroup) 22nd March 2018		PACIFIC (PD-L1 ≥1% subgroup) 11th January 2021	
	Durvalumab (n=212)	Placebo (n=91)	Durvalumab (n=212)	Placebo (n=91)
Any post-discontinuation disease-related anti-cancer therapy, n (%)	81 (38.2)	50 (54.9)	[redacted]	[redacted]
Radiotherapy, n (%)	31 (14.6)	20 (22.0)	[redacted]	[redacted]
Immunotherapy, n (%)	18 (8.5)	22 (24.2)	[redacted]	[redacted]
Cytotoxic chemotherapy, n (%)	54 (25.5)	29 (31.9)	[redacted]	[redacted]
Systemic therapy, n (%)	24 (11.3)	13 (14.3)	[redacted]	[redacted]
Source: Table 7, company submission[2]				

3.2.5 Health-related quality of life

Section A.7.4 of the CS states that: *'As more mature data on health-related quality of life has not been collected in further data cuts, the utility values applied in this cost-effectiveness analysis have remained unchanged.'*[2]

ERG comment: The ToE stated that: *'The company should use more mature quality of life data from PACIFIC to inform the progression free and progressed health states in the economic model.'*[1] The ERG therefore requested confirmation, in the clarification letter, that no additional quality of life data had been collected.[5] This was confirmed by the company.

The ERG notes that this assumption was not adhered to in the CS (as detailed in Section 4).

3.3 Summary of the new clinical effectiveness evidence according to the terms of engagement for the CDF review

The ERG can confirm that data presented from the PACIFIC trial are for the specified population i.e., adults with locally advanced, unresectable NSCLC whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based CRT only if they had concurrent chemoradiation are the relevant population for the CDF review. The ERG notes that there is a discrepancy between this population and those patients treated with durvalumab from whom the SACT data were obtained in that 12% of the patients had unknown PD-L1 status. Whilst this did not affect the summary statistics for OS very much, it is unclear to the ERG why these patients received durvalumab. The ERG notes that the survival benefit for durvalumab treated patients, observed at the 22nd March 2018 DCO is maintained at the 11th January 2021 DCO (5-years). It notes that the SACT data appear to

indicate that the survival benefits observed in the PACIFIC trial may not be fully achieved in, but are plausibly applicable to the real world, UK setting. There is also a potential lack of generalisability of the PACIFIC trial in that, instead of the 10 mg/kg Q2W) dose administered in the trial, a fixed dose regimen (1,500 mg Q4W) will be used in clinical practice. As discussed in Section 2.2, this might result in a reduction in survival in clinical practice. Although some patients from whom the SACT data were obtained did receive 1,500 mg Q4W, this number and the effect on survival are unknown.

4. COST EFFECTIVENESS

4.1 Population

Terms of Engagement: *"Adults with locally advanced, unresectable non-small cell lung cancer whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based chemoradiation therapy only if they had concurrent chemoradiation are the relevant population for the CDF review."*

The company's modelled population is in line with the population considered by the committee for entry into the CDF and it was anticipated that the population would not change for the CDF review.

4.2 Comparators

Terms of Engagement: *"The company should present clinical and cost-effective evidence for durvalumab compared to standard care."*

The company's modelled comparator (standard care) is in line with the comparator considered by the committee for entry into the CDF and it was anticipated that the comparator would not change for the CDF review.

4.3 *Updated survival modelling*

Terms of Engagement: *"The company should use updated survival data from PACIFIC and fully explore the most appropriate method to extrapolate survival outcomes."*

The company updated their original cost effectiveness model with the final analysis of the PACIFIC trial. The model structure was identical to that previously submitted to NICE. This entailed modelling of PFS, time-to-progression (TTP), and post-progression survival (PPS).

