NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from Astrazeneca
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submission** from:
   a. British Thoracic Oncology Group (BTOG)
   b. Royal College of Radiologists (RCR)
4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews
5. **Evidence Review Group – factual accuracy check**
6. **Public Health England Study Report**
7. **Technical engagement response** from Astrazeneca
8. **Technical engagement response & expert statement from experts:**
   a. Dr Patricia Fisher – clinical expert, nominated by AstraZeneca
   b. Dr Elizabeth Toy – clinical expert, nominated by AstraZeneca
9. **Technical engagement response from consultees and commentators:**
   a. Roy Castle Lung Cancer Foundation
10. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA578

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

January 2022

File name	Version	Contains confidential information	Date
ID3885_Durvalumab_CDF review company evidence submission_v4_fully redacted_07.04.22	**4**	**Yes**	**7th April 2022**

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Tables and figures

Cancer Drugs Fund review submission

Executive summary

- In May 2019, NICE published guidance recommending durvalumab monotherapy 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 only if they have had concurrent platinum-based chemoradiation and the conditions in the managed access agreement are followed.[1]
- At the time of the original submission, data from the PACIFIC trial with approximately 2-years of follow up was available, which demonstrated a PFS and OS benefit in the favour of durvalumab (PFS HR 0.44 [95%CI: 0.31, 0.63]); OS HR 0.54 [95% CI: 0.35, 0.81]).[2]
- The final analysis of the PACIFIC trial has now been conducted, which provides approximately 5-years of follow-up. PFS and OS outcomes have remained consistent (PFS HR: 0.47 [95% CI: 0.35, 0.64]; OS HR: 0.61 [95% CI: 0.44, 0.85])[3] and a clear and sustained separation in the Kaplan-Meier curves for both outcomes is observed beyond 60 months.[4]
- Data from the SACT database confirms the benefit of durvalumab demonstrated in the PACIFIC trial as generalisable to the UK population. The OS rate at 24 months was 68% (95% CI: 62%, 74%) for the SACT PD-L1 ≥1% group (Appendix C, page 4) compared with 72.9% (95% CI: 66.2%, 78.4%) for the durvalumab treated PACIFIC PD-L1 ≥1% group.[5]
- The health economic model has been updated with 5-year data from the final analysis from PACIFIC (DCO5, 11 Jan 2021). The model was also updated to include the fixed 4-weekly dosing schedule which is now standard-of-care in UK clinical practice.[6] There were no other changes made to the model.
- Improved longer-term PFS and OS for durvalumab and the greater use of subsequent immunotherapies in the placebo arm, which further substantiates the clinical value of introducing immunotherapy use at an earlier stage of disease, have significantly reduced the ICER for the committee's preferred analysis from TA578 by £13,000 (~£35,000 to ~£22,000). This marked improvement in cost-effectiveness reflects durvalumab’s proven long-term sustained benefit at 5 years.

- Health economic modelling assumptions in the Company's base case analysis have been revisited with the availability of 5-year data from PACIFIC. The better informed selection of parametric survival curves for PFS and removal of the treatment waning effect for durvalumab, which is now clinically implausible given the 5-year PFS data, has resulted in an improved base case ICER of £11,719.
- The generalisability of the PACIFIC trial to UK clinical practice was further validated by UK clinical experts, who confirmed their experience with durvalumab is reflective of the PACIFIC clinical trial outcomes. In general, clinicians considered the 5-year data to be impressive and in particular commented on the sustained separation of the PFS and OS KM curves at 5-years. Additionally, all clinicians interviewed unanimously stated they did not consider durvalumab to be associated with a treatment waning effect when used in this setting.[6]
- The clear clinical benefit of durvalumab in the unresectable stage III NSCLC population is also reflected in patient selection reported by KEEs and in the SACT data. The majority of KEEs report using concurrent CRT in all patients considered fit enough to receive the regimen, particularly in PD-L1 positive patients, in order to ensure patients have the best chance of receiving durvalumab monotherapy.[6] Several clinicians also described an increase in concurrent CRT rates compared to sequential CRT due to the availability of durvalumab. The SACT cohort also suggests the real-world patients treated with concurrent CRT have slightly worse performance status, proportionally, compared to the PACIFIC trial (Appendix B, page 22) , yet achieve relatively similar OS rates at 24 months (Appendix C page 4). This infers clinician intention to treat with concurrent CRT wherever possible to ensure eligibility for durvalumab due to the superior long-term survival benefits demonstrated by the PACIFIC data.
- Overall, the final analysis of the PACIFIC trial clearly demonstrates durvalumab monotherapy is a highly beneficial cost-effective therapy in this setting, producing an ICER of £11,719 per QALY. Durvalumab monotherapy should be considered standard of care for all eligible patients in this setting.

A.1 Background

- 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 only if they have had concurrent platinum-based chemoradiation and the conditions in the managed access agreement are followed.

- ICERs presented to the committee included a patient access scheme 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 NHS resources. 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 progression-free, overall survival and the duration of any treatment effect. The committee understood that the key trial, PACIFIC was ongoing, and agreed that additional survival data would reduce these uncertainties and provide additional information on the treatment effect duration and cure rates.

A.2 Key committee assumptions

The key committee assumptions as per the Terms of Engagement[7] are detailed in Table 1.

Table 1: Committee preferred assumptions

Area	Committee preferred assumptions
Population	The scope stated that the population was adults with locally advanced, unresectable non-small cell lung cancer whose disease has not progressed after platinum-based chemoradiation therapy. Regulatory approval was granted for those whose tumours express PD-L1 on ≥1% of tumour cells. The trial inclusion criteria specified concurrent chemoradiation and excluded those who had had sequential chemoradiation. The committee heard that in clinical practice people would have sequential chemoradiation. Clinical experts explained that the population having concurrent chemoradiation may be in better health and there is evidence to suggest that concurrent chemoradiation may produce better outcomes. The committee concluded that the evidence from PACIFIC is not generalisable to people who have had sequential chemoradiation, but is broadly generalisable to those whose tumours express PD-L1

	on at least 1% of tumour cells and whose disease has not progressed after at least 2 cycles of concurrent platinum-based chemoradiation. Committee optimised the recommendation to those who had had concurrent platinum-based chemoradiation only. **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.**
Comparators	The committee agreed that standard care (which involves surveillance every 6 months for 2 years, and a volume chest CT scan at least every year) was the appropriate comparator for this appraisal. **The company should present clinical and cost-effective evidence for durvalumab compared to standard care.**
Survival outcomes	The key trial was PACIFIC which assessed durvalumab versus standard care in people with locally advanced unresectable stage III NSCLC whose disease had not progressed after at least 2 cycles of concurrent platinum-based chemoradiation. The committee agreed that the immaturity of the PACIFIC survival data generated uncertainty about the long-term projections. The company chose a generalized gamma distribution to extrapolate PFS, however the ERG preferred a log-normal extrapolation due to statistical fit and external validity. The committee also preferred the log-normal based on clinical expert and ERG advice but appreciated that the company's generalized gamma extrapolation could be plausible. **The company should use updated survival data from PACIFIC and fully explore the most appropriate method to extrapolate survival outcomes.**
Assumption of cure	There was also uncertainty about whether durvalumab had the potential to be curative. Clinical experts expected people on standard care who did not have progressed disease at 5 years would have low risk of future progression. They added that

	they didn't know if durvalumab would cure the disease or delay progression. Committee agreed that data were too immature to support a cure model and that there was uncertainty in all extrapolations due to data immaturity and the small number of people informing the tail of the KM curve. **The company should use updated survival data from PACIFIC to inform the appropriateness of a cure assumption.**
Treatment effect duration	The company's base case assumed a treatment effect duration of 5 years. The committee thought that a long-term treatment effect was plausible and but their preference in previous appraisals had been 3 to 5 years. However, committee also noted that these appraisals tended to include a 2 year stopping rule, whereas durvalumab had a 1 year stopping rule and the treatment effect duration for durvalumab may be lower because of this. Committee concluded that the long-term treatment effect after stopping treatment was highly uncertain. In extrapolating the outcomes, the company capped the underlying hazard functions of the distributions to prevent the risk of progression in the durvalumab arm exceeding the standard of care arm. The company explained that this limited the modelled treatment effect duration to 39 months and committee accepted this acknowledging that it fell into their 3-to-5-year range. **The company should use updated survival data from PACIFIC and fully explore the treatment effect after stopping treatment.**
Utility values	The company used the utility value from the PACIFIC trial for the progression-free health state. The committee noted that this was slightly higher than that for the general population but concluded that it was acceptable. For consistency they also thought the company should use the trial to inform the utility value for the progressed disease health state rather than the Chouaid et al reference they had used. The committee also agreed that it was appropriate to apply a treatment related decrement to reflect that the incidence of adverse events was higher in the treatment arm. However the committee did note that this would not apply indefinitely.

	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.
Most plausible ICER	The cost-effectiveness results are commercial in confidence because they include the confidential discounts for subsequent therapies. Using the log-normal extrapolation for PFS in the durvalumab arm generated an ICER higher than £30,000 per QALY gained. However, using the generalised gamma extrapolation generated an ICER below £30,000 per QALY gained. The committee concluded that there was a high level of uncertainty in the clinical evidence, but did accept that some scenarios were within the range considered a cost-effective use of NHS resources. **The committee agreed that durvalumab demonstrated plausible potential to be cost-effective.**
End of life	Durvalumab does not meet the end-of-life criteria.

A.3 Other agreed changes

As outlined in the Data Collection Arrangement (Appendix D, outcome data, clinical trial, page 10) and as discussed in the CDF review kick-off meeting, data on subsequent therapies was also collected during the data collection period. These data have been used to update the frequency, duration and overall cost of subsequent therapies in the economic model.

The economic model has also been updated to include the option to select the fixed 4-weekly dosing option for durvalumab. Further details on this dosing regimen are provided below.

The company have not altered the decision-problem, submitted additional evidence beyond that agreed in the DCA or made any further alterations to the model during the CDF review period.

A.4 The technology

The only change since durvalumab was recommended for use in the CDF in May 2019 is an update in dosing. At the time of the original appraisal the only approved dose for use in NSCLC was 10mg/kg administered every 2 weeks. This has now been updated to include an additional option; a fixed dose of 1500mg administered every 4 weeks. This was introduced as part of COVID-19 interim guidance in April 2020[8] and subsequently updated in the SmPC in early 2021.[9] Key clinical experts confirmed the 1500mg 4-weekly dose was implemented over the COVID-19 interim period and is now used as standard in UK clinical practice in the majority of patients due to reduced resource requirement and improved convenience for patients. Clinicians considered the ability to provide the 4-weekly 1500mg dose rather than the 2-weekly 10mg/kg dose a highly positive change for clinical practice, which was also preferred by the majority of patients.[6]

Table 2: Technology being reviewed

UK approved name and brand name	Durvalumab (IMFINZI™)
Mechanism of action	Durvalumab is a highly selective human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) against programmed cell death ligand 1 (PD-L1), which blocks its interaction with receptors, programmed cell death protein 1 (PD-1) and cluster of differentiation (CD) 80.[10, 11] In doing so, it releases the inhibition of immune responses in the tumour microenvironment, resulting in prolonged T-cell activation and anti-tumour activity.[10]
Marketing authorisation/CE mark status	On 26 July 2018, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for durvalumab monotherapy for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells (TCs) and whose disease has not progressed following platinum-based CRT.[12] The European Commission decision (marketing authorisation) for durvalumab in this indication was issued on 21st September 2018.[13]
Indications and any restriction(s) as described in the summary of product characteristics	• Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.[10] • Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).[10]

Method of administration and dosage	• Treatment must be initiated and supervised by a physician experienced in the treatment of cancer[10]
	• The recommended dose of durvalumab for using in locally advanced NSCLC is[10]:
	  o 10mg/kg every 2 weeks, or,
	  o 1500mg every 4 weeks until disease progression, unacceptable toxicity, or a maximum of 12 months[a]
	  o Note: patients with a body weight of 30kg or less must receive weight-based dosing, equivalent to durvalumab 10mg/kg every 2 weeks or 20mg/kg every 4 weeks as monotherapy until weight increases to greater than 30kg
	• Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be required, based on individual safety and tolerability.[10]
	• Guidelines for management of immune mediated adverse reactions are described in Table 2 of the SmPC[10]

Additional tests or investigations	Patients with locally advanced NSCLC should be evaluated for treatment based on the tumour expression of PD-L1 confirmed by a validated test.[10]
List price and average cost of a course of treatment	List price: • £592 per 120mg vial • £2,466 per 500mg vial Total mean cost of treatment (Q4W, list price): [redacted]
Commercial arrangement (if applicable)	A confidential PAS has been agreed with NHS England. The PAS provides a simple discount to the list price of durvalumab of [redacted].
Date technology was recommended for use in the CDF	May, 2019[1]
Data collection end date	PACIFIC final analysis (5-year) data cut-off date: 11 January 2021[4] Public Health England SACT data collection end date: 01 February 2021 (latest date of CDF application) (Appendix B, Methods, Initial CDF cohorts, page 13)

Key: CE, Conformité Européene; CDF, Cancer Drugs Fund; CHMP, Committee for Medicinal Products for Human Use; CRT, chemoradiation therapy; CD80, cluster of differentiation 80; CRT, chemoradiation therapy; EAP, Early Access Program; EMA, European Medical Agency; ES-SCLC, extensive-stage small-cell lung cancer; FDA, Food and Drug Administration; IgG, immunoglobulin; IV, intravenous; mAb, monoclonal antibody; NHS, national health service; NSCLC, non-small cell lung cancer; PAS, patient access scheme; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SmPC, summary of product characteristics; TC, tumour cell; UK, United Kingdom

Notes: [a], This 1500mg 4-weekly dose was not available at the time of the original submission but was introduced by NICE as part of COVID-19 interim guidance on 20 April 2020.[8] The European Commission decision to approved the 4-weekly dose for use in NSCLC was issued on 11 January 2021.[9]

A.5 Clinical effectiveness evidence

The main data source presented in support of this review is the PACIFIC trial (Phase 3, randomised, double-blind trial comparing durvalumab with placebo) and is summarised in section A.6

Table 3: Primary source of clinical effectiveness evidence

Study title	**PACIFIC;** NCT02125461
Study design	PACIFIC is a randomised, double-blind, placebo-controlled, multi-centre, international, Phase III study
Population	Patients with locally-advanced, unresectable, Stage III NSCLC whose disease has not progressed following two or more overlapping cycles of definitive, platinum-based CRT
Intervention(s)	Durvalumab (n=476)
Comparator(s)	Placebo (n=237)
Outcomes collected that address committee's key uncertainties	• **Progression-free survival** (11 Jan 2021 DCO) • **Overall survival** (11 Jan 2021 DCO) • **Subsequent therapies** (frequency and duration) (11 Jan 2021 DCO)
Reference to section in appendix	Appendix A

The SACT data cohort study and secondary sensitivity analysis of the PD-L1 ≥1% group will be presented in support of this review as additional data sources (summarised in Table 4):

Table 4 Secondary source of clinical effectiveness evidence

Study title	**SACT data cohort study**
Study design	SACT data cohort study
Population	Adults with locally-advanced, unresectable, Stage III NSCLC whose tumour express PD-L1 on ≥1% of tumour cells, or whose PD-L1 status cannot be ascertained, and whose disease has not progressed following platinum-based combination chemotherapy given concurrently with definitive radical radiotherapy
Intervention(s)	Durvalumab (n=591)
Comparator(s)	Not applicable
Outcomes collected that address	• Overall survival • Treatment duration

committee's key uncertainties	
Reference to section in appendix	Appendix B (Public Health England data review of durvalumab - final report [SACT report]) Appendix C (Public Health England data review of durvalumab - secondary sensitivity analysis of overall survival PD-L1 ≥1% group [SACT report overall survival secondary sensitivity analysis])

Evidence from the SACT data cohort study was not used to update the economic model. The results of this study support the overall survival and time-on-treatment data from the PACIFIC clinical trial is generalisable to clinical practice. This study was not used to inform the economic model because it does not include a comparator arm and therefore the incremental benefit of durvalumab in this population was not established. Additionally, there were some differences in the baseline characteristics of patients included in the SACT cohort compared to the PACIFIC patient population; the SACT patients were generally older and had poorer performance status. This is further detailed in Section A.6 .

Additional real-world evidence to support the generalisability of treatment duration and PFS outcomes is also available from the PACIFIC-R study (NCT03798535), which is a large international, observational study of patients with unresectable Stage III NSCLC who received ≥1 dose of durvalumab (10 mg/kg Q2W) as part of an AstraZeneca-initiated expanded access programme (September 2017–December 2018).[14] However, based on the discussion with NICE and the ERG at the CDF exit kick-off meeting (23rd November 2021), the Company were advised not to include PACIFIC-R data as the SACT data were deemed sufficient to support generalisability of the PACIFIC data to the UK real-world setting.

A.6 Key results of the data collection

During the CDF data collection period, the final data cut-off for the PACIFIC clinical trial occurred (11 January 2021 DCO), providing approximately 5 years of follow-up.[3] This final data cut provides approximately 3 years of additional follow-up compared with the data presented in the original submission (22 March 2018 DCO).[15] The 5-year follow-up data addresses key uncertainties regarding long-term survival, treatment effect duration, cure assumptions and use of subsequent therapies. As discussed in the original submission (Company Submission Document B, Section B.1.1, Figure 4, page 40)[15] the PACIFIC trial was designed as an 'all comers' trial with regards to PD-L1 expression.[15] However, in line with the population for appraisal (Section A.2) and discussion at the kick-off meeting, only the results for patients whose tumours express PD-L1 on ≥1% of tumour cells will be presented in this submission.

Data collected by Public Health England via the systemic anti-cancer therapy dataset (SACT) from 28 March 2019 to 1 February 2021 (Appendix B, Methods, Initial CDF cohorts, page 13) is also available and addresses uncertainties regarding generalisability of overall survival and treatment duration data from the PACIFIC trial to the UK population. While the median OS was not reached in the SACT cohort, the OS rate at 24 months was 68% (95% CI: 62%, 74%) for the SACT PD-L1 ≥1% group (Appendix C, Overall survival secondary analysis, Table 1, page 4) compared with 72.9% (95% CI: 66.2%, 78.4%) for the durvalumab treated PACIFIC PD-L1 ≥1% group (Appendix A, Overall Survival, Table 5, page 12).[5] However, two key differences in baseline patient characteristics between the SACT cohort vs. the durvalumab treated PACIFIC PD-L1 ≥1% group should be noted: age and performance status. The median age of patients in the SACT cohort (67 years) was 3 years older than the durvalumab treated PACIFIC PD-L1 ≥1% cohort (64 years).[15] The SACT cohort also had a worse performance status (27% PS0; 59% PS1; 1% PS2; 14% missing PS) compared with the durvalumab treated PACIFIC PD-L1 ≥1% group (49.5% PS0; 50.0% PS1; 0.5% PS not reported).[15] A summary of baseline characteristics of patients included in the SACT cohort is presented in the final SACT report (Appendix B, Results, Patient Characteristics, page 21) and for the PACIFIC PD-L1 ≥1% group is presented in the original submission (Company Submission Document B, Section B.2.3, Table 4, page 42-45).[15] Overall, this suggests 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.6.1 *Progression-free survival*

A.6.1.1 PACIFIC

A comparison of PFS outcomes for patients whose tumours express PD-L1 on ≥1% of tumour cells in the PACIFIC trial at the 22 March 2018 and 11 January 2021 DCOs is presented in Table 5.

Consistent with the data presented in the original submission, durvalumab treatment produced a sustained benefit at the 5-year follow-up, as demonstrated by PFS KM curves (

Figure 1) which remain separated beyond 60 months.

The median PFS outcomes for durvalumab and placebo groups at the 11 January 2021 DCO are consistent with outcomes from the 22 March 2018 DCO and confidence intervals for median PFS remain separated with the more mature data (Table 5).

This sustained treatment benefit is further supported by PFS rates (Appendix A, section A.1.4.1, Table 5, page 10) which are now reported up to 60 months and demonstrate an additional 18.2% of patients remain progression-free at 5-years in the durvalumab arm compared with the placebo arm: (35.8% [95% CI: 28.0%, 43.7%] vs. 17.6% [95% CI: 9.8%, 27.3%] for the durvalumab group compared with the placebo group, respectively).[5] Of note, the CIs for the PFS rates remain separated with no overlap at the 5-year landmark analysis.

This increase in PFS rates at 5 years is of particular clinical importance, as NSCLC patients who are progression-free at 5 years following curative intent concurrent CRT are considered potentially cured by the clinical community. This perception of

potential cure at 5-years was validated by UK clinical experts, who confirmed they would discharge patients who were progression-free at this timepoint.[6]

Table 5: Comparison of PFS outcomes at 2-year follow-up vs. 5-year follow-up (BICR assessments, per RECIST 1.1); PACIFIC PD-L1 ≥1% group, 22 March 2018 and 11 January 2021 DCOs

Progression status	22 Mar 2018 DCO2		11 Jan 2021 DCO	
	Durvalumab (N=212)	Placebo (N=91)	Durvalumab (N=212)	Placebo (N=91)
Total 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)	

Key: BICR, Blinded Independent Central Review; CI, confidence interval; DCO, data cut-off; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; NR, not reached; RECIST 1.1, Response Evaluation Criteria In Solid Tumors Version 1.1.

Notes: [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 1 unless they die within 2 visits of baseline.

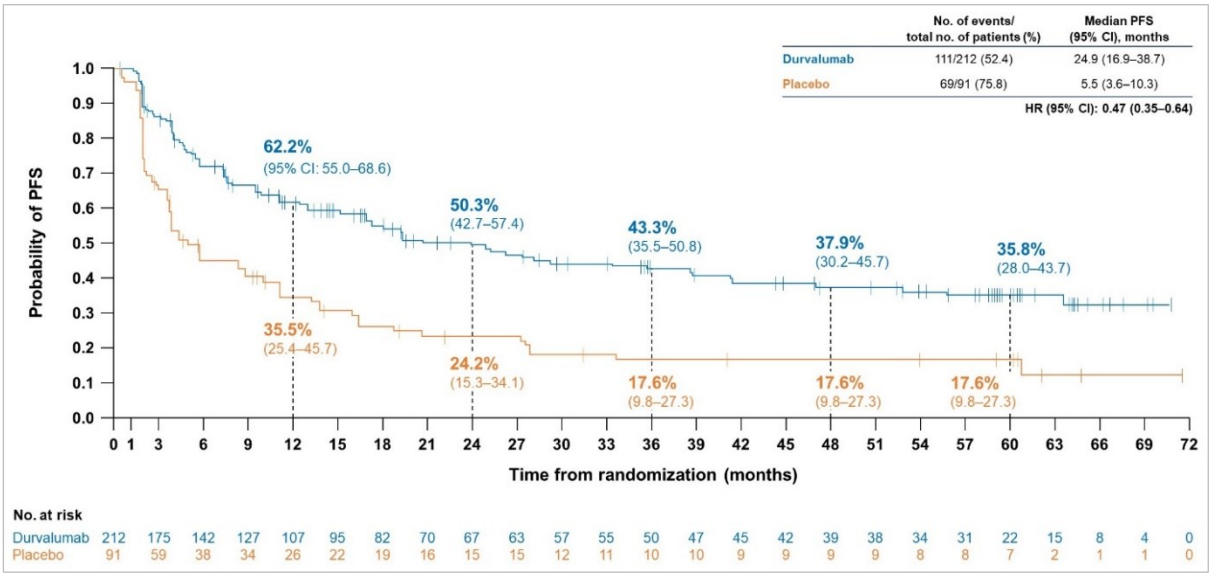
[b], calculated using the Kaplan-Meier technique.

[c], 22 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], 11 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.

Source: PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO[15]; Spigel *et al.* 2022[5]

Figure 1: KM plot of BICR assessment of PFS (per RECIST 1.1); PACIFIC PD-L1 ≥1% group (11 January 2021 DCO)[a]



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: Spigel *et al.* 2022[5]

A.6.2 *Overall survival*

A.6.2.1 PACIFIC

A comparison of OS outcomes for the PD-L1 ≥ 1% group in the PACIFIC trial at the 22 March 2018 and 11 January 2021 DCOs is presented in Table 6.

At the time of the final analysis (11 January 2021 DCO), the overall data maturity for the OS endpoint in the PD-L1 ≥1% group had increased to 52.5%,[3] compared with 38.0% at the time of the original submission (22 March 2018 DCO)[2] (Table 6).

The OS benefit demonstrated by the hazard ratio for durvalumab treated patients relative to placebo treated patients at the 28 March 2018 DCO was maintained at the 5-year follow-up (Table 6). The OS benefit of durvalumab is also supported by the sustained separation of the KM curves in favour of durvalumab at 75 months (

Figure 2).

At the time of the final analysis, the increase in median OS for patients treated with durvalumab compared to placebo in the PACIFIC PD-L1 ≥1% was 33.5 months[5] (Table 6).

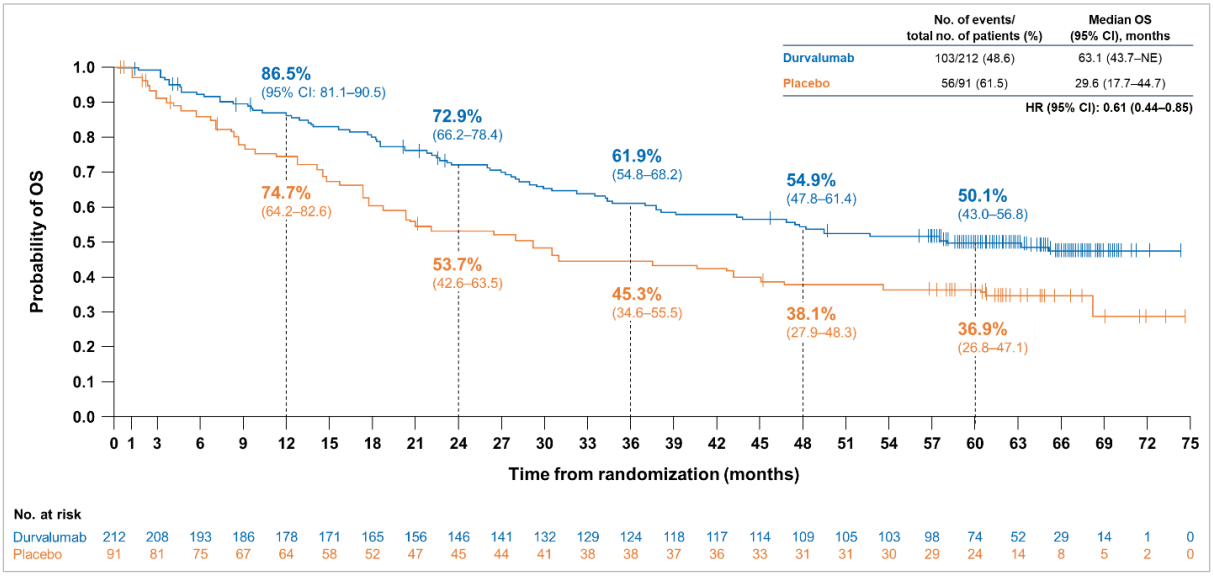
The updated survival rates (Appendix A, section A.1.4.2, Table 4, page 12), demonstrating a 50.1% (95%CI: 43.0, 56.8) OS rate at 60 months for durvalumab treated patients compared to 36.9% (95%CI: 26.8, 47.1) for the placebo treated patients, further support the long-term survival benefit provided by durvalumab.[5]

Table 6: Comparison of OS outcomes at 2-year follow-up vs. 5-year follow-up; PACIFIC PD-L1 ≥1% group, 22 March 2018 and 11 January 2021 DCOs

Overall survival	2yr OS (22 Mar 2018 DCO2)		5yr OS (11 Jan 2021 DCO)	
	Durvalumab (N=212)	Placebo (N=91)	Durvalumab (N=212)	Placebo (N=91)
Death, n (%)	70 (33.0)	45 (49.5)	103 (48.6)	56 (61.5)
Censored patients, n (%)	142 (67.0)	46 (50.5)	109 (51.4)	35 (38.5)
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)
Hazard ratio (95% CI)[b,c]	**0.54** (0.35, 0.81)		**0.61** (0.44, 0.85)	

Key: CI, confidence interval; DCO, data cut-off; PD-L1, programmed death-ligand 1; NE, not estimable; NR, not reached; OS, overall survival.
Notes: [a], Calculated using the Kaplan–Meier technique
[b], 22 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.
Source: PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO[15]; Spigel *et al.* 2022[5]

Figure 2: Kaplan-Meier plot of OS; PACIFIC PD-L1 ≥1% group (11 Jan 2021 DCO)



Key: CI, confidence interval; DCO, data cut-off; M: durvalumab; PD-L1, programmed death-ligand 1; OS overall survival
Note: [a,] figure enhanced for illustrative purposes
Source: Spigel *et al.* 2022[5]

A.6.2.2 SACT dataset

The Public Health England provided overall survival secondary sensitivity analysis in patients with PD-L1 ≥1% (Appendix C, pages 4-6), is the most relevant dataset to compare the generalisability of the outcomes for the PACIFIC PD-L1 ≥1% group to the real-world UK setting, as the full SACT dataset also included some patients with an unknown PD-L1 status. Although the baseline characteristics for only the patients with PD-L1 ≥1% was not available, it should be noted the baseline characteristics of the full SACT dataset, i.e. including those patients with PD-L1 status unknown, had poorer performance status and an older median age than the PACIFIC PD-L1 ≥1% group, as detailed in section A.6 .