For PFS, the company fitted parametric survival curves (exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma) to patient level data. The parametric distributions that inform the base-case analysis were selected based on statistical goodness-of-fit, visual inspection and clinical plausibility. Goodness of fit statistics were presented in Tables 8 and 9 of the CS. For durvalumab, the generalised gamma had the best statistical fit based on AIC and BIC, followed by the lognormal, and in third place the Gompertz. For standard of care (SoC), the generalised gamma also had the best statistical fit based on AIC and BIC, followed by the lognormal and Gompertz which had identical goodness of fit. Nine clinical experts were consulted to assess the clinical plausibility of these distributions. Almost all experts (n=seven out of nine) selected the Gompertz as most consistent with their expectations of durvalumab's long-term PFS. Almost all experts (n=seven out of nine) selected the generalised gamma for the SoC arm. In the company base-case, the stratified generalised gamma was used for both treatment arms.

For TTP, the company did not provide any new analyses. The company stated in response to the clarification letter that the TTP analysis remained unchanged – however, the ERG noted that, whilst the selection of distributions was maintained (generalised gamma for both arms), the parameters were updated. Unfortunately, no detail was provided on this analysis. The generalised gamma was used in both treatment arms.

For PPS, the company continued to estimate PPS jointly for the durvalumab and SoC arms, assuming that PPS was the same across both treatment arms. The parametric distributions that informed the base-case analysis were selected based on statistical goodness-of-fit and visual inspection. Goodness of fit statistics were presented in Table 10 of the CS. The log-logistic had the best statistical fit, and was very

closely followed by the lognormal, Gompertz and the generalised gamma (which were still approximately within two AIC points; the generalised gamma performed slightly worse according to BIC). The company stated that all distributions had good visual fit. The clinical plausibility was not assessed. Upon request, the company provided pooled PPS Kaplan Meier data from PACIFIC and modelled PPS and compared it with the stratified PPS Kaplan Meier data from PACIFIC and stratified models. This comparison showed that pooled and stratified PPS were fairly similar between the two treatment arms, with a slight PPS advantage for the durvalumab arm. The exponential was used in the company base-case.

The ERG requested, in clarification question B7 external validation of the TTD, TTP, PFS and PPS data from PACIFIC with the SACT data for the durvalumab arm, but the company stated that collection of these data was not part of the managed access agreement and validation could therefore not be provided. Clinicians confirmed that the 5-year PFS outcomes of both the durvalumab and placebo arms for the PD-L1≥1% subgroup were consistent with their expectations based on clinical practice (although with the caveat that their experience was limited to approximately three years). The company provided real world evidence from the PACIFIC-R study for the external validation of PFS, reporting a median PFS of 22.4 months (95% CI: 18.7, 25.5). However, these data were suboptimal, as patients in PACIFIC-R had the option to receive sequential or concurrent CRT, as opposed to the PACIFIC study, which was limited to concurrent CRT only. Although TTD was not collected in the SACT data, the company considered ToT from SACT as a proxy for TTD. The median ToT in the SACT cohort was 10.3 months.

ERG comment: The ERG has concerns about a) the company's modelling approach and lack of internal consistency between modelled survival and observed trial data; b) the time-to-event analysis for PFS; c) lacking update for TTP; and d) insufficient data and expert experience to externally validate modelled PFS, OS and TTD.

a) The ERG considers that the most appropriate method to extrapolate survival outcomes (as stipulated in the ToE) was not explored by the company. The company continue to use their original PFS/TTP/PPS modelling approach and justified this with their understanding that *"the model approach and structure should remain unchanged compared with the original submission"*. The company's original approach was criticised by the ERG in the original submission, as it relies on post-hoc analyses and small patient numbers for the PPS analysis, it assumes that PPS is the same for both treatment arms, and it over-estimated PFS of durvalumab in the company's previous base-case. At the time of the original submission, the company justified their approach stating that it avoided the logical inconsistency of OS and PFS curves crossing. However, it was noted previously by the ERG that the company's adopted PFS/TTP/PPS did not solve this issue. It is the ERG's view that, in order to *"fully explore the most appropriate method to extrapolate survival outcomes"*, this methodological uncertainty should have been explored as well.

   The ERG is not completely satisfied with the company's PFS/TTP/PPS approach, as it requires more assumptions than an OS/PFS approach (for example that PPS is equal for both treatment arms). Hence, the ERG considers that, in order to fully explore the most appropriate survival method, an OS/PFS approach should have been explored. In addition, the ERG noted that the company's modelled number of patients alive at five years in the durvalumab arm exceeded OS observed in the PACIFIC trial ([redacted] alive in model, [redacted] in PACIFIC), and that the company's modelled number of patients alive in the SoC arm was below OS observed in the PACIFIC trial ([redacted] alive in model, [redacted] in PACIFIC). Internal consistency between the model and the evidence used for it is therefore lacking and it appears that the company's modelling approach induces bias

in favour of durvalumab. The ERG considers that an OS/PFS approach may have removed this bias. Unfortunately, the company did not provide this modelling approach upon request. Since this bias could not be removed, the ERG considered it important to achieve better internal consistency between modelled survival and that observed in PACIFIC. The ERG explored alternative PFS models and found that the lognormal may be a plausible alternative model for durvalumab PFS (third best statistical fit, [redacted] alive in model at five years). Unfortunately, no PFS distribution provided better internal consistency with PACIFIC than the generalised gamma in the placebo arm. The ERG considers the lognormal to be a more conservative choice for the durvalumab arm, given that relative effectiveness with the current model structure and chosen distributions in the company base-case is likely to be over-estimated. However, uncertainty remains over the appropriateness of the company's modelling of survival.

b) The ERG noted the preference of most of the consulted clinical experts for the Gompertz to model PFS in the durvalumab arm. The company also explored whether the proportional hazards assumption held and concluded that it did indeed hold. However, the company noted that the best-fitting joint generalised gamma did not exhibit a good visual fit with the Kaplan-Meier data, but no further detail on this was provided. It also appeared that this was not implemented (correctly) in the model. The company's analysis is therefore not fully aligned with NICE DSU TSD 14. The best way to model PFS therefore remains unclear. The ERG explored using the individual Gompertz in the durvalumab arm in a scenario. Jointly fitted models should be further explored by the company (also by including them in the economic model) and further information provided on why these were ruled out.

c) Full details on time-to-event analysis performed to inform TTP should be provided.

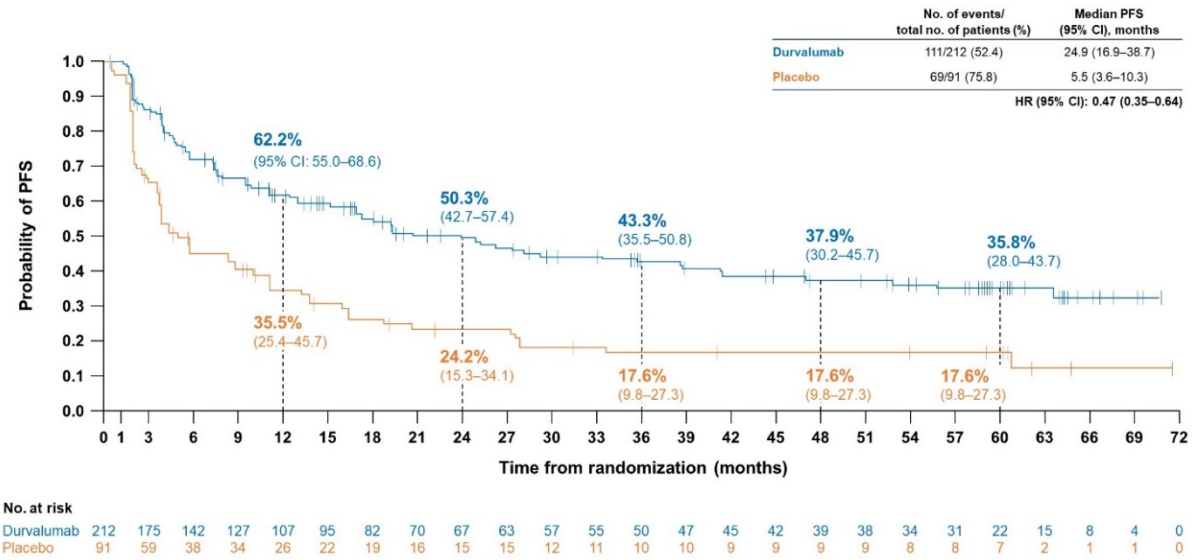
d) There were limitations in the company's ability to externally validate modelled PFS, OS and TTD, based on limited data availability and lack of clinician's long-term experience with durvalumab.