522 patients with PD-L1 ≥1% were identified for survival analysis from the SACT dataset, with a median follow-up time of 14.3 months. At the time of the analysis, 115 (22%) of the patients had died and 407 (78%) patients were censored (Appendix C, Table 2 and 3, page 3). The median OS was not reached for this cohort of patients and the KM survival plot (Appendix C, Figure1, page 2) demonstrates the high level of censoring from approximately 6 months.

The OS rates reported in the OS sensitivity analysis (Appendix C, Table 1, page 4) reflect the OS rates experienced by patients in the durvalumab treated arm in the PACIFIC study (Table 6); 24 month OS rates were 68% (95% CI: 62%, 74%) for the SACT PD-L1 ≥1% group compared with 72.9% (95% CI: 66.2%, 78.4%) for the durvalumab treated PACIFIC PD-L1 ≥1% group (Appendix A, Overall Survival, Table 5, page 12).[5] As highlighted above, the slightly lower OS rate at 24 months for the SACT dataset compared with the PACIFIC outcomes can be attributed to differences in baseline patient characteristics.

A.6.2.3 Summary

The updated PACIFIC data demonstrates that durvalumab treatment provides a long-term survival benefit compared to patients receiving only BSC. The SACT dataset confirms that the PACIFIC trial is generalisable to the UK population and this incremental benefit provided by durvalumab treatment can be expected in real-world UK patients.

A.6.3 *Time on treatment*

A.6.3.1 PACIFIC

As described in the Company Submission Document B (Section B.2.10, Table 17, page 83) the median actual treatment duration was 41.7 weeks (approximately 9.6 months), where actual treatment duration is calculated as follows: actual treatment duration = total treatment duration, excluding total duration of dose delays.[2]

A.6.3.2 SACT dataset

Treatment duration data for 591 patients was available from the SACT dataset (Appendix B, Treatment duration, pages 23-25). However, treatment duration was not analysed by PD-L1 ≥1% expression, and therefore also includes data from patients with unknown PD-L1 expression.

The median follow-up time for the SACT dataset was 7.3 months and median treatment duration was 313 days, or 10.3 months (95% CI: 9.4, 11.1).

The KM plot for treatment duration (Appendix B, Figure 3, page 24.) demonstrates some patients received durvalumab treatment beyond the 12 months maximum treatment duration stipulated by the regulatory label. However, the SmPC states "dose withholding or discontinuation may be required based on individual safety and tolerability"[10] and the Blueteq eligibility criteria states "the total active treatment period is a maximum of 12 months i.e. in those patients who have toxicity and thus have dose interruptions, the maximum number of treatment cycles is 26 x 2-weekly cycles or 13 x 4-weekly cycles".[16] Clinical experts also confirmed that treatment breaks may be required in a minority (approximately 10-15%) of patients.[6] Therefore, the extension of durvalumab treatment beyond 12 months as seen in the KM plot is likely due to patients requiring treatment breaks.

A.6.4 *Subsequent therapies*

A.6.4.1 PACIFIC

Updated data for post-discontinuation disease-related anti-cancer therapy use in the PD-L1 ≥1% group in the PACIFIC trial was available following the final data cut-off for the PACIFIC trial (11 January 2021). A summary of subsequent therapy use at the 2-year follow-up compared with the 5-year follow-up is provided in Table 7. This data demonstrates a greater proportion of patients in the placebo arm received a subsequent therapy [redacted] compared with patients in the durvalumab arm [redacted] at the 5-year follow-up. Of particular note is the [redacted] frequency of immunotherapy use in the placebo arm [redacted] compared with the durvalumab arm [redacted]. The mean duration of immunotherapy use was [redacted] in the placebo arm [redacted] compared with the durvalumab arm [redacted] (see Appendix A, section A.1.3.2, table 3, pages 7-8).

While some subsequent immunotherapy use was observed in the PACIFIC trial following durvalumab treatment, 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 patients who have received previous PD-1/L1 therapy are not eligible for further PD-1/L1 treatment.[16] This was also confirmed by key clinical experts, the majority of whom confirmed patients in England do not receive re-treatment with immunotherapy as part of standard clinical practice.[6]

Further details regarding subsequent therapies at the 5-year final analysis is available in Appendix A, section A.1.3.2, table 2 and table 3, pages 6-8.

Table 7: Post-discontinuation disease-related anti-cancer therapy use in the PACIFIC trial; PACIFIC PD-L1 ≥1%, 22 March 2018 and 11 Jan 2021 DCOs

	DCO2 (22 Mar 2018)		DCO5 (11 Jan 2021)	
	Durvalumab (N=212)	**Placebo (n=91)**	**Durvalumab (N=212)**	**Placebo (n=91)**
Number of patients with 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]

Key: DCO, data cut-off; n, number; PD-L1, programmed death-ligand 1
Notes:
Source: PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO[15]; PACIFIC PD-L1 subgroup analyses, 11 January 2021 DCO. AstraZeneca data on file[4]

A.6.5 *Summary*

Overall, the outcomes of the data collection period confirm durvalumab treatment is associated with a substantial long-term survival benefit for patients whose tumours express PD-L1 on ≥1% of tumour cells and who have received concurrent CRT compared with BSC, with a reduction in the risk of death of 39% based on the analysis of the 5-year follow-up data (OS HR:0.61 [95%CI: 0.44, 0.85]).[3] Key clinical experts confirmed the PFS and OS benefit demonstrated in the PACIFIC trial is representative of their experience in real-world clinical practice during a series of interviews and considered the 5-year data impressive.[6] Therefore, durvalumab maintenance therapy for this population should be considered standard of care.

A.7 Incorporating collected data into the model

During the NICE technology appraisal for durvalumab in locally-advanced, unresectable, Stage III NSCLC patients whose tumours express PD-L1 on ≥ 1% of TCs and whose disease has not progressed after ≥2 overlapping cycles of concurrent platinum-based CRT (TA578), the committee stated that the immaturity of the PACIFIC data generated uncertainty about the long-term benefit of durvalumab (FAD 3.5, 3.6).

In order to address this uncertainty, the original cost-effectiveness model has been updated with the final analysis of the PACIFIC trial (11 January 2021 DCO), in line with the terms of engagement. The model structure is identical to that previously submitted in NICE TA578. Please refer to the Company Submission Document B, Section B.3.2 for details on the model structure. The updates made to the health economic model are described in the following sections. As in section A.6, the population presented here is patients whose tumours express PD-L1 on ≥1% of tumour cells (referred to as the 'PD-L1 ≥1% group').

A.7.1 *Progression-free survival*

Progression-free survival data were derived from the final data cut-off from PACIFIC (11 January 2021 DCO). The process for fitting parametric survival curves to patient level data was based on standard methods guidance from the NICE Decision Support Unit.[17] In line with the original submission, the following parametric distributions were considered in the analysis: exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma. The parametric distributions that inform the base case analysis were selected based on statistical goodness-of-fit, visual inspection and clinical plausibility.

PFS – Durvalumab

Goodness of fit

A summary of the AIC and BIC goodness of fit statistics for each distribution explored is provided in

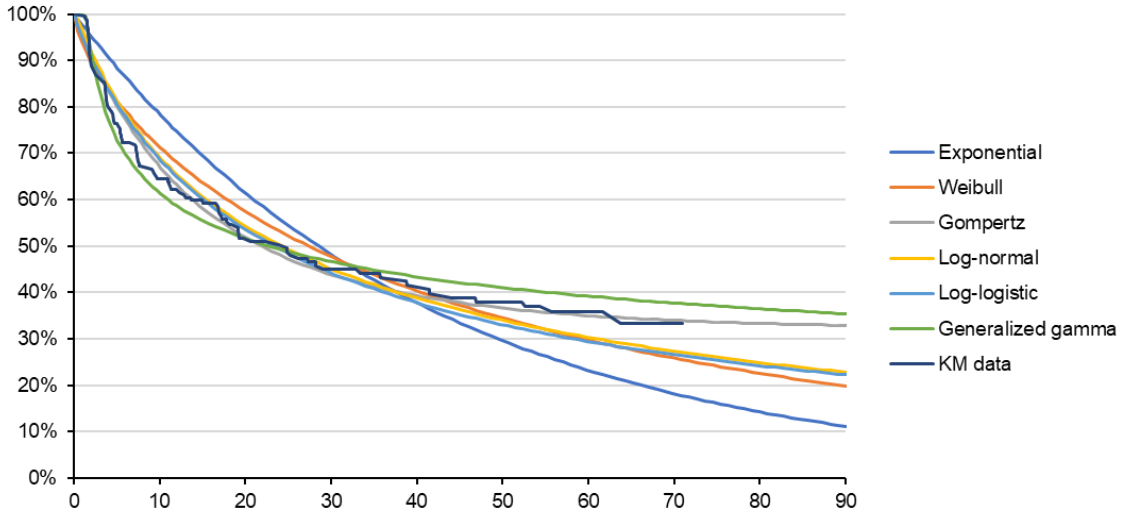
Table 8. A plot of the survival functions is shown in Figure 3 for visual assessment of fit.

Table 8: Summary of goodness of fit data for the parametric survival analysis of durvalumab PFS data

Distribution	Durvalumab	
	AIC	BIC
Exponential	1049	1052
Generalised Gamma	**974**	**984**
Gompertz	1010	1017
Log-logistic	1016	1023
Log-normal	1006	1013
Weibull	1030	1036

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
Note: Bolded values indicate the best scores.

Figure 3: Visual fit of PFS parametric functions to PACIFIC data; durvalumab arm



Key: KM, Kaplan–Meier; PFS, progression-free survival.

The generalised gamma function has the best statistical fit in the durvalumab arm, based on AIC and BIC scores. The generalised gamma and Gompertz curves are visually good fits to the KM curve. The log-normal underestimates PFS after approximately 3-4 years, when compared to PFS KM data.

External validity of extrapolated PFS

The extrapolated PFS curves were also assessed for clinical plausibility by a survey of nine clinical experts. When discussing the PFS extrapolations for durvalumab, clinical experts unanimously stated that they expected the curves to be relatively flat

3-5 years after treatment initiation.[6] The clinical experts explained that very few patients in their clinical practice experience disease progression after experiencing 3-5 years without disease progression following curative-intent concurrent CRT.[6] Almost all clinical experts surveyed (n=8) selected the gompertz or generalised gamma as the extrapolations that were most consistent with clinical expert's expectations of durvalumab's long-term PFS, with more clinical experts selecting the gompertz function (n=7).[6]

Choice of PFS curve – durvalumab

The majority of clinical experts surveyed selected the gompertz function as the most clinically plausible extrapolation for PFS in the durvalumab arm. However, the generalised gamma distribution showed the best statistical fit to the PFS KM data. Therefore, the generalised gamma is applied in the base case analysis for the durvalumab arm. The gompertz function for PFS is explored in a scenario analysis.

PFS – Placebo

Goodness of fit

A summary of the AIC and BIC goodness of fit statistics for each distribution explored is provided in

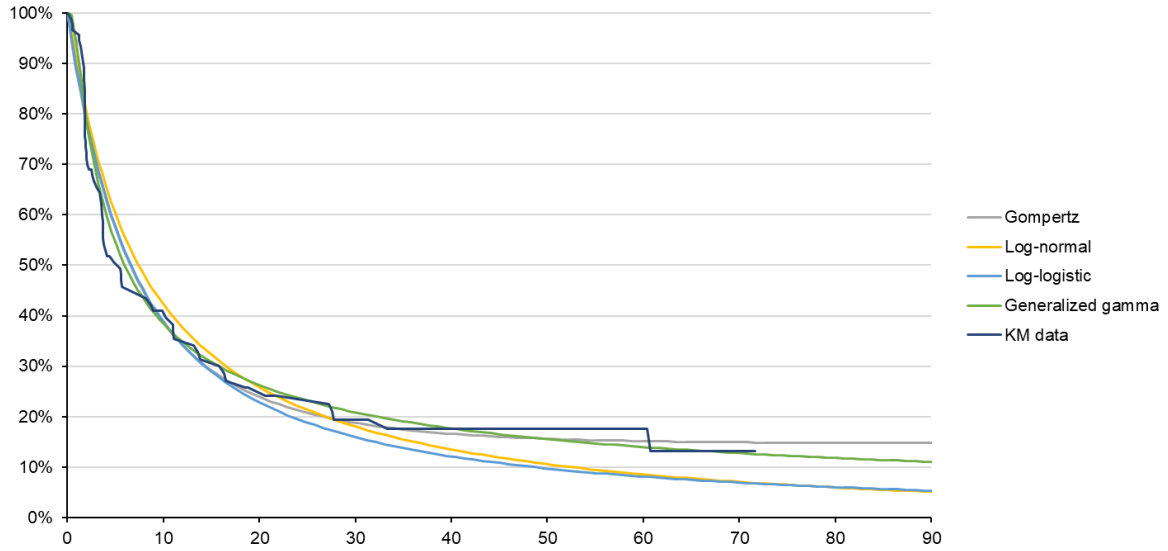
Table 8. A plot of the survival functions is shown in Figure 3 for visual assessment of fit.

Table 9: Summary of goodness of fit data for the parametric survival analysis of placebo PFS data

Distribution	Placebo	
	AIC	BIC
Exponential	532	534
Generalised Gamma	**480**	**488**
Gompertz	492	497
Log-logistic	494	499
Log-normal	492	497
Weibull	513	518

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
Note: Bolded values indicate the best scores.

Figure 4: Visual fit of PFS parametric functions to PACIFIC data; placebo arm



Key: KM, Kaplan–Meier; PFS, progression-free survival.

The generalised gamma function has the best statistical fit in the placebo arm, closely followed by Gompertz, based on AIC and BIC scores. The generalised gamma and Gompertz curves are also visually good fits. The log-normal underestimates PFS after 3-4 years, compared to the PFS KM data.

External validity of extrapolated PFS

To further assess the clinical validity of the extrapolated curves (particularly long-term outcomes), extrapolated PFS curves in the placebo arm were also assessed for clinical plausibility by a survey of nine clinical experts. The vast majority of clinical experts (n=7) felt that the generalised gamma function was most consistent with clinical expert's expectations of placebo's long-term PFS.

Choice of PFS curve – Placebo

The generalised gamma distribution showed the best statistical and visual goodness of fit to the PFS KM data in the placebo arm. It was also selected as the most clinically plausible extrapolation by a survey of nine clinical experts. Furthermore, DSU TSD 14 recommends applying the same type of structural model for treatment and placebo, when applying independent models.[17]

Therefore, the generalised gamma was chosen for the base case analysis for the placebo arm. Sensitivity analysis was conducted using other parametric functions (Gompertz).

A.7.1 *Long-term treatment effect of durvalumab*

In line with the original submission, the cost-effectiveness model includes an option to explore different cut-off points for the treatment effect of durvalumab (Company Submission Document B, Section B.3.3, Pages 138-139). The duration of treatment effect was a key uncertainty in the original appraisal and the committee concluded that further data on progression-free survival would reduce uncertainty about the treatment effect duration (FAD 3.15).

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 (Section A.6.1). The median duration of follow-up at 11 January 2021 DCO was 34.2 months (all patients) and 61.6 months (censored patients).

The Company also sought clinical expert opinion on the treatment waning effect of durvalumab. All nine clinical experts surveyed stated that they did not expect the treatment effect of durvalumab to wane over a patient's lifetime. Clinical expert's rationale for the absence of a treatment waning effect was based on the fact that 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. Clinical experts also stated that the 5-year follow-up PACIFIC PFS data confirmed the lack of treatment waning effect of durvalumab, as both curves were considered to be 'flat' after 3-5 years.

Based on the 5-year PACIFIC PFS data and feedback from clinical experts, a treatment waning effect was not applied in the base case analysis. A treatment waning effect at 10 years was explored in a conservative scenario analysis.

A.7.2 *Post-progression survival*

The post-progression survival (PPS) analysis was conducted on the final analysis from PACIFIC (11 January 2021 DCO). In line with the original appraisal, PPS data was pooled across arms which reduces the uncertainty of the parametric models fit to the data. This conservatively assumes that PPS is equal for both treatment arms.

Goodness of fit

A summary of the AIC and BIC goodness of fit statistics for each distribution explored is provided in

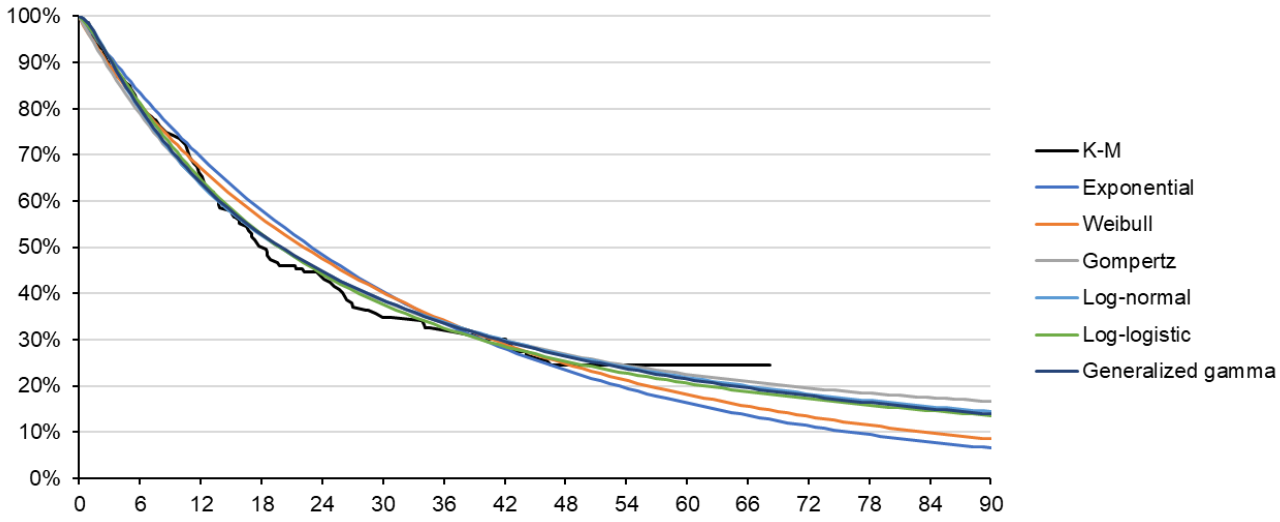
Table 8. A plot of the survival functions is shown in Figure 3 for visual assessment of fit.

Table 10: Summary of goodness of fit data for the parametric survival analysis of PPS data

Distribution	AIC	BIC
Exponential	964.78	967.83
Generalised Gamma	959.37	968.52
Gompertz	959.08	965.18
Log-logistic	**957.27**	**963.37**
Log-normal	957.41	963.51
Weibull	965.17	971.27

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PPS, post-progression survival.
Note: Bolded values indicate the best scores.

Figure 5: Visual fit of PPS parametric functions to PACIFIC data



Key: KM, Kaplan–Meier, PDL, programmed cell death ligand 1; PPS, post-progression survival.

All parametric curves had a good visual fit to the data. The log-logistic function has the best statistical fit based on AIC and BIC scores.

Choice of PPS curve

The log-logistic distribution showed the best statistical fit to the PPS KM data and had good visual fit. Therefore, this distribution was selected in the base case analysis.

A.7.3 *Subsequent therapies*

In line with the PACIFIC study and UK clinical practice, patients in the model who experience disease progression go on to receive further therapy and/or end-of-life care. These patients can be treated with immunotherapy if they meet the criteria required for treatment. A detailed summary of subsequent therapy use at 5-year follow-up in the PACIFIC trial is provided below.

Table 11: Proportion of patients receiving subsequent therapy (at progression)

	PD-L1 ≥1% group	
Subsequent therapy	**Durvalumab (N=96[a])**	**Placebo (N=61[a])**
IO therapies		
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Durvalumab (re-treatment)	[redacted]	[redacted]
Non-IO therapies		
Ramucirumab	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]

Subsequent therapy	PD-L1 ≥1% group	
	Durvalumab (N=96[a])	Placebo (N=61[a])
Paclitaxel	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]
Tegafur/Gimeracil/Oteracil	[redacted]	[redacted]
Crizotinib	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Watchful waiting/No Treatment	[redacted]	[redacted]

[a] The total number of progressed patients (excluding deaths) was used to calculate the proportions of patients receiving subsequent therapies at disease progression.
Key: IO, immune-oncology
Source: PACIFIC PD-L1 subgroup analyses, 11 January 2021 DCO. AstraZeneca data on file[4]

The proportions of patients receiving subsequent therapies in the durvalumab and placebo arms were also ratified by nine clinical experts. The majority of clinical experts stated the overall proportion of patients treated with durvalumab and placebo who go onto receive any subsequent therapies were reasonable and in line with their real-world experience. Chemotherapy was the most commonly-used subsequent treatment modality in both durvalumab and placebo groups, which is also aligned with clinical expert opinion of UK real-world practice. A greater proportion of patients in the placebo arm received subsequent immune-oncology therapies. Clinical experts stated that the majority of patients treated with placebo would receive an immuno-oncology therapy following disease progression.

Once patients progress in the model, a one-off cost for subsequent therapy is accrued. This cost is informed by the type of therapy, the required therapy dose, the dosing schedule, the unit drug cost, and the duration of therapy. The required therapy dose, dosing schedule and unit drug costs have remained unchanged from the original cost-effectiveness model.

Treatment duration of subsequent therapies was updated using the final data cut of the PACIFIC trial (11 January 2021 DCO). Treatment durations for subsequent therapies included in the model are provided below.

Table 12: Duration of subsequent therapy

Subsequent therapy	PD-L1 ≥1% group	
	Durvalumab (N=212)	Placebo (N=91)
IO therapies		
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Durvalumab (re-treatment)	[redacted]	[redacted]
Non-IO therapies		
Ramucirumab	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]
Tegafur/Gimeracil/Oteracil	[redacted]	[redacted]
Crizotinib	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Watchful waiting/No Treatment	[redacted]	[redacted]

Key: IO, immune-oncology.
Source: PACIFIC PD-L1 subgroup analyses, 11 January 2021 DCO. AstraZeneca data on file[4]

A.7.4 *Health-related quality of life*

In the original appraisal, health state utility values in the base case analysis were informed by data from PACIFIC (Company Submission Document B, Section B.3.4,

Pages 155-156). 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.

A.8 Key model assumptions and inputs

Table 13: Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption in new Company base case	Source/Justification
Progression-free survival (PFS) extrapolations	Company: generalised gamma in both arms NICE committee / ERG: Log-normal distribution in the durvalumab arm, generalised gamma in the placebo arm	Generalised gamma distribution in both arms	• Generalised gamma is the statistically best fitting curve to updated PACIFIC PFS data • Long-term PFS estimates produced by generalised gamma are in line with clinical expert opinion
Post-progression survival (PPS) extrapolations	Exponential distribution (both arms pooled)	Log-logistic distribution (both arms pooled)	• The log-logistic distribution is the statistically best fitting curve to the 5-year PPS KM data and has good visual fit
Treatment duration effect	Company: Treatment effect duration of 10 years NICE committee / ERG: Treatment effect duration of 3 to 5 years	No treatment duration effect in the base case analysis (10 year treatment waning effect to be explored in a scenario analysis)	• Supported by updated PFS data from the PACIFIC study and clinical expert opinion • Clinical experts stated the 5-year PACIFIC PFS data demonstrates the lack of a treatment waning effect
Source of utilities	PACIFIC (22 March 2018 DCO)	PACIFIC (22 March 2018 DCO)	• There were no further updates to health-related quality of life data from PACIFIC and therefore utility values applied in the cost-effectiveness analysis have remain unchanged
Durvalumab dosing regimen	10mg/kg administered every 2 weeks (Q2W)	Fixed dose of 1500mg administered every 4 weeks (Q4W)	• Surveyed clinical experts confirmed the 1500mg 4-weekly dose is now used as standard in UK clinical practice in the majority of patients due to reduced

			resource requirement and improved convenience for patients
Subsequent treatment approach	PACIFIC (22 March 2018 DCO) – no adjustments applied	PACIFIC (11 Jan 2021 DCO) – no adjustments applied	• Subsequent therapy use and duration were updated with the final analysis from the PACIFIC trial

A.9 Cost-effectiveness results (deterministic)

A.9.1 *Cost-effectiveness analyses used to determine entry into CDF*

The key cost-effectiveness analyses considered by the Committee for entry into the CDF, based on the original twice-weekly weight-based dose and using PACIFIC DCO2 data, have been replicated in Table 14 (Cost-effectiveness analysis 1a-1b). All ICERs presented are based on the simple discount PAS for durvalumab of [redacted].

Table 14: Cost-effectiveness results considered by the Committee for entry into the CDF – PACIFIC DCO2 (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1(a): Replication of analysis considered by the Committee for entry into the CDF (treatment waning at 3 years, Q2W dosing)							
Durvalumab	[redacted]	5.63	[redacted]	[redacted]	1.86	[redacted]	£35,992
Placebo	[redacted]	3.77	[redacted]				
Cost-effectiveness analysis 1(b): Replication of analysis considered by the Committee for entry into the CDF (treatment waning at 5 years, Q2W dosing)							
Durvalumab	[redacted]	5.63	[redacted]	[redacted]	1.86	[redacted]	£35,979
Placebo	[redacted]	3.77	[redacted]				

A.9.2 *Cost-effectiveness analyses incorporating updated clinical evidence*

Cost-effectiveness analyses that incorporate the mature PACIFIC data collected during the CDF period (PFS, PPS and subsequent therapies – 11 Jan 2021 DCO), with all other model inputs and parameters unchanged from the Committee's preferred cost-effectiveness analysis are shown in Table 15 (2a-2b). All ICERs presented are based on the fixed 4-weekly dose for durvalumab which is now standard-of-care in UK clinical practice and incorporate the simple discount PAS for durvalumab of [redacted].

Including mature data from PACIFIC has reduced the ICERs in the Committee's preferred analyses from TA578 by roughly £13,000 (~£35,000 to ~£22,000). Extrapolating more mature TTP/PFS and PPS/OS PACIFIC data resulted in increased incremental life-years and QALYs gained for durvalumab. Longer follow-up from the PACIFIC trial has meant that more patients in the placebo arm have progressed and therefore received subsequent therapies. The greater use of subsequent therapies, coupled with increased duration on subsequent therapy, has increased the treatment costs in the placebo arm and this in turn has reduced the ICER.

Results for the new Company base case (Cost-effectiveness analysis 3) are also provided in Table 15Table 1. A detailed overview of the model parameters updated in the base case analysis is provided in Table 13. The parametric model used to extrapolate PFS was updated to reflect the best fitting curve to the 5-year PACIFIC PFS data, in terms of statistical fit and clinical plausibility. The treatment waning effect on durvalumab's PFS was removed from the base case analysis as it is now clinically implausible given the mature PFS data from PACIFIC and this is in line with UK clinical expert opinion.

In the updated Company base case analysis, durvalumab resulted in [redacted] additional QALYs compared with placebo and incremental costs of [redacted], resulting in an ICER of £11,719. Removing the treatment waning effect and selecting generalised gamma for PFS in both arms reduces the ICER by approximately £10,000 (~£22,000 to £11,719).

Table 15: Cost-effectiveness analyses incorporating updated clinical evidence from PACIFIC DCO5 (Q4W dosing)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Cost-effectiveness analysis 2(a): Analysis considered by the Committee for entry into the CDF – incorporating updated clinical evidence from PACIFIC (treatment waning at 3 years)							
Durvalumab	[redacted]	7.00	[redacted]	[redacted]	1.98	[redacted]	£22,581

Placebo	[redacted]	5.02	[redacted]				
Cost-effectiveness analysis 2(b): Analysis considered by the Committee for entry into the CDF – incorporating updated clinical evidence (treatment waning at 5 years)							
Durvalumab	[redacted]	7.00	[redacted]	[redacted]	1.98	[redacted]	£22,441
Placebo	[redacted]	5.02	[redacted]				
Cost-effectiveness analysis 3: New Company base case, including the most plausible assumptions based on updated clinical evidence (no treatment waning effect, generalised gamma PFS both arms)							
Durvalumab	[redacted]	8.08	[redacted]	[redacted]	3.06	[redacted]	£11,719
Placebo	[redacted]	5.02	[redacted]				
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PFS, progression-free survival; QALYs, quality-adjusted life years							

A.10 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) was run for 1,000 iterations for the new Company base case analysis (durvalumab versus placebo). Results from the PSA are presented in Table 16. The probabilistic ICER is £11,101 per QALY gained, which compares well with £11,719 in the deterministic analysis.

Table 16: Updated base-case results (probabilistic) – B.3.8 (page 174)

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£11,101
Placebo	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

The cost-effectiveness plane and cost-effectiveness acceptability curve for durvalumab versus placebo are presented in **Figure 6** and **Figure 7**, respectively. At a cost-effectiveness threshold of £30,000, durvalumab has a 93.6% probability of being cost-effective compared with placebo.

Figure 6: Cost-effectiveness plane – B.3.8 (page 174)

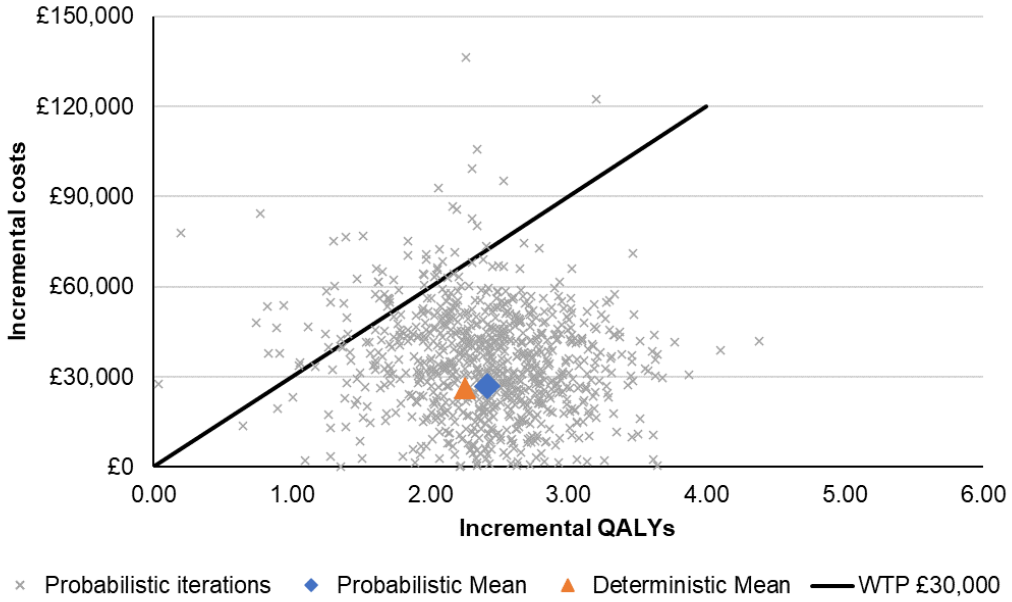
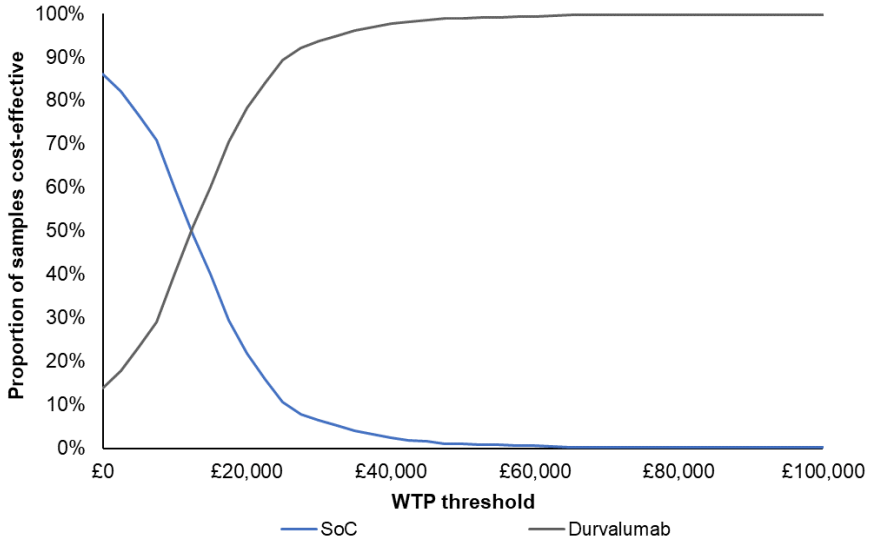


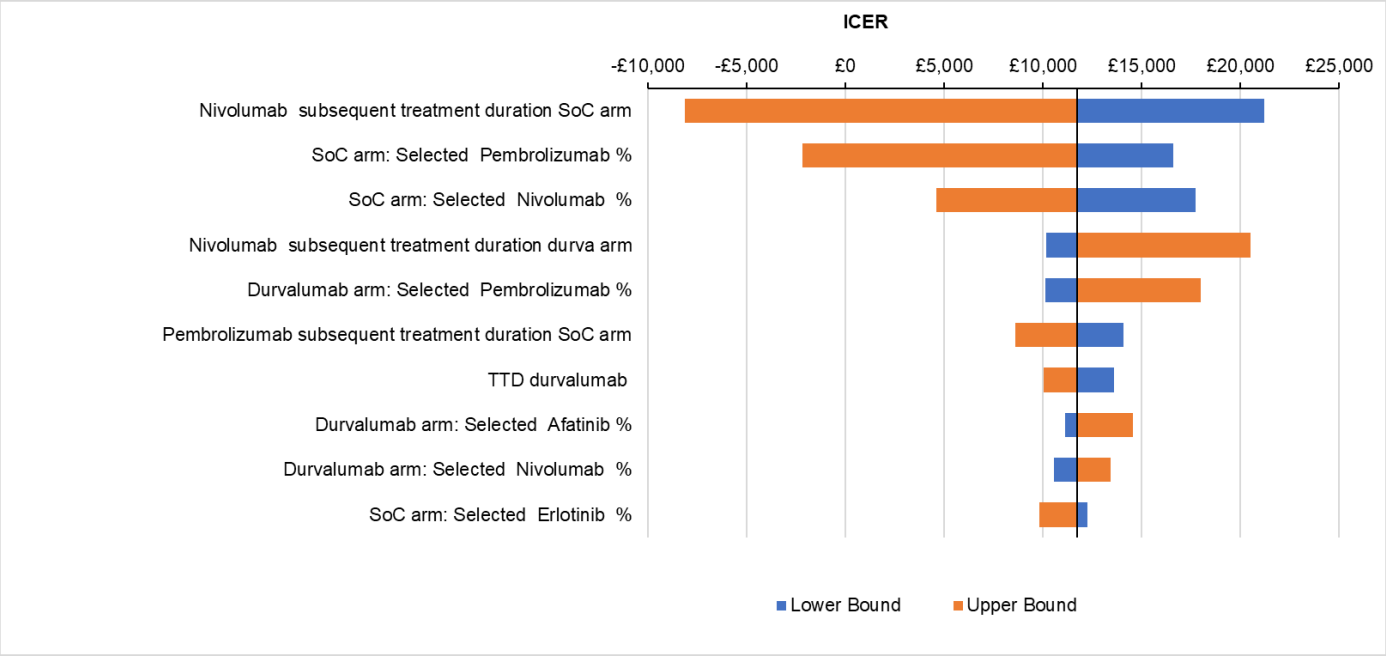
Figure 7: Cost-effectiveness acceptability curve – B.3.8 (page 174)



A.11 Key sensitivity and scenario analyses

Deterministic sensitivity analyses were conducted by varying key model parameters between the upper and lower 95% CIs of the expected value used in the deterministic base case. The results of the deterministic sensitivity analyses for the top 10 parameters are presented in Figure 8. Overall, the results show that the ICER is most sensitive to the duration and proportion of subsequent therapies in the placebo arm.

Figure 8: Tornado diagram – B.3.8 (page 175)



Various scenario analyses were conducted to assess alternate model settings and structural uncertainty of the base case analysis. Key scenarios are presented in Table 17.

Table 17: Key scenario analyses

Scenario	Values	Source / rationale	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Base case	-	-	[redacted]	[redacted]	£11,719
Alternative PFS distributions (durvalumab)	Gompertz	The majority of clinical experts surveyed (n=7) selected the gompertz as the extrapolation that were most consistent with clinical expert's expectations of durvalumab's long-term PFS.	[redacted]	[redacted]	£12,830
Treatment waning cut-off	10 years	In line with the original Company base case (Company Submission Document B, Section B.3.6, Page 172)	[redacted]	[redacted]	£12,375
Utility	PF utilities at general population levels (PF = 0.79, PD = 0.76)	-	[redacted]	[redacted]	£11,321
	Include AE dis-utilities	Company Submission Document B, Appendix P	[redacted]	[redacted]	£11,718
Vial sharing	Assume 30% vial sharing for subsequent therapies	-	[redacted]	[redacted]	£11,731

Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.

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

The 5-year follow-up data from the PACIFIC trial confirms the long-term survival benefit of durvalumab, robustly addressing the key uncertainties outlined at the time of the original appraisal and validating that use of durvalumab in this setting is highly cost-effective.[18]

The 19.4 month improvement in median PFS (HR: 0.47 [95% CI: 0.35, 0.64]) and median OS improvement of 33.5 months (HR: 0.61 [95%CI: 0.44, 0.85) for the PACIFIC PD-L1≥1% group treated with durvalumab compared to the placebo treated patients confirms that durvalumab in this setting can be considered potentially curative and its use is not associated with a treatment waning effect.[5] The curative effect of durvalumab in this setting was confirmed by UK clinical experts, who, although describing some challenges with defining cure, unanimously stated patients who have not experienced disease progression at 5-years are discharged and considered cured.[6] They also confirmed that no treatment waning effect is expected for durvalumab when used as part of a curative intent treatment regimen,[6] as evidenced by the KM curves, which demonstrate an early and sustained separation beyond 60 months for both PFS and OS outcomes.[4]

In addition to addressing uncertainties regarding treatment waning in the economic model inputs, the final analysis of the PACIFIC trial has also confirmed the most appropriate choice of PFS extrapolation as generalised gamma. This was validated by key external experts, who also considered the Gompertz extrapolation to be an appropriate choice.[6] Uncertainties in model inputs regarding the frequency, duration and overall cost of subsequent therapies have also been addressed with the 5-year PACIFIC data, confirming that use of durvalumab at an earlier stage of disease in the locally advanced, unresectable setting produces cost-savings in later lines of therapy. Overall, the updated economic model demonstrates durvalumab is highly cost-effective, with a base case ICER of £11,719 and scenario analyses with ICERs of £11,321 to £12,830.

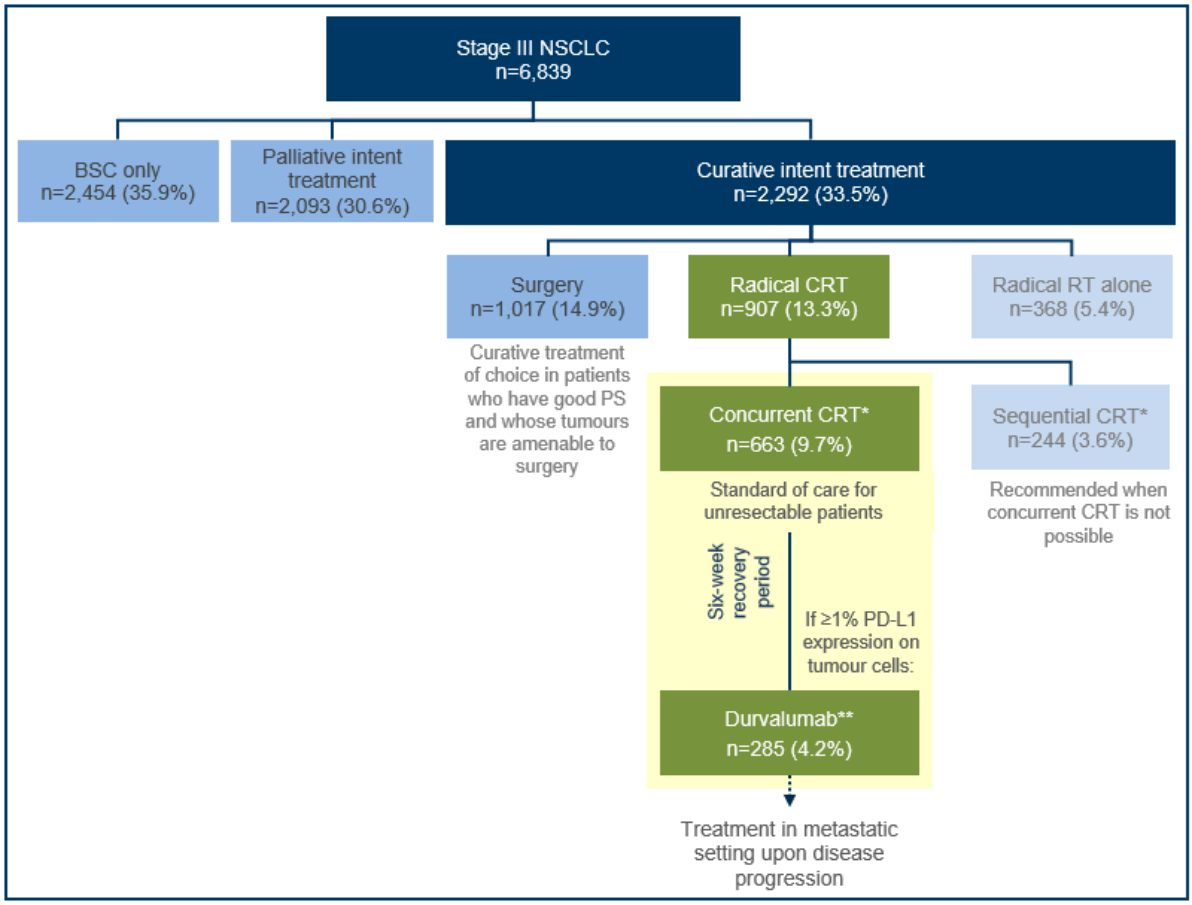
Additionally, OS and treatment duration data collected via the SACT database, while less mature than the PACIFIC trial data, substantiates the use and benefit of

durvalumab observed in the PACIFIC trial, and hence the cost-effectiveness associated with its use, is generalisable to real-world UK clinical practice.

Clinician intent to treat with durvalumab wherever possible due to the clear clinical benefit demonstrated by the PACIFIC trial should also be noted. The majority of clinicians interviewed reported using concurrent CRT in all patients considered fit enough to receive the regimen, particularly in PD-L1 positive patients, in order to ensure patients have the best chance of receiving durvalumab monotherapy. Several clinicians also described an increase in the proportion of concurrent CRT use compared with sequential CRT due to the availability of durvalumab after completion of concurrent CRT.[6] This intent to treat can also be inferred from the SACT cohort data, which included patients with slightly worse performance status, proportionally, compared to the PACIFIC trial. However, patients in the SACT cohort achieved relatively similar OS rates at 24 months compared to patients in the PACIFIC trial.

Overall, the updated data clearly demonstrate durvalumab monotherapy for the treatment of adults with unresectable locally advanced NSCLC with PD-L1 expression on ≥1% of tumour cells following platinum based-concurrent CRT, is a highly cost effective treatment option. Concurrent CRT followed by durvalumab monotherapy should now be considered the standard of care for all eligible patients with unresectable stage III NSCLC, as illustrated in **Error! Reference source not found.**.

Figure 9: Treatment of stage III NSCLC



Key: BSC, best supportive care; CRT, chemoradiation therapy; NLCA, National Lung Cancer Audit; NSCLC, non-small cell lung cancer; RT, radiotherapy
Notes: All patient numbers and percentages (except those indicated by **) derived from the latest NLCA data[19]; *,Determined from KEE interviews[6], relative proportion of sequential versus overlapping CRT use applied to full dataset (i.e. n=6,839); **, Determined from SACT overall survival secondary sensitivity analysis in patients with PD-L1 ≥1% (Appendix C, page 4)

A.13 References

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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

ERG Addendum

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

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None.

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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.

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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 Wiltox 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.

Issue 1 – Differences in PD-L1 status between the PACIFIC trial population and the SACT cohort

The ERG can confirm again that data presented from the PACIFIC trial are for the specified population. It is also clear how patients with unknown PD-L1 status were prescribed durvalumab. The ERG would argue that this does entail a risk of patients outside of the population specified in the ToE with a likely reduction in effectiveness and unknown effect on cost-effectiveness.

Issue 2 – Differences between the dosing used in the trial (weight based 10mg/kg, Q2W) and the fixed dose (1500mg, Q4W) given to some SACT patients

No new evidence has been provided as to the effect of any change in either effectiveness or safety due to any change in exposure to durvalumab. The ERG do not question the decision taken by the EMA, which considered the fixed dose (1500mg, Q4W) to be an acceptable alternative to the weight based (10mg/kg, Q2W) dose. However, the EMA did not address the questions being addressed as part of this appraisal, , which are precisely what the difference in effectiveness (efficacy, safety, and quality of life) is, and what implications does any difference have for whether durvalumab is cost-effective in comparison to standard care. As already stated in the ERG report, the EMA report does indicate that [redacted]

Issue 3 – No additional quality of life data was collected since durvalumab entered the CDF

The ERG is satisfied that the company sufficiently explored the impact of alternative utility values in the model. In addition, the company applied a correction to their utility values to reflect that the utility decrement associated with durvalumab only applied in the progression-free state, not in the progressed disease state, which was in line with the committee's preferences. The ERG accepted this change.

Issue 4 – Internal consistency between modelled survival and observed trial data was lacking

The company provided further explanation for their choice of a state transition model over a partitioned survival model. The ERG considers that, broadly, the approach is valid, however, it would have liked to have seen a partitioned survival analysis in addition, to be sure that no bias is introduced by this modelling approach. The main remaining concern of the ERG is that in the model OS in the placebo arm is under-estimated towards the end of the trial data, and potentially OS in the durvalumab arm slightly over-estimated. The only way of exploring the impact of this in the current model is through alternative choices of PFS curves. Whilst experts considered the generalised gamma to be the most plausible distribution, the choice of the lognormal for the durvalumab arm was not regarded as clinically plausible by clinical experts, however it illustrates the possible impact of the long-term uncertainty about PFS on the ICER. There is further uncertainty in the model because detail on estimation of TTP continues not to be provided despite ERG's request (TTP distributions continue to be set to be in line with PFS distributions, but no time-to-event analysis is provided). The full impact of the uncertainty around extrapolating PFS and OS is therefore not explored.

Issue 5 – Appropriateness of assumptions on the duration of treatment effect

The company's response is unfortunately not quite satisfactory. The ERG requested a plot examining the modelled HRs over time, 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."*

Unfortunately, this was not provided by the company. The company's additional arguments against adding treatment waning in the model do not address the issue: if by treatment waning we refer to hazards between both arms being equal (or the hazard ratio being equal to 1), it is not relevant whether the curves stay separate beyond 60 months. In fact, the company's previous plot in Figures 5 and 6 in the company's clarification response to question B4 implied [redacted]. Since it is unclear whether the chosen distributions already imply treatment waning (as the company did not provide the requested evidence to show this), the ERG considers it relevant to explore treatment waning at 3 years for PFS and 5 years for TTP (to be in line with trial data as shown in company's figures 5 and 6 in the company's clarification response to question B4). However, in the model it is only easily possible to select one time point for both PFS and TTP. Scenarios with 36 or 60 months time points for hazard ratios being set equal to 1 show a significant impact on the ICER, which likely implies that the company's selected distributions do not capture [redacted] at these time points. The ERG considers that the 36 months time point might be overly conservative given that it is unclear whether hazard ratios converge to 1 for TTP at this time point. Likewise, it may be that a the 60 months time point is potentially biased in favour of durvalumab. The ERG provides some scenarios around treatment waning in combination with different distributions for PFS. The ERG also notes that long-term relative effectiveness may be influenced by subsequent treatments (see next point).

Issue 6 – Subsequent treatments included in the model

The company provide a reference to a study that attempted to provide an adjustment for confounding due to subsequent therapy.[1] This study employed two of the three main methods available, the Rank Preserving Structure Failure Time (RPSFT) and a modified version of the Two-stage method (MTSM).[2] The former has the advantage of not requiring data on covariates to estimate the effect of subsequent therapy, but the disadvantage of having to assume a common treatment effect i.e. that due to any immunotherapy and at any time point, including durvalumab first line (on randomisation), is the same. The latter has the advantage of estimating the treatment effect of subsequent therapy independent of durvalumab first line, by creating a secondary baseline, usually the point of progression. In this case, because switching occurred a median of 6 months after progression, the decision was made to set the secondary baseline to start of subsequent treatment. In fact this was performed twice, once for 2nd or later and again for 1st subsequent treatment. The disadvantage of the TSM is that it requires the estimation of a regression model and thus relies on all prognostic factors being available. The other main alternative is the inverse probability of censoring weighting (IPCW) method, which was not employed essentially based on insufficient patient numbers. The study therefore presented results for both methods of removing the effect of immunotherapy from both arms. In addition, using the RPSFT method, the effect of assuming different percentages of chemotherapy was also presented given that it is believed that, although few patients would receive immunotherapy post-durvalumab, at least some would post-chemotherapy. The results showed that neither method produced a large effect on the HR, the MTSM having almost no effect and the RPSFT causing a decrease (increased

treatment effect) on removing the effect all subsequent immunotherapy. Not surprisingly, as more chemotherapy patients were assumed to receive immunotherapy, the HR increased.

ERG comment: The ERG recognises the challenge of estimating the treatment effect of durvalumab vs. chemotherapy given the potential for confounding due to variation of subsequent therapy both between the arms of the trial and between the trial and clinical practice. It is unclear precisely what the variation might be, and it is also uncertain which approach might be taken to attempt to adjust for this: the NICE TSD providing some guidance, but highlights the trade-offs between the various methods.[2] In this context the study cited by the company seems to provide a set of plausible estimates of the effect of adjusting for subsequent therapy confounding.[1] It seems reasonable to assume that the most plausible estimate of the treatment effect as would be observed with the type of subsequent therapy in clinical practice is probably not very different to the ITT value, but perhaps slightly higher given that few if any durvalumab patients would benefit from it, but a substantial number of chemotherapy patients would.

Cost effectiveness scenarios

Table 1: Cost effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company's base-case							
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,507
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ERG scenario: change PFS durvalumab to lognormal from generalised gamma							
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,676
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ERG scenario: change PFS durvalumab to Gompertz from generalised gamma							
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,577
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ERG base-case 1: treatment waning for PFS and TTP at 36 months, conditional on company's base-case							
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,345
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ERG base-case 2: treatment waning for PFS and TTP at 60 months, conditional on company's base-case							
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,871

SoC	[redacted]						
ERG scenario: change PFS durvalumab to Gompertz & treatment waning at 36 months							
Durvalumab	[redacted]						22,029
SoC	[redacted]						
ERG scenario: change PFS durvalumab to Gompertz & treatment waning at 60 months							
Durvalumab	[redacted]						18,032
SoC	[redacted]						
ERG scenario: change PFS durvalumab to lognormal & treatment waning at 36 months							
Durvalumab	[redacted]						21,806
SoC	[redacted]						
ERG scenario: change PFS durvalumab to lognormal & treatment waning at 60 months							
Durvalumab	[redacted]						21,676
SoC	[redacted]						

Table 2: Subsequent treatment scenarios (deterministic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company's base-case							
Durvalumab	[redacted]						11,507
SoC	[redacted]						
Company's base-case subsequent IO-therapy costs removed							
Durvalumab	[redacted]						23,427
SoC	[redacted]						
ERG base-case 1 (treatment waning for PFS and TTP at 36 months) subsequent IO-therapy costs removed							
Durvalumab	[redacted]						36,868
SoC	[redacted]						
ERG base-case 2 (treatment waning for PFS and TTP at 60 months) subsequent IO-therapy costs removed							

Durvalumab	[redacted]						29,915
SoC	[redacted]						
ERG scenario: lognormal PFS durvalumab, treatment waning at 36 months, subsequent IO costs removed							
Durvalumab	[redacted]						39,114
SoC	[redacted]						
ERG scenario: lognormal PFS durvalumab, treatment waning at 60 months, subsequent IO costs removed							
Durvalumab	[redacted]						38,936
SoC	[redacted]						

Table 3: Probabilistic results

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company's probabilistic base-case							
Durvalumab	[redacted]		[redacted]	[redacted]		[redacted]	13,231
SoC	[redacted]		[redacted]				
ERG base-case 1: treatment waning for PFS and TTP at 36 months (probabilistic)							
Durvalumab	[redacted]		[redacted]	[redacted]		[redacted]	21,718
SoC	[redacted]		[redacted]				
ERG base-case 2: treatment waning for PFS and TTP at 60 months (probabilistic)							
Durvalumab	[redacted]		[redacted]	[redacted]		[redacted]	17,041
SoC	[redacted]		[redacted]				

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

Clarification questions

January 2022

File name	Version	Contains confidential information	Date
ID3885 durvalumab clarification letter to PM_Company response [fully redacted]_v4_05.04.2022	**V4**	**Yes**	**05.04.2022**

Executive Summary

- In line with the scope for this appraisal, discussions at the CDF exit review kick-off meeting and the process for CDF exit review appraisals, the Company Submission presented an updated analysis of the population scoped for appraisal. The analysis was conducted using the model provided by the ERG and updated with the 5-year follow-up data from the PACIFIC trial as described in the data collection arrangement

- The Company consider it outside of scope to provide some of the analyses requested in the clarification questions. In particular:

    - It is not appropriate to include patients with unknown PD-L1 status in any analysis as this subgroup was not included in the original appraisal and subsequently is not included in the scope for this CDF exit review appraisal

    - As per the terms of engagement, the Company has updated the ERG provided model with the available 5-year follow-up data from the PACIFIC trial and re-explored and implemented the appropriate extrapolations and assumptions based on this data. It is thus not appropriate to implement significant structural changes to the provided model or present cost-effectiveness analyses based on the use of alternative models

- While it has not been possible to fulfil all requests laid out in the clarification questions, in part due to the significant time required to accomplish all the requested updates, additional information and scenario analyses have been provided to support the decision making as far as possible and within the scope of this appraisal. Specifically:

    - Supplementary data to further substantiate the base-case model structure and inputs has been provided

    - An exploratory simple cure analysis has been provided

    - Several additional scenario analyses have also been presented to demonstrate the impact on the ICER of an alternative PPS approach,

Q2W dosing regimen, use of alternative utility values and use of subsequent treatments more closely aligned to UK practice

Section A: Clarification on effectiveness data

Population

A1. Priority: It appears from Appendix B (Table 5) that 10% of patients in the SACT dataset received durvalumab, but their PD-L1 ≥1% status was unknown.

a. **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?**

b. **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%.**

c. **If the company could also obtain an analysis of the SACT data excluding those patients with unknown PD-L1 status, then please comment on any difference between this and the analysis including patients with unknown PD-L1 status.**

Response:

Contextual information regarding inclusion of patients with unknown PD-L1 status in Blueteq criteria for reimbursement following original submission (TA578)

Following the EMA decision to approve durvalumab for treatment of locally advanced unresectable NSCLC for patients whose tumours express PD-L1 on ≥1% of tumour cells, the company submission addressed this population rather than the originally scoped PD-L1 'all comers' population.[1]

However, as outlined by the CDF Lead at the SACT report meeting, there were concerns from clinicians at the time of the original appraisal that patients who are unable to undergo PD-L1 testing or who receive an inconclusive PD-L1 test result may be denied access to this highly efficacious therapy. Hence, the following conditions were included in the Blueteq criteria for use[2] to allow use of durvalumab when a PD-L1 TPS cannot be documented:

- The TPS result was unquantifiable for technical (assay) reasons or

- PD-L1 testing was not possible as the pathologist has documented that there is insufficient tissue for PD-L1 analysis and the Lung Cancer MDT has concluded and documented that the gaining of a further tumour sample is hazardous to the patient

All analyses provided in the original submission and subsequent decision-making was based on the PD-L1 ≥1% group from the PACIFIC trial. The decision to allow access for patients who are unable to obtain a PD-L1 TPS was not based on any analysis of data from the PD-L1 unknown cohort in the PACIFIC trial.

Company rationale for exclusion of analysis of patients with unknown PD-L1 TPS in the CDF review of TA578

As per the scope for the CDF review of TA578 (ID3885) published in November 2021 and in line with the terms of engagement[3] and discussion regarding the population for appraisal at the kick-off meeting (held 23rd November 2021), the population for appraisal was confirmed as the PD-L1 ≥1% group. The company understands the remit of the NICE CDF review process is to provide updated data to address key uncertainties in the original appraisal and re-assess the cost-effectiveness based on this updated data. As analysis of the PD-L1 unknown patient population was not included in the original appraisal, the company considers it outside of both CDF review process and appraisal scope to analyse and/or appraise this population at the CDF review. The Company would also like to clarify a pooled analysis of the PD-L1 ≥1% group and PD-L1 unknown group from the PACIFIC trial was not conducted at the 2-year follow-up and has not been conducted at the 5-year follow-up.

It should also be noted that there are fundamental differences in the PD-L1 unknown patient population in the PACIFIC trial compared with the SACT dataset. As the PACIFIC trial did not mandate PD-L1 testing, the PD-L1 unknown group contains patients who did not receive a PD-L1 test in addition to those who were unable to receive a test or received an unquantifiable results.[1, 4] As PD-L1 testing is mandatory in UK clinical practice prior to prescribing a PD-1/L1 inhibitor,[2] patients in the SACT PD-L1 unknown group are patients in whom PD-L1 testing is not possible or the

result is unquantifiable. Therefore, any comparison between these two PD-L1 unknown datasets would be inappropriate.

Use of the SACT dataset in the submission

Prior to the CDF review kick-off meeting, a secondary sensitivity analysis of OS for the SACT dataset excluding the 10% of patients with unknown PD-L1 status. i.e. OS analysis of PD-L1 ≥1% patients only was provided. This dataset was used to validate the 5-yr OS data reported from the PACIFIC trial in the company submission (CS), as it was the most relevant dataset. The full SACT report and the SACT secondary sensitivity analysis of the PD-L1 ≥1% group were both provided in their entirety as Appendix B and C, respectively. As outlined in the CS, the secondary sensitivity analysis confirmed the OS results reported in the 5-year follow-up of the PACIFIC trial for the PD-L1 ≥1% group.