4.4 *Treatment effect duration*

Terms of Engagement: *"The company should use updated survival data from PACIFIC to inform the appropriateness of a cure assumption."*

The company stated that *"Progression-free survival data from the final analysis of PACIFIC demonstrates the durable and sustained treatment benefit of durvalumab, which is observed well beyond treatment discontinuation."* (CS Section A.7.1). The company cites as justification for this statement Section A.6.1 from the CS, which presents the Kaplan Meier plot presented in Figure 4.1. This section also presents a comparison of events, median PFS and HRs at 2-year follow-up versus 5-year follow-up, which shows that an additional 18.2% of patients remain progression-free at 5-years in the durvalumab arm compared with the placebo arm.

Figure 4.1: Updated Kaplan Meier plot for PFS in PACFIC



Key: BICR, Blinded Independent Central Review; CI, confidence interval; DCO, data cut-off; M: durvalumab; PD-L1, programmed death-ligand 1; NR, not reached; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1.
Note: [a] figure enhanced for illustrative purposes
Source: CS; PACIFIC PD-L1 subgroup analyses, 11 January 2021 DCO. AstraZeneca data on file

The company's nine clinical experts stated that they did not expect the treatment effect of durvalumab to wane over a patient's lifetime because durvalumab is used in a setting where patients are already treated with curative intent: *"Clinical experts considered that if patients had reached 5 years without disease progression they would be considered to be no longer at risk of disease progression and hence a treatment waning effect after this timepoint would be clinically implausible."* (CS Section A.6.1)

ERG comment: It is not entirely clear from Figure 4.1 whether the treatment effect in PFS is indeed sustained (small numbers at risk towards the end and placebo curve seemingly flattening off more than the durvalumab curve). Upon the ERG's request, the company therefore provided smoothed HR plots for OS and PFS (Figures 6 and 5 of clarification response respectively) with numbers of patients at risk over time. [redacted] Furthermore, the [redacted] however, this could be an artefact of small patient numbers at risk. The company argued that their chosen distributions did reflect the [redacted] but the company did not support this with any graphical or numerical evidence. It would be reassuring to have this provided, for example by overlaying the implied HRs over time (using company's and ERG's base-case distributions for PFS) over Figure 5 in the company's clarification response to question B4. The ERG agrees that, if indeed, the company's and/or ERG's base-case extrapolations reflect this waning of the treatment effect, an additional treatment waning assumption is obsolete.

4.5 *Cure assumption*

Terms of Engagement: *"The company should use updated survival data from PACIFIC and fully explore the treatment effect after stopping treatment."*

Whilst the company stated that *"...NSCLC patients who are progression-free at 5 years following curative intent concurrent CRT are considered potentially cured by the clinical community...." (page 15 of company submission)*, this did not seem to be explicitly included in the modelling. In response to clarification questions, the company stated that it was not considered appropriate to formally model a

cure assumption in the base-case analysis due to ongoing debate in clinical community as to how to define a patient as 'cured'. While a cure assumption was not directly included in the base-case analysis, the company argued that the curative effect of durvalumab is reflected by the absence of a treatment waning effect in the base-case analysis. The company also considered the application of a mixture cure model to the PACIFIC data, but did not conduct this as it would require fundamental changes to the model structure and approach. To address the ERG's request, the company explored a simple cure analysis, assuming that patients in the PFS health state at five years are functionally cured, regardless of treatment arm. This analysis was only exploratory in nature.

ERG comment: The ERG, like the company, considers it preferable to use extrapolations based on the available data to model survival, rather than relying on additional assumptions about cure.