Overall, the exclusion of the 10% of patients with unknown PD-L1 TPS from the full SACT dataset had minimal impact on the overall OS outcomes. A comparison is provided in Table 1.

Table 1: Comparison of OS outcomes for the full SACT cohort vs. the secondary sensitivity analysis of patients with PD-L1 TPS ≥1% only

	Full SACT dataset (n=591)	SACT secondary sensitivity analysis of OS: PD-L1 ≥1% patients only (n=522)
Median OS, months (95% CI)	NR	NR
Survival rate:		
6 months, (95% CI)	93% (90%, 95%)	93% (91%, 95%)
12 months, (95% CI)	84% (81%, 87%)	85% (82%, 88%)
18 months, (95% CI)	73% (69%, 77%)	75% (70%, 79%)
24 months, (95% CI)	67% (61%, 72%)	68% (62%, 74%)

Key: CI, confidence interval; NR, not reached; OS, overall survival; PD-L1, programmed death-ligand 1; SACT, systemic anti-cancer therapy

Company expectation for continued inclusion of patients with unknown PD-L1 status in Blueteq criteria for reimbursement

The Company understand that the population for analysis in the CDF exit review will remain consistent with the population evaluated at the original appraisal and as

outlined in the scope for the appraisal and terms of engagement i.e. the PD-L1 ≥1% group. Assuming durvalumab receives a positive recommendation for routine commissioning, the Company anticipates the CDF criteria for use will remain consistent with the current wording. More specifically, we anticipate the current situation will continue, in which those PD-L1 unknown patients will receive access to durvalumab given there has been a reasonable attempt to obtain a PD-L1 test result. This would be to ensure that patients who have an unknown PD-L1 TPS, despite a reasonable attempt to obtain a test result, have access to this highly efficacious treatment.

Intervention

A1. Priority: 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.

Response:

The durvalumab regimen evaluated in the PACIFIC trial remained 10mg/kg administered every 2 weeks throughout the entirety of the trial.[4]

However, it should be noted the Q4W dose was introduced as part of COVID interim guidance in the NHS from April 2020.[5] As patients in the SACT cohort received doses of durvalumab between 28 March 2019 and 1 February 2021, it is expected that a proportion of patients in the SACT cohort received the 1500mg Q4W dose.

A2. Priority: 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).

Response:

The updated posology regimen of 1500mg administered every 4 weeks for the treatment of locally advanced unresectable NSCLC whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based CRT was evaluated by the EMA and approved in January 2021.[6]

The Company application to the EMA contained data including: target occupancy with the proposed 1500mg Q4W dosing regimen; population pharmacokinetic simulations of the 10mg/kg Q2W, 20mg/kg and 1500mg Q4W dosing regimens; relationship of exposure to efficacy and safety; availability of a phase III study demonstrating a safe and efficacious use of the proposed regimen. The CHMP type II variation assessment report has been provided as a confidential reference in response to this question.[7]

The EMA accepted there were no clinically significant differences in efficacy and safety between the 10mg/kg Q2W dose and the 1500mg Q4W dose.[6]

We have provided a scenario analysis using the 10mg/kg Q2W dose (Table 2), which clearly demonstrates that the dosing regimen for durvalumab has a minimal impact on the ICER (increase of £403).

Table 2: Results of the Q2W scenario analysis

Treatment	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	**£12,122**
Placebo	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

As per the CS, clinicians reported the Q4W regimen is now considered SoC in the UK due to more convenient dosing for patients and reduced resource use.[8]

Outcomes

A3. Section A.7.4 of the CS states *that 'more mature data on health-related quality of life has not been collected in further data cuts'*. Please confirm that no additional quality of life data were collected despite these data being requested in the 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.'*

Response:

As outlined in the data collection arrangement (provided as Appendix D to the company CDF review submission and available online)[9], outcome data collected

from the PACIFIC trial during the data collection period included 5-yr PFS and OS data and data on subsequent therapies. Continued collection of health-related quality of life data from the PACIFIC trial was not listed as outcome data to be collected during the managed access period.

Additionally, the Company highlighted in the Terms of Engagement pro-forma, which was provided to NICE and the ERG ahead of the CDF review kick-off meeting on 27th November 2021, that this data had not been collected during the managed access period. The Company also specified the approach in the model would be to keep utility values consistent with those provided at the time of the original submission.

The Company confirms no additional quality of life data were collected, consistent with the DCA[9] and our previous communications.

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. Priority: It is stated in the Terms of Engagement that *"The company should use updated survival data from PACIFIC and fully explore the most appropriate method to extrapolate survival outcomes."* The ERG doubts that the most appropriate method to extrapolate survival outcomes has been explored. The company continues to estimate PFS and time-to-progression (TTP) for both treatment arms separately, and PPS jointly for both treatment arms. This approach was criticized 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 in the company's previous base-case. The company had justified this approach stating that it avoided the logical inconsistency of OS and PFS curves crossing. However, the ERG notes discrepancies between the company's modelled number of patients alive at 5 years and OS in the PACIFIC trial (OS for durvalumab over-estimated in model and OS for placebo under-estimated

in model). This means the current model lacks internal consistency and probably biases cost effectiveness results in favour of durvalumab.

a. Please explain whether OS and PFS are still crossing in the updated survival analysis using the newly available data. If this is no longer the case, please provide additional justification for the use of the PFS/TTP/PPS modelling approach. Please also explore whether OS (patients alive) and PFS cross in the company's model using the current approach.

b. Please comment on the appropriateness of assuming that PPS is the same across treatment arms. Particularly given the large differences in use of subsequent treatments, and the above-mentioned discrepancies between modelled and observed OS, the ERG considers that this assumption appears increasingly unrealistic. Please provide evidence of internal consistency, comparing the pooled PPS Kaplan Meier data from PACIFIC and chosen distribution with the stratified PPS Kaplan Meier data from PACIFIC and chosen distributions (e.g. in one figure). Please also provide external validation for PPS per treatment arm if possible, for example using the SACT data.

c. Please provide details on the time-to-progression models used for the updated model (including full time-to-event analysis in accordance with NICE DSU TSD 14), or confirm that this is the same as in the original submission and justify that this is appropriate.

d. Please provide a full partitioned survival analysis model using OS and PFS for both treatment arms and include this either in the company's base-case or as a scenario analysis. Please provide a cross comparison of disaggregated results with those of the original approach.

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. In line with this understanding, as per the terms of engagement pro-forma, the Company have updated the ERG model from the original submission that was provided by NICE on the 9th November 2021.

There were no changes to the model structure as agreed upon during the kick-off meeting, with only the parameters outlined in the terms of engagement pro-forma being updated: PFS and OS outcomes and extrapolations, treatment effect duration, any relevant cure assumptions and subsequent treatment data.

Validation of overall survival predictions

It is necessary to ensure that the model structure and choice of parametric curves produce clinically plausible long-term outcomes in the cost-effectiveness analysis. In response to the ERG's claim that the economic model may under/over-predict OS compared to the PACIFIC trial, we have provided a comparison of observed OS data from PACIFIC (DCO5, 11 January 2021) and predicted OS from the economic model that was submitted for this CDF review. Extrapolated OS outcomes shown in **Table *3*** were generated using on the Company's base case analysis, which applied generalised gamma for PFS (ICER: £11,719).

Table 3: Comparison of extrapolated OS outcomes from the economic model (PFS: generalised gamma) and observed OS from PACIFIC DCO5

	Median (months)	1 year	2 years	3 years	5 years	10 years	15 years	20 years
Placebo								
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PACIFIC (PD-L1 ≥ 1%)	29.6	74.7%	53.7%	45.3%	36.9%	-	-	-
Durvalumab								
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PACIFIC (PD-L1 ≥1% group)	63.1	86.5%	72.9%	61.9%	50.1%	-	-	-

The long-term OS extrapolated by an economic model is not expected to perfectly match observed OS data derived from the clinical trial. However, the modelled OS should not significantly deviate from observed data. Given this, the observed and modelled OS in both the durvalumab and placebo arms are generally comparable (Table 3). When comparing the observed and modelled median OS, the economic

model overestimates the median OS by a similar proportion in both arms (approximately [redacted] months longer than observed in the durvalumab arm and [redacted] months longer in the placebo arm). While the model slightly underestimates OS in the placebo arm at 5 years, the model overestimates placebo OS in the first four years of the time horizon.

We have also conducted a comparison of observed data from PACIFIC DCO5 with modelled OS, using the Gompertz function to extrapolate PFS in both arms (ICER: £15,687). The Gompertz function had a good visual fit to the observed data in both arms of the PACIFIC study and was most consistent with UK clinical expert's expectations of durvalumab's long-term PFS (CS, Section A.7.1).

Table 4: Comparison of extrapolated OS outcomes from the economic model (PFS: Gompertz) and observed OS from PACIFIC DCO5

	Median (months)	1 year	2 years	3 years	5 years	10 years	15 years	20 years
Placebo								
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PACIFIC (PD-L1 ≥ 1%)	29.6	74.7%	53.7%	45.3%	36.9%	-	-	-
Durvalumab								
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PACIFIC (PD-L1 ≥1% group)	63.1	86.5%	72.9%	61.9%	50.1%	-	-	-

The median OS predicted by the economic model when Gompertz function is used to extrapolate PFS is a close match to the observed median OS from PACIFIC DCO5, particularly in the durvalumab arm (modelled: [redacted] months, observed: 63.1 months). The difference between the modelled and observed median OS in the placebo arm is also significantly smaller, when compared to the predicted OS using generalised gamma for PFS (Table 3). Applying the Gompertz function to PFS could address the concern that the model may be overestimating OS in the durvalumab

arm when compared to observed data, as there is only a [redacted] difference in the OS rate at 5 years, compared to a [redacted] difference when using generalised gamma.

The original economic model submitted to NICE in 2018 (TA578) was able to accurately predict the overall survival for durvalumab-treated patients at 5 years. The cost-effectiveness model, based on 2-years of follow-up from PACIFIC (DCO2, 22 March 2018), predicted an OS rate of [redacted] at 5 years for patients treated with durvalumab. The observed OS rate from the PACIFIC trial at 5 years in the durvalumab was 50%. This extremely accurate prediction of durvalumab's long-term OS demonstrates the robustness of the economic model.

a. PFS and OS curves based on the 5-year PACIFIC data for durvalumab, and placebo-treated patients are provided below. The PFS curves included in the durvalumab and placebo arms are generalised gamma and Gompertz, as these curves have the best statistical and visual fit to the observed KM data. The generalised gamma and Gompertz were also selected by a panel of UK clinical experts as the extrapolations that were most consistent with their expectations of durvalumab's long-term PFS. If either the generalised gamma or Gompertz functions are used for PFS, the PFS and OS curves will always cross, as demonstrated in the figures below. The only exception to this is the Gompertz placebo OS curve, which does not cross the generalised gamma and Gompertz PFS curves. However, the Gompertz OS curve predicts that approximately [redacted] of patients treated with placebo would be alive at 10 years, which is in direct contradiction to UK clinical expert views that ~10% of patients treated with placebo would be alive at this timepoint. Therefore, since all clinically viable OS curves cross with PFS in the durvalumab and placebo arms, a partitioned survival analysis would be associated with significant limitations. Therefore, a state transition modelling approach has remained as the base case analysis in order to avoid logical inconsistencies.

Figure 1: Extrapolated PFS and OS – durvalumab

Figure 2: Extrapolated PFS and OS – placebo

b. As discussed above, it was initially agreed with NICE that the model structure and approach would remain unchanged from the original submission. Therefore, in line with the cost-effectiveness analysis from TA578, post-progression survival from PACIFIC DCO5 was pooled across both arms. PPS data was pooled across both arms as it increases the sample size and thus the power. This decreases the uncertainty of the parametric models fit to the data. Pooling PPS data across both arms assumes that PPS is equal for both treatment arms, which is generally supported by the KM data for PPS from DCO5, which demonstrates there is no clear separation between the durvalumab and placebo-treated patients for the first few years of the study.

Figure 3: KM plot of stratified post-progression survival; PACIFIC PD-L1 ≥1% group (11 January 2021 DCO)

It is not possible to use the SACT data as an external validation source for PPS, as the data is limited to overall survival for patient treated with durvalumab only. Additionally, the data is immature with a limited follow-up period.

In the absence of external SACT data to validate the use of pooled PPS in this economic analysis, we have compared pooled PPS Kaplan Meier data from PACIFIC, and its best-fitting distribution, with treatment-stratified PPS Kaplan Meier data and its best-fitting extrapolation in the graph below. The best-fitting

distribution for PPS was log-logistic in the durvalumab arm and log-normal in the placebo arm, as indicated by the AIC scores (Table 5).

Table 5: Extrapolation AIC and BIC scores for PPS; PACIFIC PD-L1 ≥1% group (stratified)

	Durvalumab		Placebo	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	592.76	595.32	373.66	375.76
Weibull	593.03	598.16	375.53	379.72
Gompertz	588.4	593.53	374.09	378.28
Generalized Gamma	590.26	597.95	374.44	380.72
Log logistic	588.2	593.33	372.49	376.68
Log normal	588.27	593.4	372.46	376.65

The graph below shows that pooled and treatment-stratified PPS are generally comparable, with small [redacted] differences in extrapolated survival at 5 and 10 years. Extrapolated PPS data in the durvalumab arm performs slightly better when compared to extrapolated placebo PPS data, which confirms that using pooled PPS in the Company base-case analysis is a conservative assumption.

Figure 4: Pooled and stratified PPS KM data and best-fitting extrapolations

We have also conducted a scenario analysis in which extrapolated stratified PPS data from PACIFIC is used to inform the cost-effectiveness analysis. Results of this scenario analysis are provided below. Applying stratified PPS improved the ICER by £787 (£11,719 to £10,932). The improved cost-effectiveness when applying stratified PPS in the economic model further confirms the PPS approach undertaken in the base case analysis (assuming PPS is equal for both treatment arms) was conservative.

Table 6: Results of the stratified PPS scenario analysis

Treatment	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	**£10,932**
Placebo	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

c. The Company can confirm that the time-to-progression models used for the CDF exit review submission are consistent with those used in the original submission. In line with the scope of a CDF review, the model approach and structure should remain unchanged compared with the original submission

d. As discussed in response to QB1a, a partitioned survival analysis approach has not been presented as all clinically-plausible PFS and OS-curves cross, making a partition survival approach complex and prone to logical inconsistencies.

B2. Priority: Time-to-event analysis: the full NICE DSU TSD 14 guidance was not followed. Notably, the appropriateness of the proportional hazard assumption was not assessed. There are notable differences in the fitted distributions, and they do not all seem to fit the Kaplan Meier curves well.

a. Please follow the full guidance of NICE DSU TSD 14, including checking whether the proportional hazards assumption holds, and joint modelling is warranted (for the OS/PFS approach, and for the PFS/TTP/PPS approach if still used).

b. Please provide smoothed hazard plots per treatment arm for the observed and modelled PFS, TTP, OS and PPS data, with numbers of patients at risk.

c. Please elaborate on whether other approaches were considered, such as mixture cure modelling or spline models and whether these may be appropriate.

d. If considered appropriate, please provide these analyses and include them in the modelling as an updated base-case or scenario analyses.

Response:

a. Proportional hazards assumption

The appropriateness of the proportional hazards assumption was assessed following the 5-year PACIFIC update. This was omitted from the company submission due to the limit in word count and guidance at the kick-off meeting to keep the submission concise.

TTP/PFS

The Schoenfeld residuals and cumulative hazard plot for TTP and PFS are provided in Section A.1 of Appendix A. Both the cumulative hazard plot and the Schoenfeld residuals plot show on overall a linear trend (TTP: p=0.191, PFS: p=0.109). This suggests the proportional hazard assumption may be reasonable. The best fitting curve with this assumption (generalised gamma) showed an inadequate visual fit to the KM data for both arms. For consistency with the modelling approach taken in TA578, individual fitted models were applied in the base case analysis. As noted in the CS for TA578 (Page 134), it is unnecessary to rely upon the proportional hazards assumption when patient-level data are available, as independent models fitted to patient level data capture both proportional and non-proportional effects.

PPS

The Schoenfeld residuals and cumulative hazard plot for TTP and PFS are provided in Section A.1.3 of Appendix A. Both the cumulative hazard plot and the Schoenfeld residuals plot showed a linear trend (p=0.752), indicating the proportional hazards assumption holds. The best fitting curve with this assumption (log-logistic) showed a

good visual fit to the KM data. Therefore, PPS data was pooled in the base case analysis and a parametric model was applied. This was also conducted to maintain consistency with the modelling approach taken in TA578.

b. **Smoothed hazard plots:**

A plot of the smooth hazard function for each of the time to event endpoints has been produced using smoother functions to approximate the shape of the observed hazard: muhaz which approximates the hazard function from right-censored data using kernel-based methods, and bshazard which approximates the hazard function non-parametrically using B-splines. These smoothing approximators, have been overlaid with the shape of the hazard function resulting from each of the preferred fitted parametric model distributions. The smoothed hazards plots per treatment arm for the observed and modelled PFS, TTP, OS and PPS data are provided in Section A.2 of Appendix A.

TTP/PFS

Overall, the smoothed hazard plots for TTP and PFS showed an overall good fit for the parametric curve selected in the base case analysis (generalised gamma). We have also produced smoothed hazard plots for the Gompertz function, which also demonstrates to be a good fit.

PPS

The smoothed hazard plots for PPS showed an overall good fit for the parametric curve selected in the base case analysis (log logistic), in both the durvalumab and placebo arms.

c. As per our answer to question B1, it remains the Company's understanding that the modelling approach for a CDF exit review should remain consistent with that used in the original submission. Use of a mixture cure model and other approaches explicitly incorporating cure would represent fundamental changes to the model structure. However, we have incorporated a simple cure analysis into the economic model. Further details on this scenario analysis are provided in response to question B3.

B3. Priority: The Terms of Engagement state: *"The company should use updated survival data from PACIFIC to inform the appropriateness of a cure assumption."* Whilst the company state 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 does not seem to be included in the modelling.

a. Please explain whether and how the model takes potential cure into account.

b. Please provide a scenario analysis in which cure is included in the modelling, potentially by using mixture cure modelling.

Response:

The base-case analysis was conducted using the provided model with a structure consistent with the original submission, which was aligned with the guidance provided at the CDF review kick-off meeting.

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'. UK clinical experts however did confirm the curative effect of durvalumab in this setting, based on the PACIFIC 5-year data and their experiences of durvalumab in the real-world setting.[8] While a cure assumption has not been directly included in the base case analysis, the curative effect of durvalumab is reflected by the absence of a treatment waning effect in the base-case analysis. The lack of treatment waning effect was also supported by UK clinical experts, as noted in Section A.7.1 of the CS for this CDF exit review.[8]

The Company would also like to highlight that while clinicians may consider NSCLC patients who are progression-free 5-years following curative intent concurrent CRT as potentially cured, inevitably death events will occur after this 5-year time point due to mortality from natural and/or other causes, especially considering the median age of the PACIFIC population was 64 years.

The Company considered application of a mixture cure model to the PACIFIC data. However, this was not conducted as it would require fundamental changes to the model structure and approach, which is outside the scope of the CDF exit review as noted during the kick-off meeting.

To address the ERG's request to explicitly model cure, the Company have updated the health economic model to include an exploratory simple cure analysis. The cure analysis assumes that patients in the progression-free health state at 5 years, regardless of treatment arm, are functionally cured. The 5-year timepoint is aligned to UK clinical expert feedback that confirmed that patients in this setting are discharged from clinical practice after 5 years without disease progression. In line with accepted methodology in previous NICE appraisals in NSCLC,[10] patients who were cured were deemed to no longer be at risk of disease recurrence, or at risk of dying from NSCLC; cured patients were instead subject to age-matched general population mortality.

Top-line results for the cure scenario analysis are provided in the table below. Please note, this analysis is exploratory and intended to address the questions in the given timeframe.

Table 7: Results of the cure scenario analysis – assuming cure at 5 years

Treatment	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	**£12,756**
Placebo	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

B4. Priority: The Terms of Engagement state: *"The company should use updated survival data from PACIFIC and fully explore the treatment effect after stopping treatment."* Please provide smoothed hazard ratio plots for OS and PFS with numbers of patients at risk over time to justify assuming no durvalumab treatment waning effect.

Response:

Smoothed hazard ratio plots for PFS and OS are provided in Figure 5 and

Figure **6**.

Figure 5: Smoothed hazard ratio plot – PFS (PD-L1 ≥1% group, reference arm = placebo)

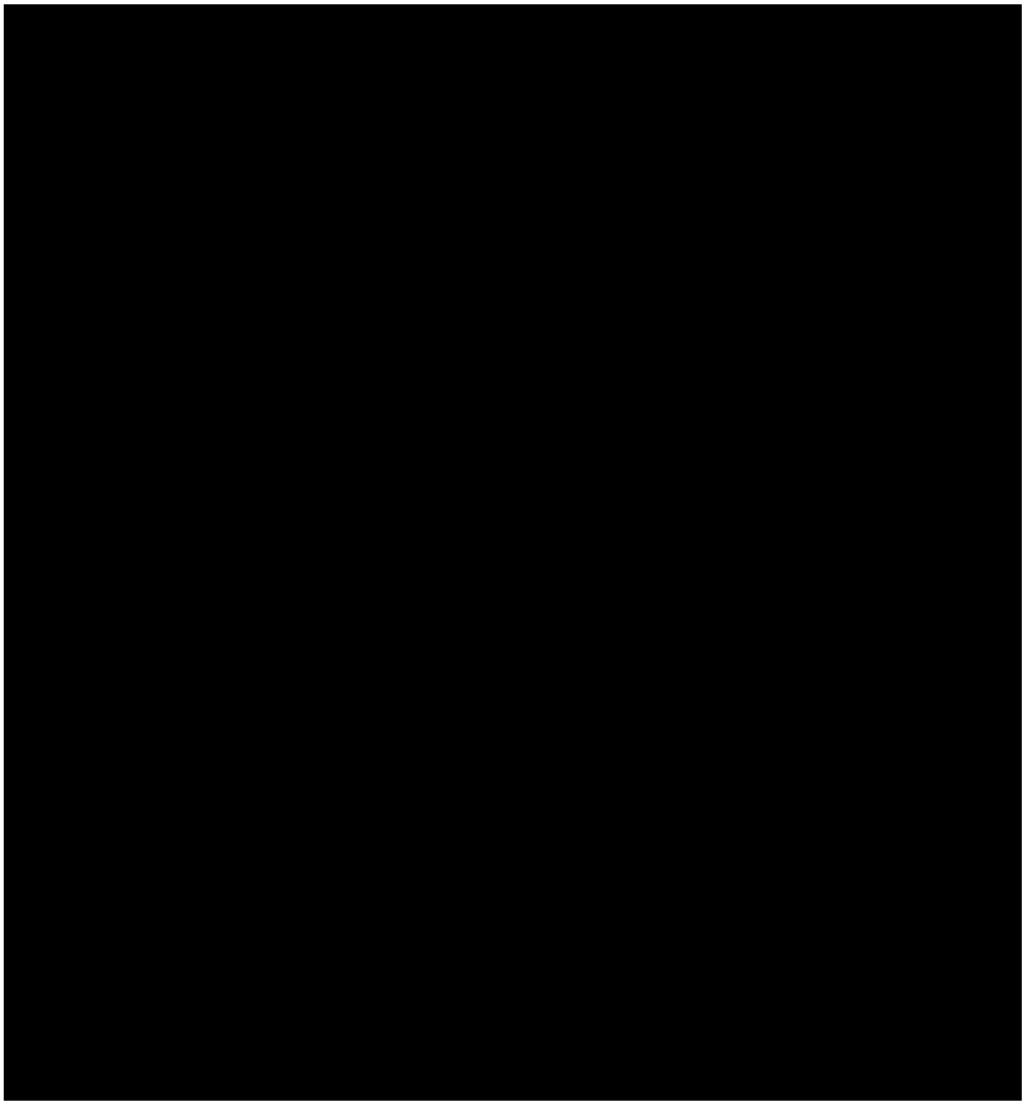
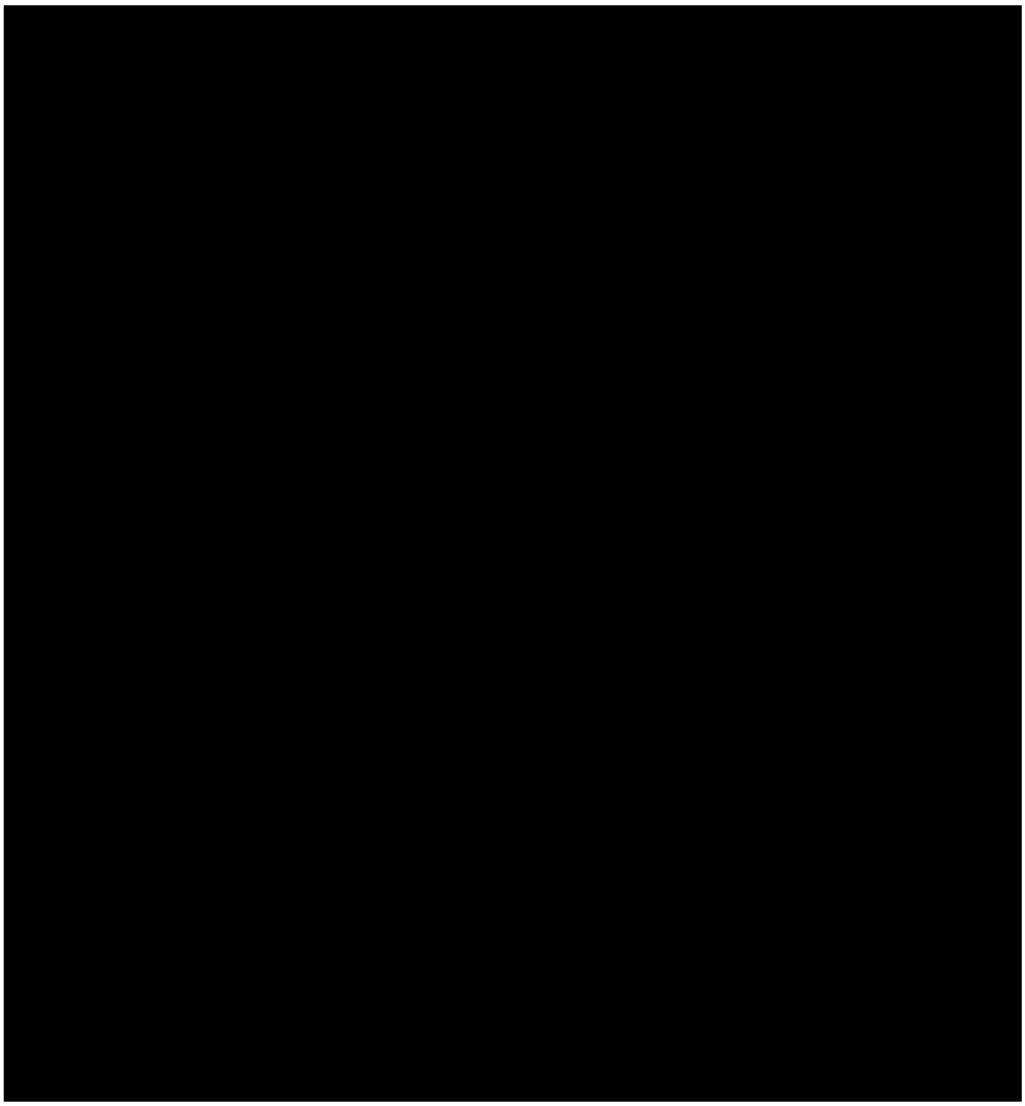


Figure 6: Smoothed hazard ratio plot – OS (PD-L1 ≥1% group, reference arm = placebo)



The hazard ratio plots for PFS and OS reflect the KM plots (CS, Figure 1 and Figure 2), with clear differentiation between the durvalumab and placebo-treated arms in the first few months of trial. The PFS KM curves for durvalumab and placebo begin to flatten at around 3 years, indicating the risk of progression remains stable in both arms, which is aligned with the [redacted] (Figure 5). The flattening of the PFS KM curve is clearly reflected in the parametric extrapolations applied in the base case analysis.

As the difference in the risk of progression in the PACIFIC trial is already incorporated into the parametric curves applied, a treatment waning effect could be regarded as effectively 'double-counting' the risk of progression in the durvalumab arm.

Furthermore, UK clinical expert feedback states that the majority of patients progress within the first 5 years following cCRT, with very few patients progressing between 5 and 10 years. Therefore, it is expected that parametric extrapolations based on 5-years' worth of data will be highly precise and accurately account for the treatment waning of durvalumab. Therefore, applying an arbitrary treatment waning effect to durvalumab-treated patients could reduce model accuracy by overriding the trends observed with the parametric extrapolations.