4.6 *Health-related quality of life estimates*

Terms of Engagement: *"The company should use more mature quality of life data from PACIFIC to inform the progression free and progressed health states in the economic model."*

The company did not use more mature quality of life data from PACIFIC to inform the progression free and progressed health states in the economic model, stating that "*As more mature data on health-related quality of life has not been collected in further data cuts, the utility values applied in this cost-effectiveness analysis have remained unchanged*". The ERG requested an updated systematic literature review to identify any relevant studies that could inform health state utilities in the economic model, but the company was unable to provide this because of (1) the given timeframe (five business days); and (2) lack of product launches and published data in this indication since the original submission. In addition, the ERG requested scenario analyses using health state utility values from other recent NICE appraisals and asked the company to elaborate on how these utilities compared to utility vales currently used in the economic model. The company provided one scenario analysis applying a utility value of 0.713 (from TA713) to the progressed disease health state in the current model.

ERG comment: Contrary to what was requested in the ToE, the company did not use more mature quality of life data from PACIFIC to inform the progression-free and progressed health states in the economic model. The company's scenario analysis reducing the progressed disease utility to 0.713 resulted in only a small change in the ICER (decrease). There continues to be uncertainty about health-related quality of life (HRQoL) in this population.

4.7 *Changes to inclusion of subsequent treatments*

The company updated the modelled proportion of patients receiving subsequent therapies and its duration following the final DCO for the PACIFIC trial (11th January 2021). An overview of the updated proportion and duration of subsequent therapies is provided in Table 4.1. The proportion of patients that received a subsequent therapy at the 5-year follow-up DCO in the placebo arm was [redacted] compared with [redacted] in the durvalumab. Subsequent immunotherapy was given to [redacted] of patients in the placebo arm (mean duration [redacted]) compared with [redacted] in the durvalumab arm (mean duration [redacted]). The company stated in its update that some subsequent immunotherapies included in the PACIFIC trial would not be expected in UK clinical practice. The ERG asked justification for this based on the SACT data and clinical opinion. In response to question B6 of the clarification letter, the company stated that subsequent treatments were not collected in the SACT dataset. Clinical experts confirmed that the choice and proportions of subsequent therapies reported in the PD-L1 ≥1% group were broadly aligned with their experience in clinical practice. The majority of clinicians, however, confirmed that patients in England do not receive re-treatment with immunotherapy as part of standard clinical practice. In addition, the Blueteq criteria for PD-1/L1 inhibitors for use in

locally advanced and metastatic NSCLC also explicitly states patients who have received previous PD-1/L1 therapy are not eligible for further PD-1/L1 treatment. Hence, patients who have received durvalumab would not routinely receive another PD-1/L1 inhibitor as a subsequent therapy upon disease progression. The company further clarified that ramucirumab, irinotecan and the tegafur/gimeracil/oteracil combination are not routinely used for treatment of NSCLC in NHS clinical practice, and performed a scenario analysis removing these subsequent treatments in both treatment arms, as well as removing subsequent immunotherapies in the durvalumab arm.

ERG comment: The ERG noted that the majority of clinical experts confirmed that patients in UK clinical practice are not re-treated with immunotherapy after durvalumab. In addition, ramucirumab, irinotecan and the tegafur/gimeracil/oteracil combination were not considered to be routinely used for treatment of NSCLC in NHS clinical practice. Hence, the company excluded the costs of these subsequent treatments in both treatment arms, as well as the costs of subsequent immunotherapies in the durvalumab arm. However, the ERG notes that subsequent treatments remained implicitly included in the modelling through the survival analyses. In order to perform an unbiased assessment of the impact of excluding subsequent treatments that are not routinely used in NHS clinical practice from the model, the company could perform an analysis adjusting for treatment switching.

Table 4.1: Proportion and duration of subsequent therapies

Subsequent therapy	Durvalumab		Placebo	
	Frequency	Duration (months)	Frequency	Duration (months)
Immunotherapies				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab (re-treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Non-immunotherapies				
Ramucirumab	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
Tegafur/Gimeracil/Oteracil	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]

Subsequent therapy	Durvalumab		Placebo	
	Frequency	Duration (months)	Frequency	Duration (months)
Irinotecan	[redacted]	[redacted]	[redacted]	[redacted]
Watchful waiting/No Treatment	[redacted]	[redacted]	[redacted]	[redacted]

4.8 Changes to durvalumab dosing

The approved durvalumab dose for use in NSCLC was 10 mg/kg administered Q2W at the time of the original appraisal. As part of the COVID-19 interim guidance, an additional option of 1,500 mg as a fixed dose administered Q4W was included, which the company used for the modelling of durvalumab treatment costs (slightly decreasing the ICER). In response to clarification question A1 the company confirmed that the Q2W regimen was applied throughout the entirety of the PACIFIC trial, and hence, any potential differences between the two dosing regimens regarding efficacy or safety were not reflected in the economic model.

4.9 The updated economic model

The ERG successfully verified all functionalities as stated in assumption 7 of the terms of engagement.

5. COST EFFECTIVENESS RESULTS

The ERG made one change to the company's base-case (results presented in Table 5.1:

- PFS durvalumab modelled using lognormal instead of generalised gamma

In addition, one scenario analysis was performed.

- PFS durvalumab modelled using the Gompertz.

Table 5.1: Cost effectiveness results

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company's new base-case							
Durvalumab	[redacted]	8.082	[redacted]	[redacted]	3.064	[redacted]	11,719
SoC	[redacted]	5.018	[redacted]				
ERG base-case: change PFS durvalumab to lognormal from generalised gamma							
Durvalumab	[redacted]	7.003	[redacted]	[redacted]	1.985	[redacted]	22,441
SoC	[redacted]	5.018	[redacted]				
ERG scenario: change PFS durvalumab to Gompertz							
Durvalumab	[redacted]	7.905	[redacted]	[redacted]	2.887	[redacted]	12,830
SoC	[redacted]	5.018	[redacted]				

6. END-OF-LIFE

The Terms of Engagement (ToE) stated that durvalumab does not meet the end-of-life criteria.

7. REFERENCES

[1] National Institute for Health and Care Excellence. *Terms of engagement for CDF review. Durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation (TA578). Data on file*. London: National Institute for Health and Care Excellence, 2021

[2] AstraZeneca. *Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]. Company evidence submission for committee*: AstraZeneca, 2022

[3] AstraZeneca. *Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]. Appendix D. Company evidence submission for committee*: AstraZeneca, 2022

[4] National Institute for Health and Care Excellence. *Interim treatment change options during the COVID-19 pandemic, endorsed by NHS England [Internet]*. London: National Institute for Health and Care Excellence, 2020 [accessed 12.1.22] Available from: https://www.nice.org.uk/guidance/ng161/resources

[5] AstraZeneca. *Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]. Response to request for clarification from the ERG*: AstraZeneca, 2022

[6] European Medicines Agency. *Type II variation assessment report. Procedure No. EMEA/H/C/004771/II/0023. Invented name: Imfinzi. International non-proprietary name: durvalumab*. Amsterdam, The Netherlands: European Medicines Agency, 2020

[7] National Disease Registration Service (NDRS), NHS Digital. *Durvalumab for treating unresectable non-small cell lung cancer (TA578): overall survival secondary sensitivity analysis. Commissioned by NHS England and NHS Improvement*: NHS England, NHS Improvement, 2021

[8] AstraZeneca. *Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]. Appendix B. Company evidence submission for committee*: AstraZeneca, 2022

[9] AstraZeneca. *PACIFIC CSR addendum; PD-L1 subgroup; 22 March 2018 DCO: a phase III, randomized, double-blind, placebo-controlled, multi-center, international study of MEDI4736 as sequential therapy in patients with locally advanced, unresectable non-small cell lung cancer (stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy (PACIFIC). (Clinical study report)*: AstraZeneca, 2018

[10] AstraZeneca. *Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]. Appendix A. Company evidence submission for committee*: AstraZeneca, 2022

[11] AstraZeneca. *Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]. Appendix C. Company evidence submission for committee*: AstraZeneca, 2022

[12] AstraZeneca. *Durvalumab for treatment of locally advanced, unresectable, Stage III non-small cell lung cancer in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based chemo-radiation therapy [ID1175]. Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B*: AstraZeneca, 2019

[13] National Health Service England. *National Cancer Drugs Fund List. Version 1.198*: NHS, 2021