Health-related quality of life

B5. The Terms of Engagement state: *"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."* However, in their updated submission the company 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"*.

a. Please perform an updated SLR to identify any relevant studies that could inform health state utilities in the economic model, and if so, provide an updated model and scenario analysis.

b. Please elaborate on how the utility vales currently used in the economic model compare to utility values from other recent NICE appraisals (e.g. TA713, TA653, TA531) and provide an updated model and scenario analyses using utility values from these appraisals.

Response:

The progression-free health state utility values applied in the base case analysis for this CDF review are conservative when compared to the base case analysis submitted by the Company in NICE TA578. The progression-free utility value applied

in the company submitted model from TA578 were based on a mixed effects utility model based on PACIFIC, which included progression only as a covariate.

Following ERG and NICE technical engagement, the Company made several revisions to the utility values applied in the base case analysis. The utility values applied were updated to be sourced from a mixed effects utility model that included treatment as well as progression as covariates. This update aligned the Company's approach with the ERG's preferred analysis and was intended to adequately capture the potential impact of treatment-related adverse events. This resulted in a lower utility value being applied to patients treated with durvalumab in the progression-free health state. This is a conservative assumption given the significant and proven long-term PFS benefit demonstrated with durvalumab at DCO5. The lowered utility value for durvalumab has remained in the base case analysis for this CDF review.

An updated SLR has not been conducted for two reasons: (1) it was not possible to perform an updated SLR within the given timeframe (5 business days); (2) lack of product launches and published data in this indication since the original submission.

We are not aware of availability of any additional published studies for the locally advanced unresectable indication and durvalumab remains the only novel therapy indicated in this setting. Therefore, it is not expected that there is any further data to support utility values in the progression-free setting of the model.

The same utility value is applied to both the placebo and durvalumab arms following progression, in line with the pooled PPS approach in the model and remains consistent with the values applied in the original model. As per the original submission (pg 156), using utility values dependent on progression only is a conservative approach.

In the original submission (pg 157), a comparison of PACIFIC utility values against published sources was conducted. This analysis demonstrated broad consistency with the values reported for advanced metastatic disease, with the post-progression utility value for PACIFIC being above, but similar to, that reported for advanced metastatic disease. This was considered to be aligned with the PACIFIC population, as not all patients in the trial progressed to the metastatic state.

Additionally, analyses exploring different HRQoL scenarios were included in the CS for this CDF exit review (Section A.11) as follows:

1. PF utilities at general population levels (PF=0.79, PF=0.76): decreased the ICER BY £398 compared to the base-case

2. Inclusion of AE dis-utilities: decreased the ICER by £1 compared to base-case

We have also reviewed the health state utility values applied in recent NICE appraisal in NSCLC (TA713, TA653, TA531).

TA653 evaluated osimertinib for EGFR T790M mutation-positive advanced non-small-cell lung cancer.[11] Utility values applied in the economic analysis for this appraisal were derived from the AURA2 trial, which only enrolled patients with EGFRm. The utility values derived from this cohort are therefore not applicable to the population under scope for this CDF review.

TA531 evaluated pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer.[12] The utility values applied in the Company base case have been redacted from all committee papers published on the NICE website. Therefore, we have been unable to conduct a scenario analysis based on this appraisal.

TA713 appraised nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy.[13] In the Company's base case analysis during CDF review, a utility value of 0.713 was applied in the progression-free health state. This was aligned to the committee's preferred assumptions from the original submission. As this appraisal was in a metastatic population, we have applied this utility value to the progressed disease health state in this economic model. Results for this scenario analysis are provided below. Reducing the utility value for the progressed disease health state to 0.713 has improved the ICER by £539 (£11,719 to £11,180).

Table 8: Results of the HRQoL scenario analysis – applying a utility value of 0.713 to the PD health state

Treatment	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	**£11,180**

Placebo	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Costs and resource use

B6. Priority: Updated data for post-discontinuation disease-related anti-cancer therapy use in the PD-L1 ≥1% group in the PACIFIC trial was used to inform subsequent treatment use in the economic model.

a. The proportion of patients per treatment arm per subsequent immunotherapy that was used as input for the economic model seems inconsistent with the proportion of patients per treatment arm per subsequent immunotherapy as reported in Table 3 of Appendix A (e.g. subsequent treatment sheet, cells V17 and W17 of the economic model report [redacted]% and [redacted]% of subsequent nivolumab for the durvalumab and placebo strategies respectively, whereas these percentages are [redacted]% and [redacted]% for the durvalumab and placebo strategies respectively in Table 3 of Appendix A). Please justify this inconsistency and/or provide a corrected economic model.

b. Based on clinical opinion and SACT data, please justify per treatment arm whether all subsequent treatments as reported in the PD-L1≥1% group in the PACIFIC trial are also given in current NHS clinical practice. If not, please provide a scenario analysis removing those treatments that are not used in NHS clinical practice

c. Please justify that the use of subsequent immunotherapies in both arms of the PACIFIC trial (i.e. third line of treatment) reflects current NHS clinical practice.

Response:

The proportion of patients per treatment arm per subsequent immunotherapy was expressed as a proportion of patients that had progressed in the economic model and expressed as a proportion of the overall cohort in the Appendix. No corrections are required.

Subsequent therapy data was not collected via the SACT dataset. Subsequent treatments in the PACIFIC trial were reviewed by clinical experts during a series of

interviews. Clinicians confirmed the choice and proportions of subsequent therapies reported in the PD-L1 ≥1% group were broadly aligned with their experience in clinical practice based on the high-level summary presented in Table 7 in the CS.[8] However, as outlined in the CS, the majority of clinicians confirmed that patients in England do not receive re-treatment with immunotherapy as part of standard clinical practice. 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.[2] Hence, patients who have received durvalumab for treatment of locally advanced unresectable stage III NSCLC would not routinely receive another PD-1/L1 inhibitor as a subsequent therapy upon disease progression.

The Company has re-reviewed table 11 in the Company CS against available NICE appraisal guidance and can clarify the following treatments are not routinely used for treatment of NSCLC in NHS clinical practice: ramucirumab, irinotecan and the tegafur/ gimeracil/ oteracil combination.

While there are is no formal TAG published for the cytotoxic chemotherapies docetaxel, gemcitabine and vinorelbine, the Company assumes these are routinely used in NHS clinical practice as they are listed in the BNF with indications in NSCLC.[14]

A scenario analysis removing use of subsequent immunotherapy in the durvalumab arm and removing ramucirumab, irinotecan and the tegafur/ gimeracil/ oteracil combination in both treatment arms has been conducted, which reduces the ICER by almost £3,800 compared with the base-case. The results are provided below.

Table 9: Results of the scenario analysis removing treatments not routinely used in NHS clinical practice

Treatment	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	**£7,936**
Placebo	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

The Company would like to clarify there is no ‘third line’ option in the model structure. As outlined in section A.7.3 in the CS for this CDF exit review, a one-off cost is accrued in the model for patients who experience disease progression. This cost is informed by the type of therapy, the required therapy dose, the dosing schedule, the unit drug cost, and the duration of therapy. The required therapy dose, dosing schedule and unit drug costs have remained unchanged from the original cost-effectiveness model.

All immunotherapies listed as subsequent therapies in the PACIFIC trial have received a positive NICE recommendation for routine use for treatment of metastatic NSCLC (see Table 10). As described above, clinicians confirmed that subsequent immunotherapy use was aligned with their experience in clinical practice based on the high-level summary presented in Table 7 in the CS for the placebo arm, but would not expect patients treated with durvalumab to receive further immunotherapies.[8] This is also outlined in the Blueteq criteria for use.[2]

Table 10: Overview of Immunotherapies recommended for routine use for treatment of advanced and metastatic NSCLC in NHS clinical practice

Immunotherapy	TA	Indication
Pembrolizumab	683[15]	Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC
	531[12]	Pembrolizumab for untreated PD-L1 positive metastatic NSCLC
	600[16]	Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous NSCLC *Note: CDF review complete, FAD published detailing positive recommendation, awaiting TAG publication*
	428[17]	Pembrolizumab for PD-L1 positive NSCLC after chemotherapy
Nivolumab	713[13]	Nivolumab for PD-L1 positive locally advanced non-squamous NSCLC after chemotherapy
	655[18]	Nivolumab for advanced squamous NSCLC after chemotherapy
Atezolizumab	705[19]	Atezolizumab monotherapy for treatment of untreated PD-L1 positive advanced NSCLC (PD-L1 expression on at least 50% of tumour cells or 10% of tumour-infiltrating immune cells)
	584[20]	Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel for treating metastatic NSCLC in patients who have not received previous treatment for their metastatic NSCLC and have PD-L1 TPS 0% - 49%
	520[21]	Atezolizumab monotherapy for treating locally advanced or metastatic NSCLC after chemotherapy
Key: NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; TPS, tumour proportion score		

Validation

B7. In the CS, the OS rates reported in the PACIFIC trial were externally validated using OS data from the SACT dataset. Please also externally validate the TTD, TTP, PFS and PPS data reported in the PACIFIC trial using the SACT dataset, if possible.

Response:

As outlined in the data collection arrangement (provided as Appendix D to the company CDF review submission and available online),[9] during the managed access agreement period, Public Health England collected data via the SACT dataset to provide information on overall survival and duration of therapy. TTD, TTP, PFS and PPS data were not collected as part of this agreement and as such, is not reported in

the SACT report or secondary survival analysis, provided as Appendix B and C respectively to the company CDF review submission.

While the 5-yr PFS data from the PACIFIC trial could not be externally validated using the SACT dataset, this data was externally validated in a series of clinical expert interviews.[8] The clinicians confirmed that the 5-yr PFS outcome of the both the durvalumab and placebo arms for the PD-L1≥1% were consistent with their experience in clinical practice. However, they did acknowledge that their experience of using durvalumab in clinical practice is limited to approximately 3 years.[8]

The Company proposed presenting RWE for PFS outcomes from the PACIFIC-R study to confirm generalisability of the PACIFIC data, as outlined in the terms of engagement pro-forma. However, at the kick-off meeting this was deemed unnecessary due to the availability of the SACT dataset. PACIFIC-R is an international observational study which enrolled patients who received durvalumab through the early access programme from September 2017 – December 2018. 701 patients in PACIFIC-R had PD-L1 expression ≥1% and this group achieved a median PFS of 22.4 months (95% CI: 18.7, 25.5).[22] Importantly, 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.[4] As sequential CRT is associated with poorer outcomes, it is logical to assume patients in the PACIFIC-R study may achieve a lower median PFS compared to patients in the PACIFIC trial. Overall, this RWE is supportive of the PFS outcomes for the PACIFIC PD-L1 ≥1% group treated with durvalumab, who achieved a median PFS of 24.9 months (95% CI: 16.9, 38.7).[23]

As outlined in the CS for this CDF exit review, time on treatment data from the SACT dataset was available and could be considered a proxy for TTD. The median actual time on treatment in the PACIFIC trial was 41.7 weeks and median treatment duration for the SACT cohort was 10.3 months.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

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

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

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**BTOG/NCRN**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**BTOG : Charity** NCRN national cancer research network
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	**BTOG Sponsorship for annual conference**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**None**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve cure rates following chemoradiotherapy for stage 3 inoperable NSCLC. This is also likely to delay any recurrence. These cancers have a high risk of recurrence often due to location and the propensity for metastases
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	This is essentially adjuvant treatment following chemoradiotherapy. CT scan is performed at the end of concurrent treatment to make sure there is no progression and then durvalumab for 12 months is recommended

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The survival for these patients is approaching 50% at 4 years. Median OS in Pacific study (reported 2020) for durvalumab: 47.5m vs 29.1m for placebo. Surgical series suggest 40% at 5 years for those cancers that were operable. Pacific study recruited those stage 3 cancers that were inoperable so generally higher stage than in surgically resectable series.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently inoperable stage 3 should be treated with concurrent chemoRT but due to patient and clinician reasons very few of these patients receive the SOC. Most end up having sequential treatments or palliative radiotherapy alone. Sequential treatment patients are currently ineligible for durvalumab.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Introduction of durvalumab has led to critical appraisal of these cases so that all stage 3 patients that can receive concurrent chemoRT do so. Stage 3 NSCLC is a very diverse stage and can vary significantly in volume and distribution of disease and mediastinal lymph nodes

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is significant variation throughout the country and one report showed that the number of patients receiving CCRT varies between 10-60% of all eligible stage 3 patients. There are patient and clinician reasons for this.
• What impact would the technology have on the current pathway of care?	Currently adapted in SOC and should now go to specialised commissioning within NICE funded drugs. Numbers are small but prevalence is high as required to be given for 12 months
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Currently adapted through CDF
• In what clinical setting should the technology be used? (For example,	Specialist care only

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Already absorbed
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	These are being shown in the RCT as 50% survival rate at 4 years
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes as prevents or delays recurrence

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Currently only available for PDL1 positive or unknowns (if lack of tissue). All PDL1 were randomised in the trial and the survival data is from the ITT population. A bigger advantage was seen in the PDL1 positives
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	IV treatment every 4 weeks. Usual toxicity support required with CPI therapy. Requires monitoring and attendance by patient for IV treatment

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Make sure no progression on chemoRT and on completion
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Delay recurrence. More chance of cure. Hypothyroidism and hypopituitarism most common long term effects requiring life long treatment
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	As survival better with durvalumab at 4 years. Beginning to believe that this may be better than surgery for stage 3 patients

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes a big change and allowed more patients to receive the best for their stage ie. Concurrent chemoRT
• Does the use of the technology address any particular unmet need of the patient population?	As above
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Pneumonitis risk is probably greater in RWE. Chemotherapy optimisation is likely required to weekly treatment during CCRT
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	WE have long term data on survival HR 0.71 in the ITT population

21. How do data on real-world experience compare with the trial data?	Compares well but need to get more units/centres giving concurrent chemo RT for eligible patients
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. Consider whether these issues are different from issues with current care and why.	None
Topic-specific questions	
Key messages	

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

- HS 0.71 in ITT population
- OS at 4 years is 49.6m for durva vs 36.3m for placebo
- Need to give to all patients irrespective of PDL1 as per ITT population OS difference
- Increase cure rates for the first time in NSCLC
- Need to improve access for patients to CCRT as huge variation in practice throughout he country

Thank you for your time.

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Professional organisation submission

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted] **on behalf of** [redacted], [redacted]

2. Name of organisation	**Royal College of Radiologists**
3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Radiologists (RCR) is the professional membership body for doctors specialising in the fields of clinical radiology (including interventional radiology) and clinical oncology. We provide leadership to improve the standard of medical practice and training across both disciplines. We engage with our Fellows, members and multiple clinical partners, combining the latest research with the development of guidelines to support clinical radiology and clinical oncology patient care. This enables us to effectively educate and support doctors throughout their career by providing practical guidance and supporting individuals and their clinical services to facilitate better patient outcomes. We are mostly funded through membership and exams etc.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or	**No**

comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For	See Section 23 – Key messages.

example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	See Section 23 – Key messages.
8. In your view, is there an unmet need for patients and healthcare	See Section 23 – Key messages.

professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	See Section 23 – Key messages.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	See Section 23 – Key messages.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is	See Section 23 – Key messages.

from outside England.)	
• What impact would the technology have on the current pathway of care?	See Section 23 – Key messages.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See Section 23 – Key messages.
• How does healthcare resource use differ between the technology and current care?	See Section 23 – Key messages.
• In what clinical setting should	See Section 23 – Key messages.

the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	See Section 23 – Key messages.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	See Section 23 – Key messages.
• Do you expect the technology to increase length of life	See Section 23 – Key messages.

more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	See Section 23 – Key messages.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	See Section 23 – Key messages.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or	See Section 23 – Key messages.

healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	See Section 23 – Key messages.

include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	See Section 23 – Key messages.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	See Section 23 – Key messages.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	See Section 23 – Key messages.
• Does the use of the technology address any particular unmet need of the patient population?	See Section 23 – Key messages.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	See Section 23 – Key messages.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	See Section 23 – Key messages.
• If not, how could the results be extrapolated to the UK setting?	See Section 23 – Key messages.
• What, in your view, are the most important outcomes, and were they measured in the trials?	See Section 23 – Key messages.
• If surrogate outcome measures were used, do they adequately predict long-term	See Section 23 – Key messages.

clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	See Section 23 – Key messages.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	See Section 23 – Key messages.
21. How do data on real-world experience compare with the trial data?	See Section 23 – Key messages.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	See Section 23 – Key messages.
22b. Consider whether these issues are different from issues with current care and why.	See Section 23 – Key messages.
Topic-specific questions	
Key messages	

23.

The scope document, outlining the use of adjuvant durvalumab following chemoradiation for unresectable stage II/III NSCLC, is in keeping with the published evidence (December 13, 2018 N Engl J Med 2018; 379:2342-2350 DOI: 10.1056/NEJMoa1809697).

There are no competing medications in this setting of an adjuvant maintenance treatment and the trial demonstrated significantly improved progression-free survival and overall survival for patients. It has been commented that the placebo arm did show a lower than expected progression-free survival as a comparator at interim analysis (published 2017) but despite this, the overall survival analysis (published 2018) shows significant improvement in the durvalumab arm.

The G3 and G4 toxicities demonstrated in the trial for the durvalumab arm are significant (30.5%) and therefore patients should

1) Be fully informed of the risks

2) Be well enough to undergo the treatment

3) Have no major contraindications to immunotherapy

The trial did not publish details of sizes of radiotherapy treatment volumes used. Given that lung radiotherapy can cause radiation pneumonitis and immunotherapy can also cause pneumonitis, clinicians should be asked to keep in mind the risks with both treatment modalities causing lung inflammation, fibrosis and scarring. In cases where a large lung volume is treated with radiotherapy, the resulting reduction in baseline lung function may mean a patient on durvalumab, who develops immune-related pneumonitis, may have much lower respiratory reserve post-radiotherapy to cope with this.

Despite the caution needed for adverse events, durvalumab following chemoradiation is the first intervention in this setting to show such a significant survival benefit; this is important for this group of patients where overall survival has been disappointing and not improved despite technological advances in radiotherapy.

I therefore would strongly support NICE guidance for the use of durvalumab following radical chemoradiation in unresectable NSCLC (stage II or III) within the parameters used in the PACIFIC Trial.

Thank you for your time.

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

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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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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.

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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

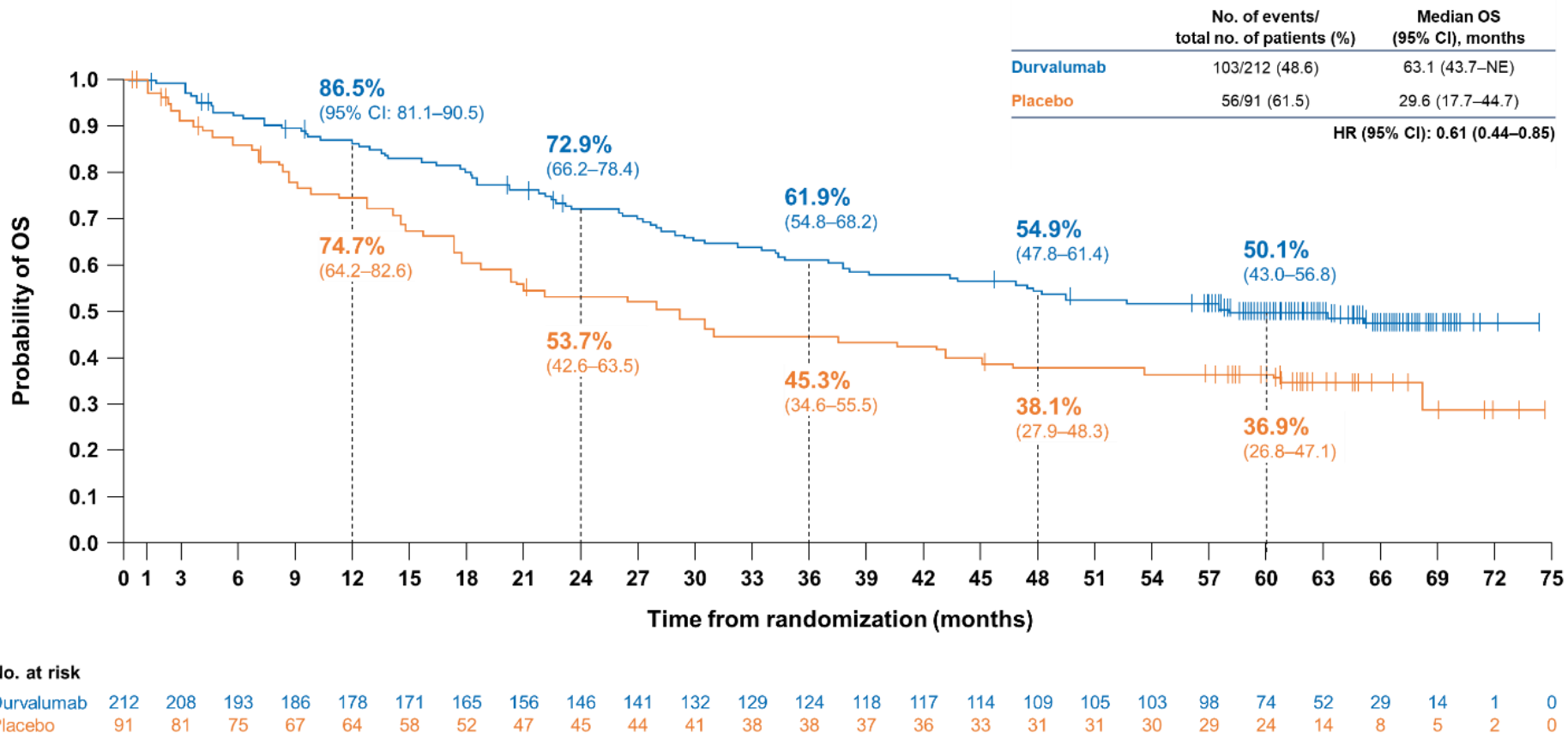
Sources: Table 6, CS[2] Appendix A, CS[10], Appendix C, CS[11] and Table 14, 2018 CS[9]

[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

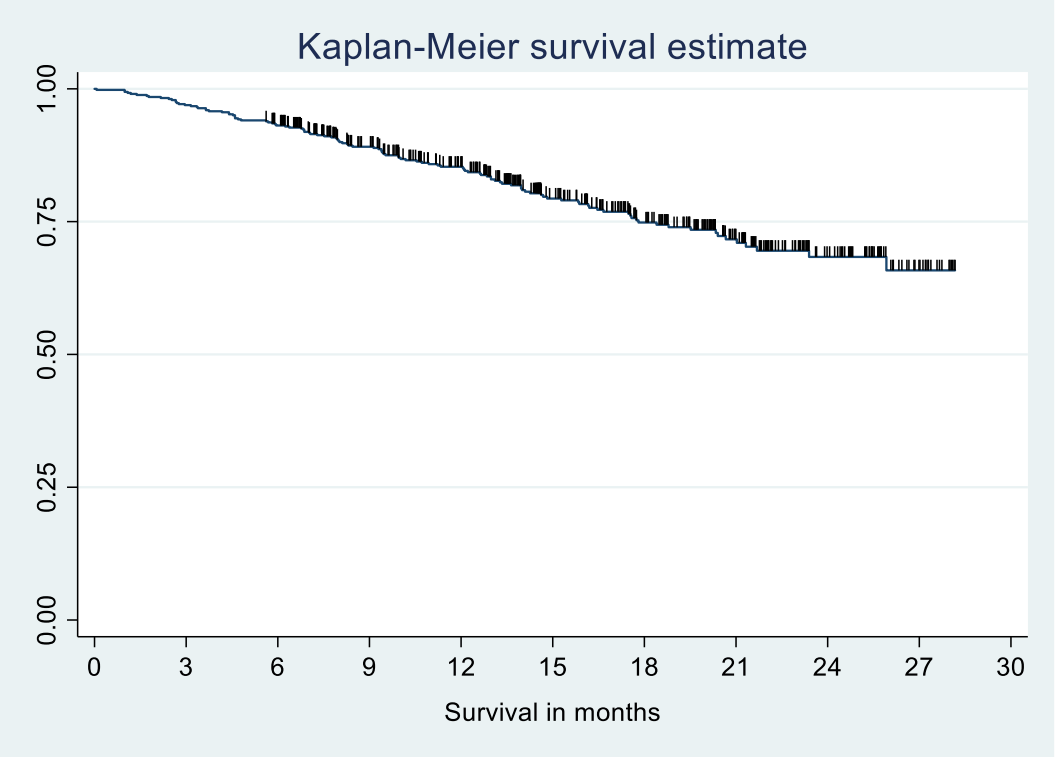
[c]The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties
CI: confidence interval; DCO: data cut-off; PD-L1: programmed death-ligand 1; NA; not applicable; NE: not estimable; NR: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

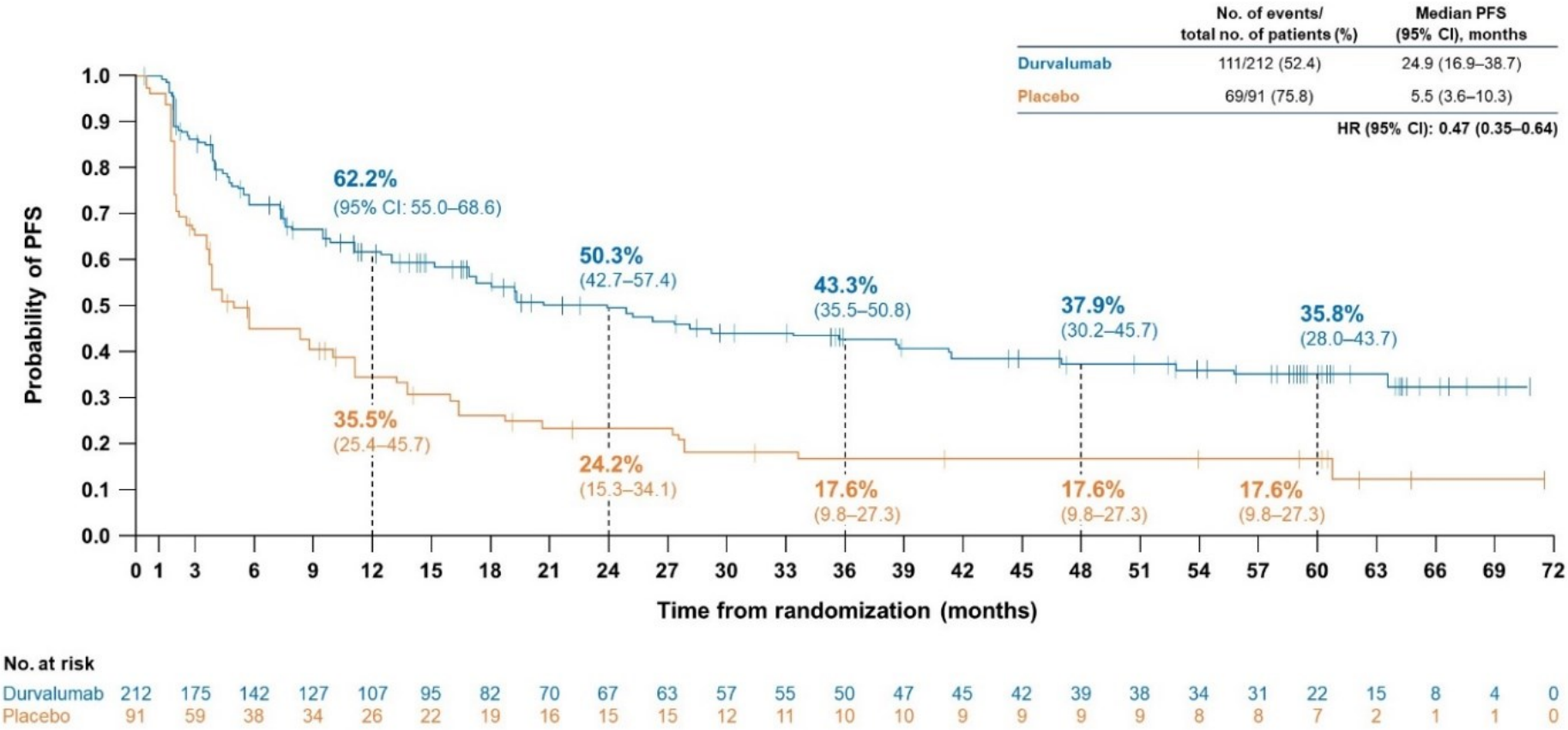
[b]calculated using the Kaplan-Meier technique

[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.

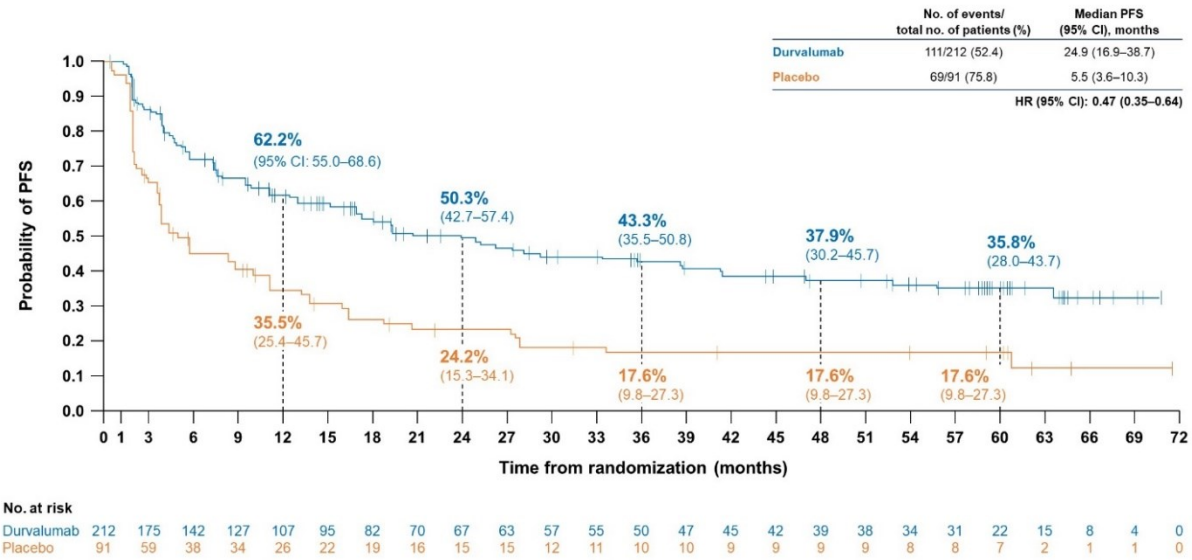
d) There were limitations in the company's ability to externally validate modelled PFS, OS and TTD, based on limited data availability and lack of clinician's long-term experience with durvalumab.

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

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **10am on Monday 21 February 2022** using the below comments table.

All factual inaccuracies will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Summary of Company response to the ERG report

The Company would like the thank NICE and the ERG for the opportunity to review the ERG report. Factual inaccuracies identified by the Company are presented in this document.

In additional to the issues outlined below, the Company would like to express their concern that the executive summary does not accurately capture the ERGs key conclusions regarding adherence to assumptions or the efforts of the Company in the CS and the clarification letter response to provide assurances regarding any remaining uncertainties. Overall, the Company considers the executive summary provides a negative reflection of our adherence to assumptions within the reasonable bounds of the time available and within the scope of this appraisal. The Company would like to ask the ERG to consider revising the executive summary to more fairly reflect our adherence to assumptions and the conclusions made by the ERG in the more detailed sections of the document. Proposals for these revisions are also included in the sections below.

The Company also request that the ERG include several of the scenario analyses provided by the Company in the CS and the clarification letter, which address some of the uncertainties highlighted by the ERG report. In response to Company Issue 3, we have provided base case and scenario analyses using the Q2W dosing regimen durvalumab (Table 1).

The key inaccuracies are summarised below and further detailed in the following pages.

- **Company issue 1: Availability and use of datasets for patients whose tumours express PD-L1 on ≥1% of tumour cells vs. patients whose tumours express PD-L1 on ≥1% of tumour cells and who have unknown PD-L1 expression and associated rationale**
    - The Company believe statements and narrative throughout the ERG report regarding the availability and use of appropriate datasets do not accurately reflect the presentation of data in the CS or clarification letter. In particular, the Company would like to ensure it is clear that both the full SACT dataset and the SACT OS secondary sensitivity analysis of patients whose tumours express PD-L1 on ≥1% of tumour cells (hereafter referred to as PD-L1 ≥1%) were used and referenced in the CS and both reports were provided as appendices at the time of the submission.
    - The Company request a number of changes regarding this issue, including the addition of the following sentence at the end of the statement under Assumption 1 on page 9 "*Therefore, this assumption was adhered to in the CS"*. We also request the cell in table 2.1 in the column indicating whether the assumption is adhered to in the Company submission states "Yes".

- **Company issue 2: Sources of external validation of PFS results from the PACIFIC trial**
    - Statements regarding availability of PFS data from the SACT dataset are inaccurate. PFS data was not collected via the SACT dataset.
    - The Company believe it is misleading to describe the PACIFIC-R dataset as 'suboptimal' and request this is revised to 'conservative'.
- **Company issue 3: Equivalence of clinical efficacy and safety of the 10mg/kg Q2W dose and the 1500mg Q4W dose**.
    - The ERG report questions the validity of the Company conclusion of equivalence of these doses in several instances. The Company would like to highlight that the EMA has published a summary on their website stating that *"…there are no anticipated clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks in locally advanced NSCLC*." While the Company are aligned with this summary, we believe it is misleading for the ERG to suggest these are the Company conclusions alone.
    - The Company would also like to highlight that additional responses to the EMA were provided to address their questions regarding [redacted]. The Company are able to provide further details if requested, however, the summary statement published by the EMA represents their final conclusion.
- **Company issue 4: Availability of HRQoL data and uncertainties regarding health state utility values**.
    - The Company believe it is factually inaccurate to state that QoL data is an 'outstanding issue' or that health state utility values are associated with 'continued' uncertainty. Neither quality of life data not health state utilities were described as key uncertainties in the original appraisal. As such, further collection of HRQoL data was not included in the DCA. The Company consider it misleading to suggest that the required evidence to address this uncertainty has not been provided, especially in light of the additional scenario analysis provided in the clarification letter response.
- **Company Issue 5: Statements suggesting the Company has not used updated survival data to fully explore the most appropriate method to extrapolate survival outcomes are factually incorrect**
    - The ERG report claims that the Company has not used updated survival data to fully explore the most appropriate method to extrapolate survival outcomes. This statement could mislead the reader into believing the Company did not use updated survival data to extrapolate survival outcomes in the model, which is incorrect.

- This statement was made as the ERG report argued that an OS/PFS modelling approach (partitioned survival analysis) would address potential bias in the model. However, the report fails to acknowledge that this modelling approach would violate the ToE, by requiring fundamental changes to the model structure. The report also ignores the robust evidence and rationale provided by the Company at clarification response, which confirmed the OS/PFS approach is still subject to a significant logical inconsistency.
- The report argues that the lognormal distribution in the durvalumab arm produces more plausible OS estimates at 5 years but fails to compare the estimated PFS at 5 years with observed data, which is highly misleading.
- **Proposed amendment to executive summary (Page 9):** *"Assumption 3: Survival outcomes: The ERG considers that this assumption was adequately adhered to, given the ToE precluded any change in model structure. Exploring an overall survival (OS)/ progression-free survival (PFS) modelling approach might have provided some insights (see Sections 2 and 4 for further details) but such analysis would have had significant limitations due to the PFS and OS curves crossing."*

- **Company Issue 6: Statements that the Company have not used updated survival data to inform the appropriateness of a cure assumption are factually incorrect**
  - The statements made in Sections 1.1 (Page 9) and 2.2 (Page 16) of the report contradict Section 4.5 (Pages 42-43). The former sections incorrectly claim that the Company did not explore the appropriateness of a cure assumption using updated survival data from PACIFIC. The latter section (Section 4.5) clearly outlines the rationale and evidence provided by the Company in response to the ERG's request to explicitly model cure. As Section 4.5 confirms the Company did use updated survival data to inform the appropriateness of a cure assumption, it is in direct contradiction to the earlier statements made in the report.
  - **Proposed amendment to executive summary (Page 9):** *"Assumption 4: Cure: The company sufficiently updated survival data from the PACIFIC trial to explore the appropriateness of a cure assumption. 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."*
- **Company issue 7: Statements that the Company have not used updated survival data to fully explore the treatment effect after stopping treatment are factually incorrect**

- The ERG report states in Sections 1.1 (Page 9) and 2.2 (Page 16) that the Company did not fully explore the treatment effect after stopping treatment using updated survival data. These two statements are factually incorrect and are contradicted by Table 2.1, which states that the Company did address this assumption in the CS. The Company fully explored the treatment waning effect in Section A.7.1 of the CS.
- **Proposed amendment to executive summary (Page 9):** *"Assumption 5: Treatment effect duration: The company did fully explore the treatment effect after stopping treatment (as detailed in Section 4)".*

- **Issue 8: Typographical and data errors**
  - The Company have corrected several typographical and data errors throughout the report.

Table 1: Base case and scenario analyses (Q2W dosing)

Scenario	Values	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Base case analysis	-	[redacted]	[redacted]	**£12,122**
Alternative PFS distributions (durvalumab)	Gompertz	[redacted]	[redacted]	**£13,259**
ERG preferred analysis: Alternative PFS distributions (durvalumab)	Lognormal	[redacted]	[redacted]	**£23,077**
Cure assumption	Assume PF durvalumab and placebo patients are 'cured' and assigned general population mortality at 5 years	[redacted]	[redacted]	**£13,175**
Treatment waning cut-off	10 years	[redacted]	[redacted]	**£12,791**
Utility	Utilities at general population levels (PF = 0.79, PD = 0.76)	[redacted]	[redacted]	**£11,710**
	Include AE dis-utilities	[redacted]	[redacted]	**£12,121**
	PD utility = 0.713 (TA713)	[redacted]	[redacted]	**£11,565**
Vial sharing	Assume 30% vial sharing for subsequent therapies	[redacted]	[redacted]	**£11,744**

Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.

Issue 1 Availability and use of datasets for patients whose tumours express PD-L1 on ≥1% of tumour cells vs. patients whose tumours express PD-L1 on ≥1% of tumour cells and who have unknown PD-L1 expression and associated rationale

Issue 1a: Details regarding availability and use of the SACT secondary sensitivity analysis and rationale for inclusion of patients with unknown PD-L1 status are factually incorrect			**ERG response**
Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Section 1.1, page 9 "*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), 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)"*	The Company proposes the statements on page 9 is revised as follows: *"With respect to the generalisability of the PACIFIC trial data to the real-world United Kingdom (UK) setting, the ERG notes that the full SACT dataset included patients with unknown PD-L1 status. However, this inclusion of patients with unknown PD-L1 status is aligned with the Blueteq criteria for prescribing, which allows durvalumab treatment for patients in whom PD-L1 testing is not possible or who have an unquantifiable result. This criteria was included to ensure that patients who are unable to undergo PD-L1 testing or who receive an inconclusive PD-L1 test result are not denied access to this*	The Company would like to clarify several points regarding the availability of SACT data which we believe are not accurately reflected in the ERG report: • The full SACT report included all patients treated with durvalumab during the CDF period. The report included patients with PD-L1 ≥1% and patients in whom PD-L1 testing was not possible, the PD-L1 result was unquantifiable and patients whose PD-L1 expression was not captured. The SACT report was supplied as Appendix B to the CS, both of which were submitted by the	Amended to acknowledge the slight difference.

	highly efficacious therapy. However, a secondary sensitivity analysis of OS was provided that included only patients with PD-L1 ≥1% in line with the scope for this appraisal. The results of this secondary sensitivity analysis were highly similar to the full SACT dataset and were included in the CS to support the generalisability of the OS results for the PACIFIC PD-L1 ≥1% group. Therefore, this assumption was adhered to in the CS."	Company on 10th January 2022 • An overall survival secondary sensitivity analysis of the SACT dataset was provided prior to the SACT review meeting on 18th October 2021. This report provided an OS analysis of the SACT dataset including only patients with PD-L1 ≥1%. This secondary sensitivity analysis was provided as Appendix C to the CS, both of which were submitted by the Company on 10th January 2022 • Both the full SACT report and OS secondary sensitivity analysis were used and referenced throughout the CS where appropriate. The use of appropriate datasets was further clarified by the Company in response to QA1 of the clarification questions, provided on 1st February 2022. The clarification letter response also reiterated that the full SACT report and the SACT	
Section 1.2, page 10 *"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."* **Section 2.2, page 15** *"…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 Company propose, either: • the statements on page 10 and 15 and all references pertaining to issues with lack of generalisability between the SACT report and PACIFIC ≥1% cohort are removed. Or, • An additional clarifying sentence is added at the end of both of these statements on page 10 and 15 as follows: "*However*, *in order to align the SACT population with the scope for this appraisal, i.e. patients with PD-L1 ≥1%, an*		Not a factual inaccuracy.

the SACT cohort had unknown PD-L1 status."	*OS secondary sensitivity analysis was provided which removed the results of patients with unknown PD-L1 status."*	secondary sensitivity analysis of the PD-L1 ≥1% group were both provided in their entirety at the time of the CS as Appendix B and C, respectively • As stated in section A6.2.2.2 of the CS and reiterated in response to QA1 of the clarification questions, it should be noted that the OS secondary sensitivity analysis results for patients with PD-L1 ≥1% were used to support the generalisability of the OS results for the PACIFIC PD-L1 ≥1% cohort as it mostly closely matched the population for appraisal as set out in the scope for this appraisal. This approach was described in the CS and Appendix C was referenced as the data source The SACT secondary sensitivity analysis of OS for patients with PD-L1 ≥1% status was provided and	
Section 2.2 page 15, "*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 that showed that the results for 12 months and 24 months excluding patients whose PD-L1 status was unknown were identical to those including these patients (see Section 3.2.1)"* **Section 2.2 page 21** "*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."*	The Company propose the statement regarding availability of the SACT data omitting the patients with unknown PD-L1 scores and in whom PD-L1 testing not possible or quantifiable on page 15 and page 21 is revised as follows: "*The Company clarified the OS results from the SACT dataset reported in the CS to support the generalisability of the PACIFIC PD-L1 ≥1% cohort were obtained from the SACT OS secondary sensitivity analysis including only patients with confirmed PD-L1 ≥1% status. These OS results were highly similar to the OS results from the full SACT dataset."*		Not a factual inaccuracy. However, text has been added to acknowledge the provision in the CS of the overall survival secondary sensitivity analysis.

Table 2.1, Assumption 1, page 17 Column 3*: "Yes, for PACIFIC trial data. Inconsistent for SACT data"*	The Company propose this statement is revised to "*Yes*."	referenced at the time of the company submission. Therefore, the Company consider statements regarding issues with the generalisability of the PACIFIC PD-L1 ≥1% cohort to the SACT dataset to be factually inaccurate as the relevant dataset has always been available and used appropriately throughout the submission. The reason for inclusion of patients with unknown PD-L1 status in the SACT dataset was described in the Company response to the clarification letter (QA1), provided on 1st February 2022. Furthermore, table 3.1 in the ERG report itself states that the SACT dataset included patients for whom a "PD-L1 TPS could not be ascertained despite an intent and reasonable attempt to do so." It is misleading to any reader of the ERG report to state there is a lack of understanding for inclusion of patients with PD-L1 unknown status in the SACT report when it has clearly been described in several instances. The current phrasing of	
Section 3.1.1, page 20 *"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*."	The Company proposed the statement on page 20 is supplemented with an additional sentence as follows: "*An OS secondary sensitivity analysis of the SACT dataset including only patients with confirmed PD-L1 ≥1% status was provided to align with the population for appraisal. This secondary sensitivity analysis of patients with PD-L1 ≥1% were used in the CS to support the generalisability of the OS outcomes for the PACIFIC PD-L1 ≥1% group presented by the Company."*		Not a factual inaccuracy.
Table 3.1, page 23 No subgroups listed for the SACT dataset	The Company propose that the table is updated to include the SACT OS secondary sensitivity analysis of patients with confirmed PD-L1 ≥1% expression		Not a factual inaccuracy. However, text has been added to acknowledge the provision in the CS of the overall survival secondary sensitivity analysis.

Section 3.2.1, page 29 ***"…and** the SACT data is provided in Table 3.3"*	The Company propose that this statement is updated to: " *and the SACT OS secondary sensitivity analysis data for patients with PD-L1 ≥1% is provided in Table 3.3*"	the ERG report suggests this is an unresolved issue despite the Company having addressed the issue in their response to the clarification letter. The Company would like to ensure the ERG report contains a fair and accurate description of the data used in the CS, datasets supplied at the time of the CS and rationale provided by the Company.	
Section 3.2.1, page 29 **"***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)."*	The Company propose the statement is updated as follows: *"…survival rates appeared slightly lower in the SACT OS secondary sensitivity analysis cohort of patients with PD-L1 ≥1% (68% [95% CI: 62, 74]) than in durvalumab treated.."*		Not a factual inaccuracy.
Section 3.2.1, page 29 **"***It should also be noted that the SACT results for 12 months and 24 months excluding patients whose PD-L1 status was unknown were identical to those in Table 3.3."*	The Company proposes this statement is removed as the SACT results reported in table 3.3 are the results of the OS secondary sensitivity analysis, which included only patients with PD-L1 ≥1%		Amended to acknowledge the slight difference.
Table 3.3, page 30 Final column "SACT data"	The Company proposes this column header is changed to: *"SACT secondary sensitivity analysis of OS: PD-L1 ≥1% patients only (n=522)"*		Corrected.

Figure 3.2, page 32 Figure caption: "*Kaplan-Meier plot for overall survival, censored at 30th July 2021, in the SACT cohort*"	The Company proposes this caption is revised to the following, in line with the reference to Appendix C, which is the SACT OS secondary sensitivity analysis of patients with PD-L1 ≥1%: ***"Kaplan-Meier plot for overall survival, censored at 30th July 2021, in the SACT OS secondary sensitivity analysis of patients with PD-L1 ≥1%."***		
Section 3.3, page 37 *"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, 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)."*	The Company proposes this statement is revised to the following: "*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 included in the SACT dataset had unknown PD-L1 status. However, this inclusion of patients with unknown PD-L1 status aligned with the Blueteq criteria for prescribing, which allows durvalumab treatment for patients in whom PD-L1 testing is not possible or who have an unquantifiable result. This criteria*		Amended to acknowledge the slight difference.

	was included to ensure that patients who are unable to undergo PD-L1 testing or who receive an inconclusive PD-L1 test result are not denied access to this highly efficacious therapy. In order to align the SACT population with the scope for this appraisal, i.e. patients with confirmed PD-L1 expression on ≥1% of TCs, an OS secondary sensitivity analysis was provided which removed the results of patients with unknown PD-L1 status. The results of this secondary sensitivity analysis of patients with PD-L1 ≥1% were highly similar to the full SACT dataset and were included in the CS to support the generalisability of the OS results for the PACIFIC PD-L1 ≥1% group."		
Issue 1b: It is factually inaccurate to state the company refused to provide pooled analysis of PD-L1 unknown and PD-L1 ≥1% patients from the PACIFIC trial			
Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Section 2.2, page 15 ***"****The company refused to perform the analysis including unknown PD-L1 status on the basis that the*	The Company proposed this statement is reworded as follows: "*The company did not provide an analysis including patients with*	In the clarification letter response (QA1), the Company stated a pooled analysis of patients with PD-L1 status unknown and PD-L1 ≥1% from the PACIFIC trial had not been	Amended to reflect the deviation from scope.

reason that the trial did not mandate PD-L1 testing."	*PD-L1 unknown status as this analysis had not been conducted and was not within the scope of this appraisal. The Company also highlighted that even if the analysis were to be provided, there would be inherent differences in the PD-L1 unknown patient population in the PACIFIC trial compared with the SACT dataset, as the PACIFIC trial did not mandate PD-L1 testing.*"	conducted. The Company also provided justification for why such an analysis would be inappropriate on the basis it lacks robust scientific rationale. The Company also explained even if such an analysis was available, it would not represent a dataset generalisable to the full SACT dataset as PD-L1 testing was not mandated in the PACIFIC trial. It is not accurate to state the company refused to provide this pooled analysis when the Company clearly stated this analysis was not available. Furthermore, it is misleading to suggest the Company refused to provide this analysis on the basis that: • The Company provided rationale to explain why such an analysis had not been conducted • Analysis of the PD-L1 unknown population was out of scope at the original appraisal and is out of scope for this CDF exit appraisal. The population for appraisal was clearly defined as	

		patients with PD-L1 expression on ≥1% of TCs and any analysis of or including PD-L1 unknown patients would be considered out of scope for this appraisal • The Company provided rationale for inclusion of the PD-L1 unknown patients in the Blueteq criteria as part of the response to clarification question Q1A. This included an explanation as to why the PD-L1 unknown patients were not included in any analysis in the original appraisal or in the CDF exit appraisal	

Issue 2 Factual inaccuracies regarding sources of external validation of PFS results from the PACIFIC trial

Issue 2a: It is factually inaccurate to state the SACT report included PFS outcomes and inaccurate to reference PFS outcomes to either the SACT report or SACT secondary sensitivity analysis of OS in patients with PD-L1 ≥1%			**ERG response**
Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Section 3.1.1, page 20	The Company propose the references to PFS data	The SACT dataset did not collect PFS outcomes	Corrected.

"*The other source of evidence is the SACT dataset… It provides evidence on progression-free survival (PFS), overall survival (OS) and treatment duration for all patients…"* *"…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, PFS OS and treatment duration."*	available from the SACT data set on page 20 are removed.	and was never intended to serve as an evidence source for PFS outcomes. All references to PFS outcomes derived from the SACT data set should be removed. Appendix C, supplied at the time of the CS, is an appendix containing the SACT secondary sensitivity analysis of OS in patients with PD-L1 expression on ≥1% of TCs. It does not contain any PFS evidence and was not used to support the PFS data supplied in the CS.	
Section 3.2.2, table 3.4, page 33-34 "Appendix C, CS" is listed as a reference source for table 3.4	The Company propose "Appendix C, CS" is removed as a reference source from table 3.4		Corrected.

Issue 2b: It is misleading to describe the PACIFIC-R dataset as 'suboptimal' for providing external validity of the PFS outcomes from the PACIFIC trial			
Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Section 4.3, page 40 *"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."*	The Company propose the word 'suboptimal' is replaced with 'conservative' in the statement on page 40	The PACIFIC-R study did include patients treated with both sequential and concurrent CRT, whereas patients in the PACIFIC study were treated with concurrent CRT only. As outlined in the clarification letter response (QB7) at the time the PACIFIC-R PFS data was supplied, the Company highlighted that patients treated with sequential CRT typically experience worse clinical outcomes compared with patients treated with concurrent CRT. This was aligned with the commentary from clinical experts in section 3.2 of TAG578. Hence, the PFS outcomes from the PACIFIC-R trial should	Not a factual inaccuracy.

		be treated as conservative. While the Company acknowledge that the PACIFIC-R and PACIFIC trial populations are not exactly comparable due to this discrepancy in CRT modalities, the use of the word 'suboptimal' is misleading as the PACIFIC-R data is conservative in this context and yet still supportive of the PFS outcomes achieved in the PACIFIC trial.	

Issue 3 It is inaccurate to state the company concluded the equivalence of the 10mg/kg Q2W and 1500mg Q4W doses; this was concluded by the EMA and is published in their summary statement following the type II variation assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
General comment	If the ERG wish to question the validity of the conclusion that there are no anticipated clinically significant differences in efficacy and safety between durvalumab doses of 10mg/kg every 2 weeks or 1500mg every 4 weeks, as summarised in the EPAR	In the CS, the Company referenced all statements concluding equivalence in safety and efficacy of the Q2W and Q4W dose to the source "Imfinzi: EPAR – Procedural steps taken and scientific information after	It is not a factual inaccuracy to question the validity of the conclusion. However, amendments to the ERG report have been made to clarify that this was the

	document, the Company proposes the following changes:	authorisation". This document is in the public domain and is available for download from the EMA website. A pdf copy of the document was provided as part of the reference pack at the time of the CS. This document, authored by the EMA, states "*Based on the modeling and simulation of exposure, exposure-safety relationships and exposure-efficacy data comparisons, there are no anticipated clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks in locally advanced NSCLC.*" In response to the clarification letter, the Company submitted the full EMA Type II variation assessment report as a confidential reference. This report provided additional details regarding the data provided to the EMA and EMA assessment of this data in support of approving the 1500mg Q4W dose. While the Company acknowledge there is some additional critique of the data in this confidential report,	conclusion stated in the EMA report.
Section 1.1, page 9 *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* [redacted] *(see Section 2 for details)."*	• The statement on page 9 is either removed or updated to reflect the ERG are questioning the conclusion of the EMA rather than the Company		Not a factual inaccuracy.
Section 1.2, page 11 *"Evidence from a report by the European Medicines Agency (EMA) shows that* [redacted]	• The statement on page 11 is replaced with the following: *"The final conclusion of the EMA was that there are no clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks in locally advanced NSCLC. Therefore, no adjustments for clinical efficacy are required."*		Not a factual inaccuracy.

Section 2.2, page 15 *"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."* ***"**The ERG further questions the validity of the company's statement 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."*	• The first statement on page 15 is either removed or updated to reflect the ERG are questioning the conclusion of the EMA rather than the Company • The second statement on page 15 is removed • A final statement is added on page 15 stating: *"The final conclusion of the EMA was that there are no clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks in locally advanced NSCLC. Therefore, no adjustments for clinical efficacy are required."*	we would like to clarify that additional responses were provided to the EMA to resolve the questions regarding [redacted] It remains accurate that the EMA concluded they did not anticipate any clinically significant differences in efficacy and safety between the Q2W and Q4W doses. This conclusion was published in the summary column of the aforementioned publicly available EPAR document. It is both inaccurate and misleading to any reader of the ERG report to question the validity of the Company's statement of equivalent efficacy between these two doses when the EMA itself has published this statement.	The second sentence has been deleted.
Section 3.3, page 38 *"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* [redacted]	• Either, this entire section is removed or re-written as: "*There is 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. However, the final conclusion of the EMA is that that no clinically significant differences in efficacy and safety between durvalumab*		Not a factual inaccuracy.

[redacted] *Although some patients from whom the SACT data were obtained did receive 1,500 mg Q4W, this number [redacted] unknown.*"	*doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks in locally advanced NSCLC. Therefore, no adjustments for clinical efficacy are required."*		
Section 4.8, page 45 *"…and hence, any potential differences between the two dosing regimens regarding efficacy or safety were not reflected in the economic model."*	• An additional statement is added as follows: "*The final conclusion of the EMA is that that no clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks in locally advanced NSCLC. Therefore, no adjustments for clinical efficacy are required."*		Not a factual inaccuracy.

Issue 4 Statements that QoL data and health state utilities are associated with ongoing uncertainty and remain outstanding issues are factually inaccurate and misleading

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1, page 10 *"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 Company propose that an additional sentence is added to the statements on page 10, 11, 16 and 37 as follows: "*However, the Company did highlight that further collection of HRQoL data was not included in the DCA. They also included an additional analysis using an alternative HSU value in the progressed*	Issues regarding uncertainties associated with quality of life data and health state utilities were not outlined in the TAG for the original appraisal (TA578). As such, further collection of HRQoL was not included in the DCA.	Not a factual inaccuracy.

The ERG notes that this assumption was not adhered to in the CS (see Sections 2 and 4 for further details).” **Section 1.2, page 11** “*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”* **Section 2.2, page 16** ***“****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”* **Section 3.2.5, page 37** “*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*	*state to provide assurances of the minimal impact on the ICER.”*	Furthermore, due to the length of follow-up of the PACIFIC trial (now 5 years), it is high impractical to continue following up patients to obtain further HRQoL The Company outlined in the ToE proforma, CS (section A.7.4) and clarification letter response (QA3 and B5) that HRQoL data was not listed in the DCA for further follow up. The Company also outlined in the clarification letter response (QB5) that the approach to health state utilities was conservative. Despite this, an additional scenario analysis was presented by the Company using a health state utility in the progressed state from a recent appraisal in metastatic NSCLC to provide assurances to the ERG that the ICER was not significantly impacted by changes in the health state utility value. Some of the statements regarding lack of use of more	

in the CS (as detailed in Section 4).”		mature QoL data are misleading, as this was not described as a key uncertainty in the original appraisal, nor was the Company obligated to continue collecting this data.	
Table 2.1, assumption 6, page 17 The table states the Company did not provide rationale for not using more mature QoL from PACIFIC	The Company propose the rationale from the ToE proforma is added to the ‘rationale’ column in table 2.1 on page 17, as follows: “*Updated data on health-related quality of life was not collected in further data cuts of the PACIFIC trial. Therefore, utility values will remain unchanged from the original submission.”*		Not a factual inaccuracy.
Section 4.6, page 43 *“There continues to be uncertainty about health-related quality of life (HRQoL) in this population.”*	The Company propose this statement is removed, as HRQoL was not described as a key uncertainty in the original appraisal.		Not a factual inaccuracy.

Issue 5 Statements suggesting the Company has not used updated survival data to fully explore the most appropriate method to extrapolate survival outcomes are factually incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1, Page 9:	The Company propose that the statement on Page 9 is amended, as follows:	The statements made on Pages 9 and 16 are potentially	Not a factual inaccuracy. The most appropriate

"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)."* **Section 2.2, Page 16:** *"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*	*The ERG considers that this assumption was adequately adhered to, given the ToE precluded any change in model structure. Exploring an overall survival (OS)/ progression-free survival (PFS) modelling approach might have provided some insights (see Sections 2 and 4 for further details) but such analysis would have had significant limitations due to the PFS and OS curves crossing."* The Company propose that an additional statement is added to Page 16, as follows: *"During the kick-off meeting for this CDF exit appraisal, held 23rd November 2021, the Company was instructed by NICE that the model approach and structure should remain unchanged compared with the original submission."*	misleading as it appears to argue that the Company did not use updated survival data from the PACIFIC trial for this CDF appraisal, which is factually incorrect. The statements also fail to mention that the Company was explicitly instructed by NICE not to amend the model structure or approach during the kick-off meeting. The statement on Page 9 should also be consistent with the statement on Page 16, which confirms 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. In line with this understanding, there were no changes to the model structure. An OS/PFS modelling approach (partitioned survival analysis) was not conducted as it would require fundamental changes to the current model structure and therefore would violate the instructions given by NICE in the	method to extrapolate survival outcomes was not explored due to the model structure and this is already made clear.

to the model during the CDF review period unless NICE requests or agrees to this in advance." (p.6)[1"]		ToE and during the kick-off meeting.	
Section 1.3, Page 11 & Section 4.3, Page 40: *"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)."*	This statement should be amended as following: *"The ERG is not completely satisfied with the company's PFS/TTP/PPS approach as it assumes that PPS is equal in both arms."*	The original statement is misleading as it does not mention that OS/PFS approach is also associated with significant assumptions, the main assumption being that the lack of fundamental structural relationship between PFS and OS in the model itself. This statement also fails to mention that the Company have demonstrated (Response to ERG clarification question B2) that all clinically viable OS curves cross with PFS in the durvalumab and placebo arms. Therefore, the OS/PFS approach would result in logical inconsistencies.	Not a factual inaccuracy. In addition, the ERG requested to show that OS / PFS do not cross with the company's model structure and the company failed to provide this. Hence, it is not clear whether the company's approach addresses this issue at all – also there would be other ways of addressing this.
Section 4.3, Page 40 & Section 4.3, Page 41: *"… OS/PFS approach …"*	The Company request this phrase to be amended as follows: *"… OS/PFS approach (partitioned survival analysis) …"*	This is to be consistent with the language used in the ERG clarification letter (QB1) and the ERG documents produced during the original submission (TA578).	Not a factual inaccuracy.

Section 4.3, Page 40: *"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."*	This statement propose that an additional statement is added to Page 40, as follows: *"The Company also demonstrated in this CDF appraisal (Clarification letter response (QB1a)) that all clinically viable OS and PFS curves continue to cross when using the updated 5-year survival data from PACIFIC."*	This statement is misleading as it fails to mention that the Company demonstrated that all clinically viable OS and PFS curves still cross when updated survival data from PACIFIC (DCO5) is used. This statement implies that the OS/PFS approach is viable for this economic analysis with the new data, which is factually incorrect and undermines the Company's response to QB1a of the ERG clarification letter.	Not a factual inaccuracy, as above.
Section 4.3, Page 41: *"The ERG considers that an OS/PFS approach may have removed this bias."*	The Company request this statement is removed from the report.	This is a speculative statement and is highly misleading to the reader. The statement is misleading as it completely ignores the evidence presented by the Company in response to the clarification letter (QB1a) which shows the OS/PFS approach is associated with a significant logical inconsistency (i.e., the curves cross).	Not a factual inaccuracy.
Section 4.3, Page 41: *"The ERG explored alternative PFS models and found that the lognormal may be a plausible*	The Company request this statement is revised to also include the predicted PFS at 5 years in the economic model using log-normal ([redacted]), compared to	By omitting the PFS estimates at 5 years, this statement could mislead the reader into accepting that the log-normal	Not a factual inaccuracy.

alternative model for durvalumab PFS (third best statistical fit, [redacted] alive in model at five years).”	generalised gamma ([redacted]), Gompertz ([redacted]) and observed data from the PACIFIC trial ([redacted]).	distribution provides the most clinically plausible estimates for both OS and PFS for durvalumab at 5 years (out of all extrapolations), which is factually inaccurate. The Gompertz function provides the PFS estimate at 5 years ([redacted]) that is closest to observed data from PACIFIC ([redacted]). Therefore, it’s important that when selecting the most plausible parametric model, the estimated PFS in the model at five years is also assessed for its comparability to observed data.	

Issue 6 Statements that the Company have not used updated survival data to inform the appropriateness of a cure assumption are factually incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1, Page 9: *“The ERG considers that this assumption was not adhered to in the CS.”*	The company propose the statement on page 9 is revised as follows: *“The ERG considers that this assumption was adhered to in the CS and clarification letter response.”*	This statement is inconsistent with Section 4.5 of the ERG report (Pages 42-43). Section 4.5 summarises the evidence provided by the Company in response to the ERG’s request	Not a factual inaccuracy. The company did mention that PFS at 5 years was greater for durvalumab than placebo, and they cited expert opinion that being

		to explicitly model cure (ERG clarification response; QB2, QB3). This section confirms that the Company did use updated survival data to inform the appropriateness of a cure assumption. In QB2-QB3 of the ERG clarification letter response, the Company argued that the curative potential of durvalumab was reflected by the lack of a treatment waning effect. The Company also provided an exploratory simple cure analysis that assumed durvalumab and placebo patients are 'cured' at 5 years.	progression free at 5 years indicated potential cure, but this is not the same as using the updated survival data to inform the appropriateness of a cure assumption. This would have required an explicit reference to a prolonged plateau in the PFS curve, which was not demonstrated.
Section 2.2, Page 16: *"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."*	The Company request that this statement is removed as it is factually inaccurate.	As discussed in the row above, this statement is contradicted by Section 4.5 of the ERG report. This statement also incorrectly claims that the UK clinical expert feedback presented in the CS was solicited during the original submission (TA578). As noted in the CS reference pack, the feedback received from UK clinical experts in this CDF appraisal was derived via	See above.

		1:1 interviews that were conducted between November and December 2021.	
Section 2.2, Table 2.1, Page 17: The table states the Company did not provide rationale for not explicitly modelling cure.	The Company request that this row is amended to reflect the substantial evidence provided by the Company in the clarification letter response.	This row is inconsistent with Section 4.5 of the ERG report (Pages 42-43). Section 4.5 summarises the evidence provided by the Company in response to the ERG's request to explicitly model cure (QB2, QB3). This section confirms that the Company did use updated survival data to inform the appropriateness of a cure assumption.	See above.

Issue 7 Statements that the Company have not used updated survival data to fully explore the treatment effect after stopping treatment are factually incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1, Page 9: *"The ERG considers that this assumption was partly adhered to in the CS."* **Section 2.2, Page 16:** *"The company did not fully explore the treatment effect*	The company propose the statement on Page 9 is revised as follows: *"The ERG considers that this assumption was adhered to in the CS."* The company propose the statement on Page 16 is revised as follows:	The statements on Pages 9 and 16 are factually incorrect. They are also contradicted by Table 2.1, which states that the Company did address Assumption 5. In Section A.7.1 of the CS, the Company used updated progression-free survival data	Not a factual inaccuracy. Section 4 provides the detail as to why the ERG considers that this is not fully explored. Further detail is required.

after stopping treatment (as detailed in Section 4).”	*“The company fully explored the treatment effect after stopping treatment (as detailed in Section 4).”*	from PACIFIC to explore the potential for any treatment waning effect. The Company provided robust rationale as to why a treatment waning effect is clinically implausible and also explored the impact of a 10-year treatment waning effect in a scenario analysis (CS, Table 17).	

Issue 8 Typographical and data errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 3.2, page 27	Company propose the row named “*TC 1%*” is corrected to “*TC ≥1%”*	Typographical error	Corrected.
Table 3.2, page 28	Company propose the data source is updated from “*Sources: Based on Table 4 of the 2108 CS*” to “*Sources: Based on Table 4 of the 2018 CS*”	Typographical error	Corrected.
Table 3.3, page 30	Company propose the 12-month survival rate for the placebo group in the PACIFIC trial is corrected from ‘4.7’ to ’74.7’	Typographical error	Corrected.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Section 3.2.1, page 29 OS data maturity (52.5%) Increase in median OS (33.5 months) 5-year survival rates and CIs (50.1%, 36.9%) 2-year survival rate and CI (72.9%) **Table 3.3, page 30, PACIFIC (PD-L1 ≥1% subgroup) column** For both durvalumab and placebo arms: • Number and % of deaths • Censored patients • Median OS • OS hazard ratio • 12, 24, 36, 48 and 60 months survival rates **Figure 3.1, page 31**	This data can be released from confidential marking	5-year PACIFIC paper is now published, containing: • PFS KMs, PFS rates and median PFS for the PACIFIC ≥1% group • OS KMs, OS rates and median OS for the PACIFIC ≥1% group	Amended.

OS KM plot for PACIFIC PD-L1 ≥1% subgroup **Section 3.2.2, page 33** PFS data maturity (59.4%) Median PFS and CIs for the durvalumab and placebo arm (24.9 months, 5.5 months) 5-year PFS rates and CIs (35.8%, 17.6%) **Table 3.4, page 33-34, PACIFIC (PD-L1 ≥1% subgroup) 11th January 2021 DCO column** For both durvalumab and placebo arms: • PFS events • Median PFS • PFS hazard ratio • 12, 18, 24, 36, 48 and 60 months PFS rates **Figure 3.3, page 35** PFS KM plot for PACIFIC PD-L1 ≥1% subgroup **Section 4.4, page 41**			

Improvement in 5-yr PFS rate (18.2%) **Figure 4.2, page 32** PFS KM plot for PACIFIC PD-L1 ≥1% subgroup			
Section 1.2, page 11 [redacted] **Section 2.2, page 14-15** [redacted]	All statements should be marked as commercial in confidence	In response to the clarification letter, the Company submitted the full EMA Type II variation assessment report as a confidential reference. This report provided additional details regarding the data provided to the EMA and EMA assessment of this data in support of approving the 1500mg Q4W dose. While the Company acknowledge there is some additional critique of the data in this confidential report, additional responses were provided to the EMA to resolve the questions [redacted] . This resulted in the EMA publishing a final conclusion as follows: "*Based on the modeling and simulation of exposure,*	

[redacted]		*exposure-safety relationships and exposure-efficacy data comparisons, there are no anticipated clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks in locally advanced NSCLC.*" The contents of the Type II variation assessment report provided by the Company are not publicly available and therefore all references to and quotations of any content in this report are considered commercial in confidence. [redacted]	

[redacted]			

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS Digital

Durvalumab for treating unresectable non-small cell lung cancer – data review

Commissioned by NHS England and NHS Improvement

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS Digital (NHSD). Its purpose is to collect and quality-assure high-quality, timely data on a wide range of diseases and provide robust surveillance to monitor and detect changes in health and disease in the population.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
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NHS Digital

Contents

1. Executive summary

Introduction

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

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

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

The NHS England and NHS Improvement and NHSD partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99.5% of patients and 84% of patient outcomes reported in the SACT dataset. NHSD and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for durvalumab for unresectable non-small cell lung cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to NHSD's routinely collected SACT data to provide SACT treatment history.

Between 28 March 2019 and 1 February 2021, 710 applications for durvalumab were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 591 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS).[1]

Results

591/594 (99.5%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 10.3 months [95% CI: 9.4, 11.1] (313 days). 68% of patients were still receiving treatment at 6 months [95% CI: 64%,71%] and 34% of patients were still receiving treatment at 12 months [95% CI: 29%, 38%].

At data cut off, 68% (N=402) of patients were identified as no longer being on treatment. Of these 402 patients:

- 21% (N=84) of patients stopped treatment due to progression
- 20% (N=82) of patients stopped treatment due to acute toxicity
- 16% (N=66) of patients completed treatment as prescribed
- 11% (N=44) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 10% (N=39) of patients died not on treatment
- 8% (N=32) of patients were treated palliatively and did not benefit from the treatment they received
- 7% (N=28) of patients were treated palliatively and did benefit from the treatment they received
- 3% (N=14) of patients chose to end their treatment
- 2% (N=7) of patients stopped treatment due to COVID, and
- 1% (N=6) of patients died on treatment.

The median OS was not reached. OS at 6 months was 93% [95% CI: 90%, 95%], 12 months OS was 84% [95% CI: 81%, 87%], OS at 18 months was 73% [95% CI: 69%, 77%] and OS at 24 months was 67% [95% CI: 61%, 72%].

A treatment duration and OS sensitivity analyses were conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real-world data for patients treated with durvalumab for unresectable non-small cell lung cancer in the CDF. It evaluates treatment duration, OS and treatment outcomes for all patients treated with durvalumab for this indication.

Introduction

Lung cancer (ICD-10: C33-C34) accounts for 12% of all cancer diagnoses in England. In 2018, 39,290 patients were diagnosed with lung cancer (males 20,453, females 18,837).[2]

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 only if:

- they have had concurrent platinum-based chemoradiation, and
- the conditions in the managed access agreement are followed[3].

2. Background to this report

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

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

The CDF is a source of funding for cancer drugs in England.[4] From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period.[5]

NHSD analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Disease Registration Service (NDRS), which is part of NHSD.

NICE Appraisal Committee review of durvalumab for the treatment of unresectable non-small cell lung cancer [TA578]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of durvalumab (AstraZeneca) in treating unresectable non-small cell lung cancer [TA578] and published guidance for this indication in May 2019.[6]

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of durvalumab for the treatment of unresectable non-small cell lung cancer through the CDF for a period of 27 months, from March 2019 to June 2021.

During the CDF funding period, results from an ongoing clinical trial (PACIFIC[7]) evaluating durvalumab in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the PACIFIC clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for durvalumab for unresectable non-small cell lung cancer in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the PACIFIC clinical trial[7].

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

- overall survival from the start of a patient's first treatment with durvalumab

Treatment duration was not an area of clinical uncertainty but has been included in this report.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, NHSD and the company (AstraZeneca) formed a working group to agree the Data Collection Agreement (DCA).[6] The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of durvalumab. It also detailed the eligibility criteria for patient access to durvalumab through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for durvalumab, approved through Blueteq® and followed up in the SACT dataset collected by NHSD.

3. Methods

CDF applications – identification of the cohort of interest

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

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NHSD has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS Digital (NHSD), through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England and NHS Improvement.

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

Durvalumab clinical treatment criteria

1. Application has been made by and the first cycle of systemic anti -cancer therapy with durvalumab will be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.

2. 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.

3. Patient has a histologically- or cytologically-confirmed diagnosis of non-small cell lung cancer.

4. Patient has locally advanced and unresectable non-small cell lung cancer which is either stage IIIA or stage IIIB or stage IIIC at the time of commencing concurrent chemoradiotherapy.

5. PD-L1 testing with an approved and validated test to determine the PD-L1 Tumour Proportion Score (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.

6. Patient has completed treatment with 2 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 dose of 54-66Gy (or a biologically equivalent dose of 54-66Gy).

7. Durvalumab is not approved by NICE for use after sequential chemotherapy and radiotherapy.

8. Patient has been re-staged since chemoradiotherapy was completed and does not have any evidence of disease progression or metastatic spread.

9. Patient will start his/her first treatment with durvalumab within 42 days of the last active treatment date of chemoradiotherapy.

10. Patient has an ECOG performance status (PS) of 0 or 1.

11. The maximum treatment duration with durvalumab will be 12 months, this being measured from the date of first durvalumab treatment.

12. The total active treatment period is a maximum of 12 months i.e. in those patients who have toxicity and thus have dose interruptions, the maximum number of treatment cycles is 26 2-weekly cycles or 13 4-weekly cycles.

13. Treatment with durvalumab will continue until loss of clinical benefit or excessive toxicity or the patient decision to stop therapy or a treatment duration of 12 months has been completed, whichever is the sooner.

14. No re-treatment with durvalumab is allowed.

15. Patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless durvalumab has been received as part of AstraZeneca's early access program for durvalumab after concurrent chemoradiotherapy.

16. Patients treated in the AstraZeneca early access program with sequential chemotherapy and radiotherapy or any patient with PD-L1 TPS <1% or PD-L1 negative disease are not eligible for durvalumab from the CDF. For such patients who have already started durvalumab, AstraZeneca will continue to supply durvalumab as a consequence of its commitment in its early access program.

17. A formal medical review as to whether treatment with durvalumab should continue or not will be scheduled to occur at least by the end of the first 3 cycles of treatment.

18. Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow any immune toxicities to settle.

19. The licensed dose and frequency of durvalumab will be used, either 10 mg/kg every 2 weeks or 1500 mg every 4 weeks.

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for durvalumab for the treatment of unresectable non-small cell lung cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for durvalumab for the treatment of unresectable non-small cell lung cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for durvalumab for the treatment of unresectable non-small cell lung cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

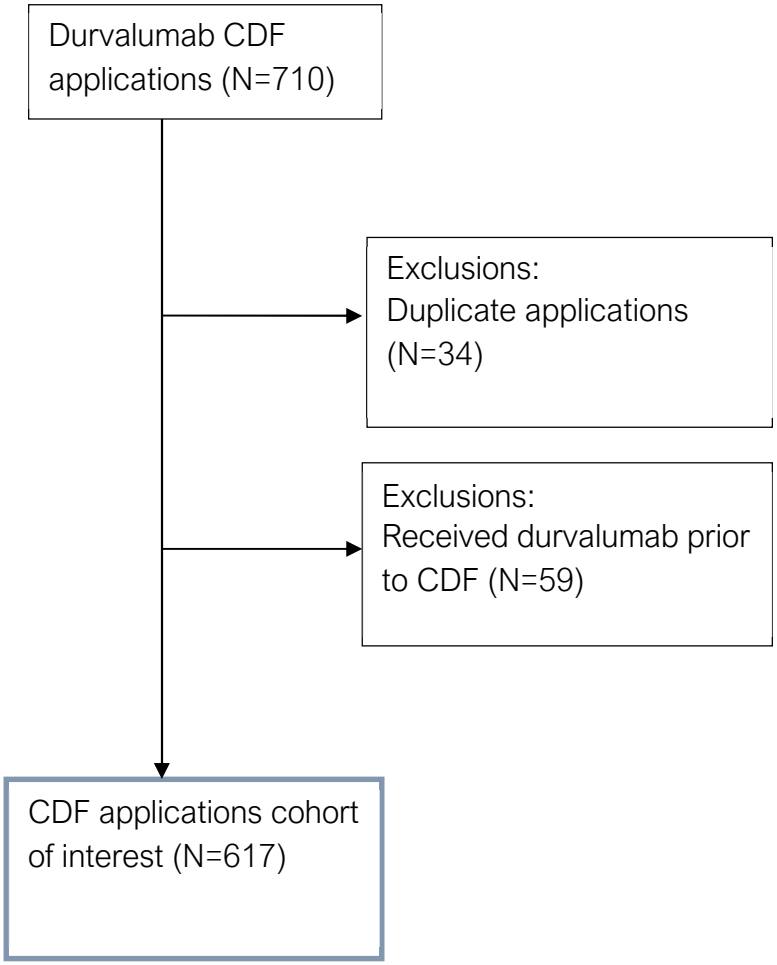
Initial CDF cohorts

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

The CDF applications included in these analyses are from 28 March 2019 to 1 February 2021. A snapshot of SACT data was taken on 3 July 2021 and made available for analysis on 12 July 2021 and includes SACT activity up to the 31 March 2021. Tracing the patients' vital status was carried out on 30 July 2021 using the Personal Demographics Service (PDS).[1]

There were 710 applications for CDF funding for durvalumab for the treatment of unresectable non-small cell lung cancer between 28 March 2019 and 1 February 2021 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 676 unique patients. Fifty-nine patients were excluded as they received durvalumab prior to the drug being available through the CDF.

Figure 1. Derivation of the cohort of interest from all CDF (Blueteq) applications made for durvalumab for the treatment of unresectable non-small cell lung cancer between 28 March 2019 and 1 February 2021



Linking CDF cohort to SACT

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

Addressing clinical uncertainties

Treatment duration

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

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

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

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

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

Additional explanation of these dates is provided below:

Start date of regimen

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

Start date of cycle

A cycle is a period over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

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

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

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

Durvalumab is administered intravenously. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that treatment administration has taken place on a specified date. A duration of 13 days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Durvalumab is a 14-day cycle consisting of one administration. In March 2020, a 4-weekly cycle was introduced, this soon became the prescription length of choice.

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

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

No longer receiving treatment (event), if:

- the patient has died
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61, and
- there are no further SACT records for the patient following a three-month period.

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

Overall survival (OS)

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

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

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

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

The patient is flagged as:

- dead (event):
    - at the date of death recorded on the PDS.

Or:

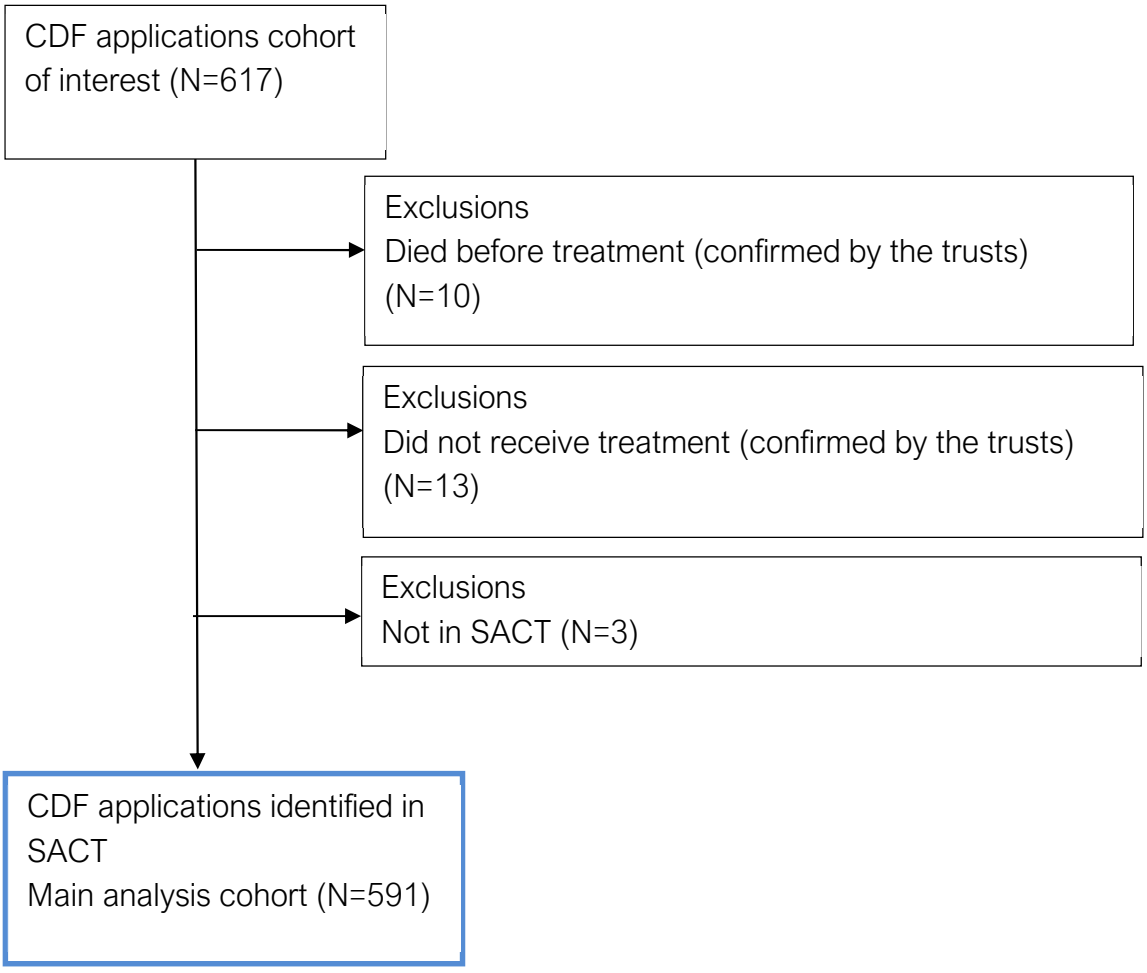
- alive (censored):
    - at the date patients were traced for their vital status as patients are confirmed as alive on this date.

4. Results

Cohort of interest

Of the 617 applications for CDF funding for durvalumab for the treatment of unresectable non-small cell lung cancer, 13 patients did not receive treatment, 10 patients died before treatment and three patients were missing from SACT[a] (see Figure 2).

Figure 2. Matched cohort - SACT data to CDF (Blueteq®) applications for durvalumab for the treatment of unresectable non-small cell lung cancer between 28 March 2019 and 1 February 2021



[a] Of the 13 patients that did not receive treatment and the 10 patients who died before treatment, all were confirmed by the relevant trust by the NHSD data liaison team.

A maximum of 594 durvalumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 99.5% (591/594) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 86% complete.

Table 1. Completeness of key SACT data items for the durvalumab cohort (N=591)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	86%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with durvalumab in at least three months.[9] These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 402 patients. Of these, 338 (84%) have an outcome summary recorded in the SACT dataset.

Table 2. Completeness of outcome summary for patients that have ended treatment (N=402)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	84%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. Stage of disease and previous immunotherapy are 100% complete. PD-L1 expression is 99% complete.

Table 3. Completeness of key data items required from Blueteq (N=591).

Variable	Completeness (%)
Stage of disease	100%
Previous immunotherapy	100%
PD-L1 expression	99%

Patient characteristics

The median age of the 591 patients receiving durvalumab for treating unresectable non-small cell lung cancer was 67 years. The median age in males and females was 67 and 66 years respectively.

Table 4. Patient characteristics (N=591)

Patient characteristics[b]			
		N	%
Sex	Male	346	59%
	Female	245	41%
Age	<40	7	1%
	40 to 49	29	5%
	50 to 59	105	18%
	60 to 69	216	37%
	70 to 79	219	37%
	80+	15	3%
Performance status	0	157	27%
	1	346	59%
	2	3	1%
	3	0	0%
	4	0	0%
	Missing	85	14%

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

Blueteq data items

Table 5 shows the distribution of Blueteq data items with 90% (N=530) of patients having stage IIIA or IIIB disease and 10% (N=61) of patients having stage IIIC disease. 88% (N=522) of patients had a PD-L1 score ≥1, and 99% (N=583) of patients did not previously receive immunotherapy for non-small cell lung cancer (NSCLC).

Table 5. Distribution of key Blueteq data items (N=591)

Blueteq data items[c]		N	%
Stage of disease distribution	IIIA	284	48%
	IIIB	246	42%
	IIIC	61	10%
PD-L1 expression	≥1	522	88%
	PD-L1 testing not possible	47	8%
	TPS result was unquantifiable	14	2%
	Not currently captured	8	1%
Previous immunotherapy	No previous immunotherapy for NSCLC	583	99%
	The only previous immunotherapy for NSCLC has been with durvalumab following concurrent chemoradiotherapy for PD-L1 TPS >=1% disease in the AstraZeneca durvalumab early access program.	8	1%

[c] Figures may not add to 100% due to rounding.

Treatment duration

Of the 591 patients with CDF applications, 402 (68%) were identified as having completed treatment by 31 March 2021 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with durvalumab in at least three months (see Table 10). The median follow-up time in SACT was 7.3 months (222 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 24 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 25 months. SACT follow-up ends 31 March 2021.

Table 6, Breakdown by patients' treatment status [d,e,f]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	133	23%
Patient died – on treatment	6	1%
Treatment stopped	263	45%
Treatment ongoing	189	32%
Total	591	100%

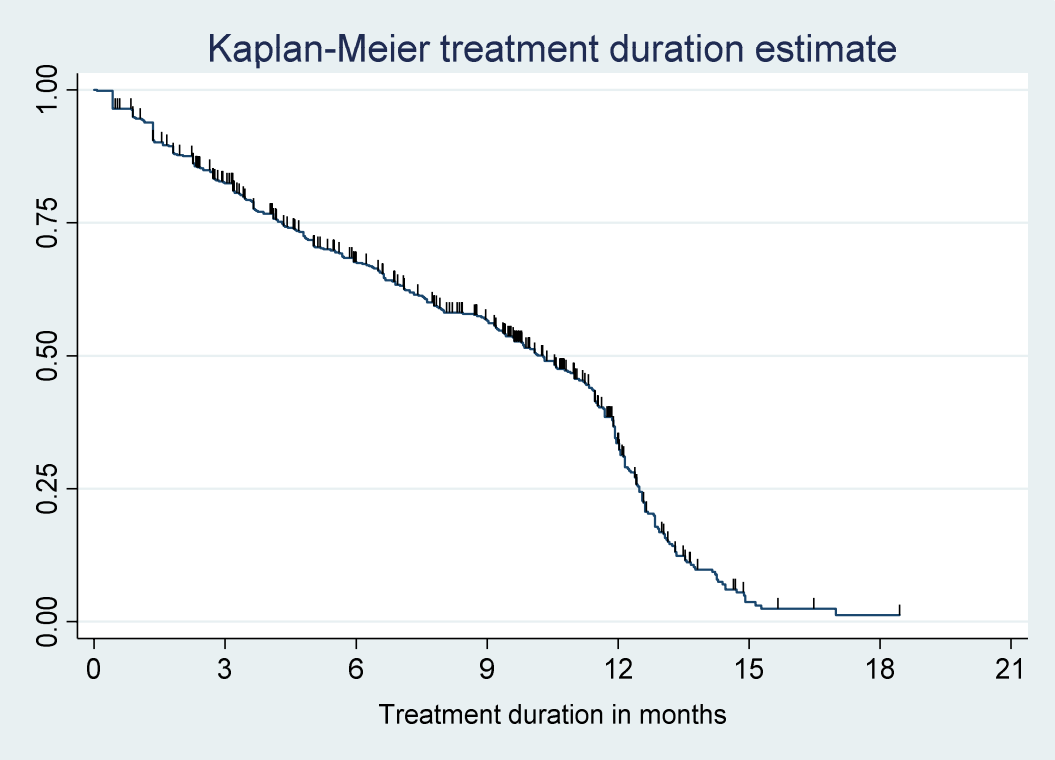
Table 7, Treatment duration at 6 and 12-month intervals[g]

Time period	Treatment duration (%)
6 months	68% [95% CI: 64%, 71%]
12 months	34% [95% CI: 29%, 38%]

d Figures may not sum to 100% due to rounding.
e Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
f 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.
g Treatment of durvalumab is only permitted for a maximum of 12 months

The Kaplan-Meier curve for ongoing treatment is shown in Figure 3. The median treatment duration for all patients was 10.3 months [95% CI: 9.4, 11.1] (313 days) (N=591).

Figure 3. Kaplan-Meier treatment duration (N=591)



Tables 8 and 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 24 months (730 days). SACT contains more follow-up for some patients.

Table 8. Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21
Number at risk	591	456	335	255	106	6	1

Table 9 shows that for all patients who received treatment, 189 were still on treatment (censored) at the date of follow-up and 402 had ended treatment (events).

Table 9. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21
Censored	189	156	113	85	23	3	1
Events	402	300	222	170	83	3	0

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 68% (N=402) of patients had ended treatment at 31 March 2021.

Table 10. Treatment outcomes for patients that have ended treatment (N=402)[h,i,j]

Outcome	Frequency (N)	Percentage (%)
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 3 months	44	11%
Stopped treatment – died not on treatment[j]	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%
Total	402	100%

h Figures may not sum to 100% due to rounding.
i Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
j 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 11. Treatment outcomes and treatment status for patients that have ended treatment (N=402)

Outcome[k]	Patient died[l] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	49	35	
Stopped treatment – acute toxicity	23	59	
Stopped treatment – completed as prescribed	4	62	
Stopped treatment – no treatment in at least 3 months		44	
Stopped treatment – died not on treatment	39		
Stopped treatment – palliative, patient did not benefit	8	24	
Stopped treatment – palliative, patient did benefit	8	20	
Stopped treatment – patient choice	2	12	
Stopped treatment – COVID		7	
Stopped treatment – died on treatment			6
Total	133	263	6

k Relates to outcomes submitted by the trust in Table 10.
l Relates to treatment status in Table 11 for those that have ended treatment.

Overall survival (OS)

Of the 591 patients with a treatment record in SACT, the minimum follow-up was 5.9 months (179 days) from the last CDF application. Patients were traced for their vital status on 30 July 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 14.5 months (441 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 12. OS at 6, 12, 18 and 24-month intervals

Time period	OS (%)
6 months	93% [95% CI: 90%, 95%]
12 months	84% [95% CI: 81%, 87%]
18 months	73% [95% CI: 69%, 77%]
24 months	67% [95% CI: 61%, 72%]

Figure 4 provides the Kaplan-Meier curve for OS, censored at 30 July 2021. The median OS was not reached.

Figure 4. Kaplan-Meier survival plot (N=591)

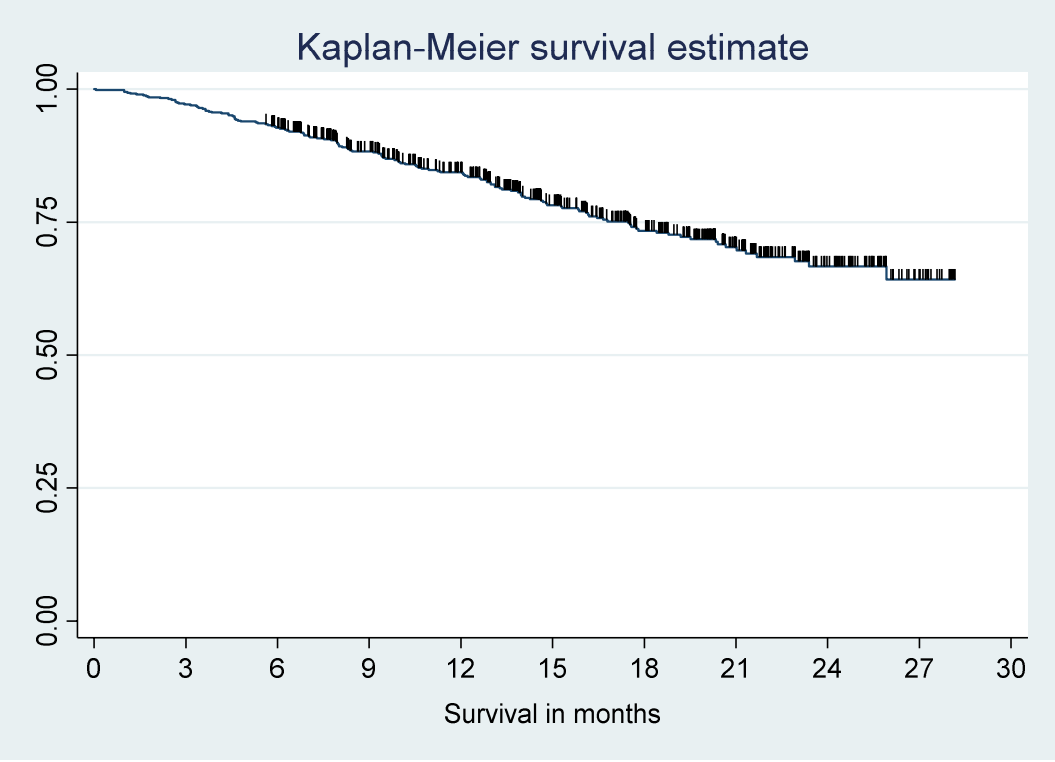


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 28.1 months (855 days), all patients were traced on 30 July 2021.

Table 13. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Number at risk	591	574	541	448	378	273	204	124	61	15

Table 14 shows that for all patients who received treatment, 452 were still alive (censored) at the date of follow-up and 139 had died (events).

Table 14. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Censored	452	452	445	376	325	245	191	118	60	15
Events	139	122	96	72	53	28	13	6	1	0

5. Sensitivity analyses

6-month SACT follow up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 28 March 2019 to 30 September 2020 and SACT activity was followed up to the 31 March 2021.

Following the exclusions above, 488 patients (83%) were identified for inclusion. The median follow-up time in SACT was 9.2 months (280 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 5. The median treatment duration for patients in this cohort was 10.3 months [95% CI: 9.4, 11.1] (313 days) (N=488).

Figure 5. Kaplan-Meier treatment duration plot (N=488)

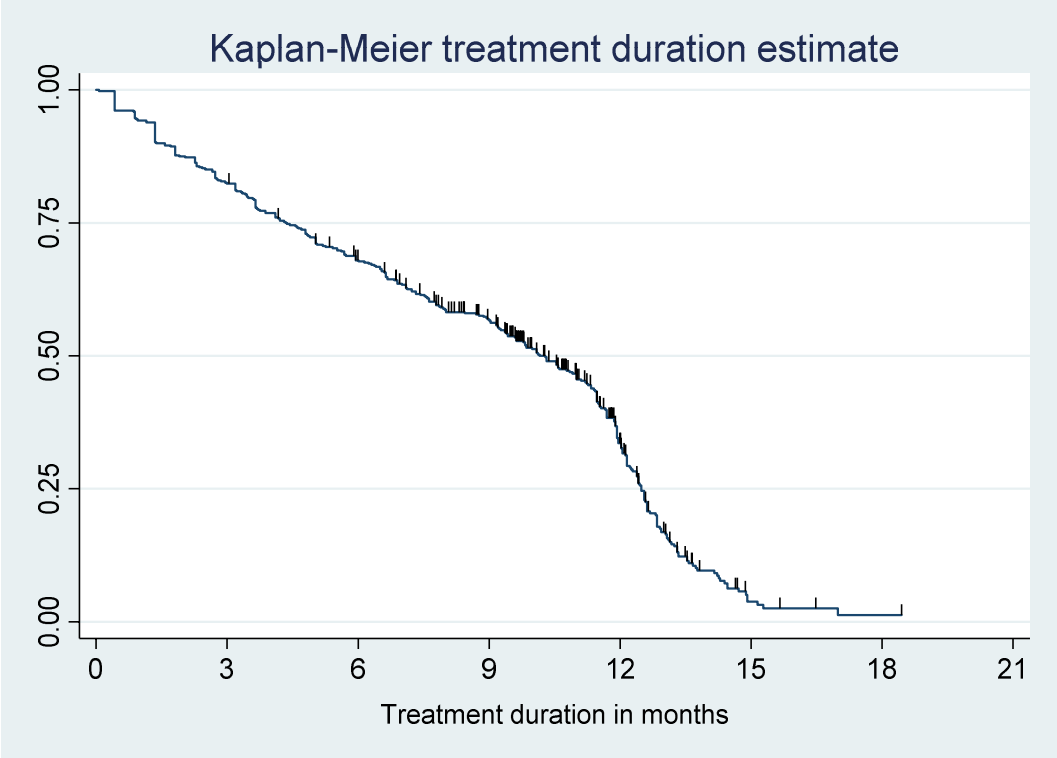


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 24.1 months (733 days).

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

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21
Number at risk	488	401	325	252	104	6	1

Table 16 shows that for all patients who received treatment, 113 were still on treatment (censored) at the date of follow-up and 375 had ended treatment (events).

Table 16. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21
Censored	113	112	106	85	23	3	1
Events	375	289	219	167	81	3	0

Overall survival (OS)

Sensitivity analyses was also carried out for OS on a cohort with at least six months follow-up in SACT. To identify the cohort, CDF applications were limited from 28 March 2019 to 30 January 2021.

Following the exclusions above, 590 patients (99.8%) were included in these analyses. The median follow-up time in SACT was 14.5 months (441 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 6 provides the Kaplan-Meier curve for OS, censored at 30 July 2021. The median OS was not reached.

Figure 6. Kaplan-Meier survival plot (N=590)

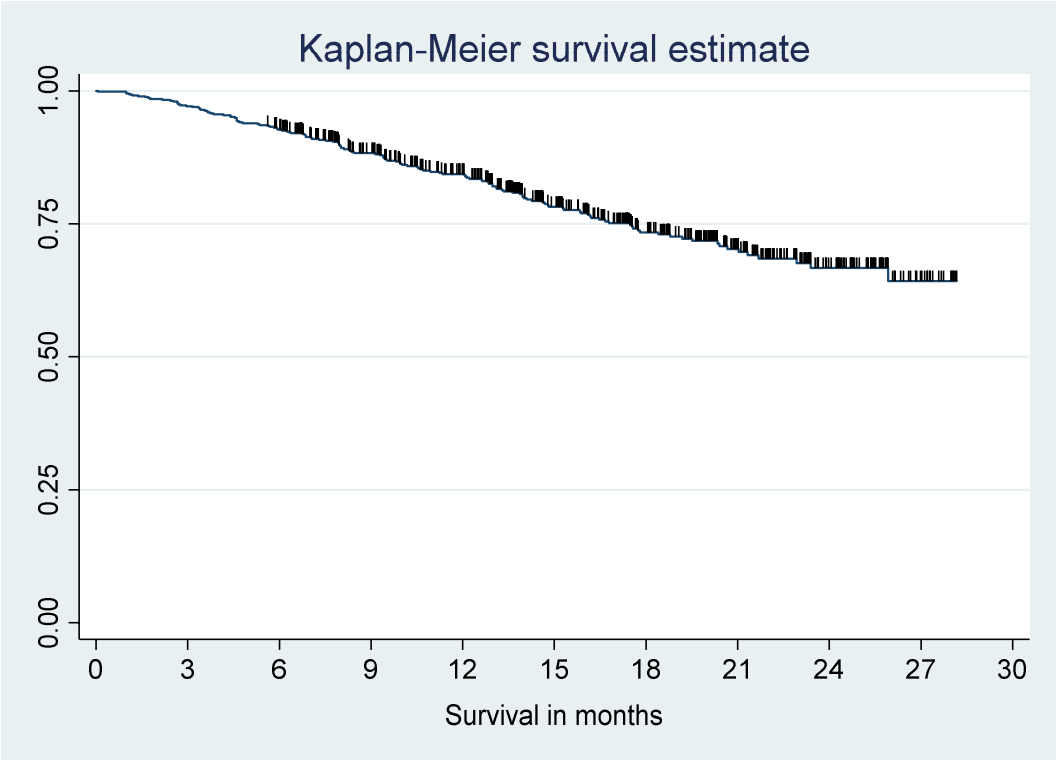


Table 17 and Table 18 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 28.1 months (855 days), all patients were traced on 30 July 2021.

Table 17. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Number at risk	590	573	541	448	378	273	204	124	61	15

Table 18 shows that for all patients who received treatment, 451 were still alive (censored) at the date of follow-up and 139 had died (events).

Table 18. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Censored	451	451	445	376	325	245	191	118	60	15
Events	139	122	96	72	53	28	13	6	1	0

Table 19. Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	591	488	590
Median treatment duration	10.3 months [95% CI: 9.4, 11.1] (313 days)	10.3 months [95% CI: 9.4, 11.1] (313 days)	
OS	Not reached		Not reached

6. Conclusions

594 patients received durvalumab for the treatment of unresectable non-small cell lung cancer [TA578] through the CDF in the reporting period (28 March 2019 and 1 February 2021). 591 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99.5%. An additional 13 patients with a CDF application did not receive treatment and 10 patients died before treatment, all were confirmed by the trust responsible for the CDF application by the team at NHSD.

Patient characteristics from the SACT dataset show that 59% (N=346) of patients that received durvalumab for the treatment of unresectable non-small cell lung cancer were male, 41% (N=245) of patients were female. Most of the cohort were aged between 50 and 79 years 91% (N=540) and 85% (N=503) of patients had a performance status between 0 and 1 at the start of their regimen.

At data cut off, 68% (N=402) of patients were identified as no longer being on treatment. Of these 402 patients:

- 21% (N=84) of patients stopped treatment due to progression
- 20% (N=82) of patients stopped treatment due to acute toxicity
- 16% (N=66) of patients completed treatment as prescribed
- 11% (N=44) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 10% (N=39) of patients died not on treatment
- 8% (N=32) of patients were treated palliatively and did not benefit from the treatment they received
- 7% (N=28) of patients were treated palliatively and did benefit from the treatment they received
- 3% (N=14) of patients chose to end their treatment
- 2% (N=7) of patients stopped treatment due to COVID, and
- 1% (N=6) of patients died on treatment.

Median treatment duration was 10.3 months [95% CI: 9.4, 11.1] (313 days). 68% of patients were still receiving treatment at 6 months [95% CI: 64%,71%] and 34% of patients were still receiving treatment at 12 months [95% CI: 29%, 38%].

The median OS was not reached. OS at 6 months was 93% [95% CI: 90%, 95%], 12 months OS was 84% [95% CI: 81%, 87%], OS at 18 months was 73% [95% CI: 69%, 77%] and OS at 24 months was 67% [95% CI: 61%, 72%].

Sensitivity analysis was carried out on treatment duration and OS to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for treatment duration showed no difference (full cohort = 10.3 months; sensitivity analysis cohort =

10.3 months). Results for OS showed no difference with the median OS not being reached in both cohorts.

7. References

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **17 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Technical engagement response form

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

NICE National Institute for Health and Care Excellence

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

About you

Table 1 About you

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

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1 – Differences in PD-L1 status between the PACIFIC trial population and the SACT cohort	Yes	**Clarification of scope for the original appraisal and the CDF exit appraisal** • The Company would like to clarify the population for appraisal as outlined in the scope for the original appraisal (TA578) and for this CDF exit appraisal is patients with PD-L1 expression on ≥1% of tumour cells. • No data for patients with unknown PD-L1 status was provided or appraised during the original appraisal.[1] **Rationale for inclusion of patient with unknown PD-L1 status in the SACT cohort** • As outlined in the Company response to the ERG clarification letter, while the scope of the original appraisal and this CDF exit appraisal is limited to patients with PD-L1 expression on ≥1% of tumour cells, the Blueteq criteria allows patients with unknown PD-L1 status to be treated with durvalumab if they have an inconclusive PD-L1 result or are unable to undergo testing.[2] • This criteria allowing durvalumab treatment in patients with unknown PD-L1 status was introduced following the original appraisal due to clinician concerns

		that patients may miss out on effective treatment in the case they receive an inconclusive PD-L1 test result or are unable to test for PD-L1. • Clinician insights obtained from 1:1 interviews with clinical oncologists confirmed that the proportion of patients with unknown PD-L1 status is small. Clinicians quoted approximately 5% of all patients treated with durvalumab for locally advanced unresectable NSCLC have an unknown PD-L1 status. Clinician insights also suggested in some cases unconfirmed PD-L1 status may be as a result of labs not accepting samples obtained via EBUS, rather than issues with tumour tissue.[3] **Availability of SACT data for PD-L1 ≥1% patients** • As outlined in the CS and the Company response to the ERG clarification questions, a full SACT report, including patients with unknown PD-L1 status, was provided prior to the CDF exit kick-off meeting. • A second report derived from the SACT dataset was also provided ahead of the CDF kick-off meeting. This report was a secondary sensitivity analysis of OS, which provided OS outcomes for only the patients with PD-L1 ≥1%. • The full SACT report was provided as appendix B to the CS and the secondary sensitivity analysis of OS for only the patients with PD-L1 ≥1% was provided as appendix C to the CS. **Further context and OS outcomes from the SACT dataset** • As described in the SACT report, 88% (n=522) of patients had confirmed PD-L1 expression ≥1%, PD-L1 testing was not possible in 8% (n=47) of patients, 2% (n=14) of patients had an unquantifiable PD-L1 test result and 1% (n=8) of patients did not have a PD-L1 result captured. • Median OS was not reached for the full SACT cohort (n=591) or SACT cohort of patients with confirmed PD-L1 expression ≥1% (n=522).

		• OS rate at 24 months for the full SACT cohort (n=591) was 67% (95% CI: 61%, 72%) and for the SACT cohort of patients with confirmed PD-L1 expression ≥1% was 68% (95% CI: 62%, 74%). • Overall, patients with unknown PD-L1 expression represent a relatively small proportion of the overall SACT cohort and their exclusion from the OS analysis did not make a material difference to the overall outcomes, which were considered supportive of the PACIFIC OS rate at 24 months for the PD-L1 ≥1% group (72.9% [95% CI: 66.2%, 78.4%]).[4] **Definition of PD-L1 unknown in the PACIFIC trial** • Unlike real-world clinical practice in England, confirmation of PD-L1 expression was not required prior to enrolment in the PACIFIC trial.[5] • Therefore, patients classified as PD-L1 unknown in the PACIFIC trial are assumed to have included patients with PD-L1 expression <1%, patients with PD-L1 ≥1%, patients who were unable to undergo PD-L1 testing and patients who received an inconclusive PD-L1 test result. • As a result, the proportion of patients with unknown PD-L1 status in the PACIFIC trial (36.7%) was greater than in the SACT cohort (11%). • Hence, even if the PD-L1 unknown population from the PACIFIC trial were to be included in an analysis from this appraisal, the PD-L1 unknown cohort would not be generalisable to the group of PD-L1 unknown patients in the SACT cohort. Overall, the Company considers the appropriate data sets from the PACIFIC and the SACT cohort have been presented, i.e. patients with confirmed PD-L1 expression in ≥1% of tumour cells, in line with the scope for this appraisal. As outlined in the ERG report, the SACT outcomes are supportive of the PACIFIC data. While the Company acknowledge the Blueteq criteria allows use of durvalumab in a slightly broader population, i.e. patients who have an inconclusive PD-L1 test result or who are unable

		to undergo testing, this is a relatively small population of the overall durvalumab treated cohort. Furthermore, exclusion of PD-L1 unknown patients from the OS analysis does not have a material impact on the OS outcomes. Therefore, even if the analysis did include these PD-L1 unknown patients treated in clinical practice, who it should be reiterated are not included in the scope for this appraisal, the Company does not consider there to be any significant uncertainty in the CE estimates presented in the base case. The Company would also like to restate their statement from the response to the ERG clarification questions that it is our expectation that the Blueteq criteria will remain unchanged in the event of a positive outcome for this CDF exit appraisal.
Issue 2 – Differences between the dosing used in the trial (weight based 10mg/kg, Q2W) and the fixed dose (1500mg, Q4W) given to some SACT patients	No	**Clarification of the EMA conclusion of clinical equivalency** [redacted] In response to the ERG clarification questions, the Company provided the EMA final assessment report of the Type II variation application submitted by the Company to request. The Company acknowledge that within this document (pg 50), ,[redacted] • [redacted] . The Company would like to clarify that their responses to this query were also contained within this document as well as the final assessment of these responses.[6] • On pg 62 of the assessment report, the assessors final comments and statement of resolution (in bold) can be found in a clearly marked box. Key comments from the assessor include: [redacted]

		[redacted] • As previously stated in the Company response to the ERG clarification questions, the final conclusion published by the EMA was that "*there are no anticipated clinically significant differences in efficacy and safety between durvalumab doses of 10mg/kg ever 2 weeks or 1500mg every 4 weeks in locally advanced NSCLC*."[7] The only exception is patients with body weight of 30kg of less, who must receive a weight-based dose of durvalumab equivalent to 10mg/kg every 2 weeks or 20mg/kg every 4 weeks.[8] **Previous immune-oncology therapies have undergone similar dose changes** • Example 1: Avelumab for maintenance treatment of locally advanced or metastatic urothelial cell cancer after platinum based chemotherapy (TA10624 – ongoing appraisal)[9] o The ERG report states that limitations in the clinical evidence base include use of weight-based dosing in the JAVELIN Bladder 100 trial (10mg/kg Q2W) but approval of a flat dose of 800mg Q2W. The company explained that the fixed licensed dose would have similar clinical outcomes to the weight-based dose and therefore no adjustment to efficacy was made in their submission. o The ERG also noted in JAVELIN Bladder 100, patients treated with avelumab + BSC had a median weight at baseline of 72.4kg, and a mean weight of 75.2kg (equating to a dosage of 724mg and 752mg, respectively). o Furthermore, the ERG highlighted that this approach was accepted in a previous NICE TA of avelumab in combination with axitinib for untreated advanced renal cell carcinoma (TA645). They also note that the SmPC also states that clinically meaningful differences were not

		expected between the weight-based and fixed dose. This is in line with the comments published by the EMA regarding clinical equivalency of the weight-based and fixed dose of durvalumab. ○ The ERG concluded they were not concerned with the difference between the licensed dose of avelumab (800mg) and the weight-based dose (10mg/kg Q2W) used in the JAVELIN Bladder 100 trial. • Example 2: Type II variation assessment of pembrolizumab to include Q6W dose for metastatic NSCLC ○ At the time of the appraisals listed below, pembrolizumab had a licensed dose of 200mg administered every 3 weeks. On 21st May 2021, the EMA approved an additional dosing regimen of 400mg administered every 6 weeks for all approved indications based on interim results from study KEYNOTE-555, an interventional PK study in patients with advanced melanoma. Additional data/ analysis from studies KEYNOTE-021, 048, 189 407 and 426 were provided. ○ At the time of the EMA approval, the following NICE TAs for pembrolizumab had been conducted in non-small-cell lung cancer with a positive outcome for routine commissioning: ▪ TA683: pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic, non-squamous NSCLC (10 March 2021).[10] ▪ TA531: pembrolizumab for untreated PD-L1-positive metastatic NSCLC (18 July 2018).[11] ▪ TA428: pembrolizumab for treating PD-L1 positive NSCLC after chemotherapy (12 Sept 2017).[12] The Company notes that pembrolizumab was not required to undergo an additional appraisal to assess cost-effectiveness of the

		new dose, but the Blueteq criteria has been updated to allow the alternative Q6W dose, provided the patient is stable and well. The Company understand that no further analyses were submitted to NICE to provide assurances of cost-effectiveness of the Q6W dose, but the clinical equivalence of the Q3W and Q6W doses were accepted following the EMA approval. **Confirmation of average dose administered in the PACIFIC trial** • The mean weight of the PD-L1 ≥1% group in the PACIFIC trial was 72.6kg (SD: 17.88).[1] Therefore, the mean dose administered as a fixed dose of 10mg/kg Q2W would be 726mg, which is equivalent to a dose of 1452mg Q4W. This is directly comparable to the Q4W fixed dose of 1500mg. **Confirmation of cost-effective ICERs regardless of dosing regimen** • The Company has implemented 1500mg Q4W in our base case ICER due to clinician advice that this fixed dose is now considered standard of care and used in almost all patients due to improved convenience for patients and reduced resource impact for the NHS. • The Company also provided a scenario analysis using the 10mg/kg Q2W dose as per the PACIFIC trial. This change in dosing has a minimal impact on the ICER, increasing it by just £403 to £12,122, therefore remaining highly cost-effective. Overall, it is not unusual for IO therapies to have a licensed dose that is different to the dose implemented in the trial. Similar to other examples of these cases (described above), the Company has taken the required steps to assure the EMA of the clinical equivalency between the 10mg/kg Q2W and 1500mg Q4W doses, hence, their approval of the Q4W dose and the conclusion of no significant differences in clinical efficacy or safety. Additionally, the Company has demonstrated durvalumab is highly cost-effective regardless of choice of dosing regimen.

		The Company do not consider there is any remaining uncertainty with regards to the clinical equivalency of these two doses or their cost-effectiveness in clinical practice.
Issue 3 – No additional quality of life data was collected since durvalumab entered the CDF	No	**Quality of life (QoL) data and health state utilities were not listed as a key uncertainty following the original appraisal** • The company would like to highlight that their approach to applying HSUs was accepted in the original appraisal following application of age-related decrements. This final agreed approach was not associated with any uncertainty.[13] • As per our response to the terms of engagement, the Company have applied the same, previously accepted approach to HSUs in the base case for this CDF exit appraisal. **Further collection of QoL data was not listed in the data collection arrangement (DCA)** • Further collection of quality of life data was not listed in the DCA.[14] • The Company can confirm further quality of life was not collected in the PACIFIC trial as it is highly impractical to patients to continue collecting QoL data for extended periods of time. **The Health State Utilities (HSUs) applied in the base case are considered conservative** • As was outlined at the time of the original appraisal, the Company's approach to applying HSUs was considered conservative.[1] • The Company would also like to reiterate a scenario analysis using an alternative HSU from a second-line metastatic 2L mNSCLC appraisal (TA713 nivolumab for advanced non-squamous NSCLC after chemotherapy) has been provided, which decreased the ICER by £539.

The Company consider all reasonable steps have been taken to use the most appropriate HSUs in the pre- and post-progression state. The base case, which applies a conservative approach to HSUs, results in a highly cost-effective ICER of £11,507. The Company have also explored the use of an alternative HSU, which has had minimal impact on the ICER. The Company do not consider there is any outstanding uncertainty as a result of quality-of-life data inputs.

Finally, it should be noted that the error identified by the NICE technical team that the model adopts a lower health state utility value (HSUV) for the progressed disease state for the durvalumab vs. the placebo arm has now been corrected. The reason that the HSUV for progressed disease for the durvalumab arm was lower than the placebo arm is because a treatment related decrement was applied to reflect that the incidence of adverse events was higher in the durvalumab arm. However, considering that it is reasonable to assume that the impact of AEs on patients who received durvalumab in the PF state will not apply indefinitely over time, the utility values have been adjusted as follows:

Table 1: Health state utility values used in the economic model

	Durvalumab	Placebo
Progression-free utility	0.803	0.827
Progressed disease utility	0.793	0.793

Source: PF & PD HSUV: PACIFIC mixed effects utility model

The HSUV for the progression-free state is aligned with the ERG's preferred analysis and adequately captures the potential impact of treatment-related adverse events. Applying the same utility value across both arms for the progressed disease state is in line with the pooled PPS approach in the model and remains consistent with the

		values applied in the original model. **Correcting this error has led to a small improvement in the base case ICER, from £11,719 to £11,507** (please see Table 5 on the final page of this document).
Issue 4 – Internal consistency between modelled survival and observed trial data was lacking	Yes/No	**A state transition model (STM) is the most appropriate model structure and produces clinically plausible long-term outcomes** • The Company acknowledges that questions have been raised about the appropriateness of adapting a semi-Markov (state transition) modelling approach vs. a partitioned survival technique, even though this was the accepted model structure in the original submission. • One of the key concerns that has been raised by the ERG is the claim that the STM approach produces discrepancies between the modelled number of patients alive at ≥5 years and the actual observed OS in the PACIFIC trial, thereby suggesting that the state transition model lacks internal consistency and potentially biases results in favour of durvalumab. • However, this concern can be directly addressed by comparing the observed OS data from PACIFIC (DCO5, 11 January 2021) with the predicted OS from the economic model using the STM approach (as presented in the Company's response to the ERG clarification question B.1.A.): o When doing so, it is clear that the long-term estimates are generally comparable to the observed rates from PACIFIC and do not significantly over- or underestimate OS for either arm. o For example, when applying the generalised gamma for PFS (Company's base case analysis), although the model slightly underestimates OS in the placebo arm at 5 years, the model overestimates placebo OS in the first four years of the time horizon. o This alignment of the observed and modelled OS curves is even more clearly observed when applying the Gompertz function for extrapolating

		PFS, based on which the model produces a 5-year OS estimate for the durvalumab arm that only differs by [redacted] from the observed rate in PACIFIC. • Furthermore, when validating the long-term OS extrapolations with five UK clinical oncologists in March 2022, all of them commented that the landmark survival probabilities for OS generated with either the generalised gamma or Gompertz functions for PFS seemed plausible and were aligned with what is observed in current UK clinical practice. • Finally, from a technical perspective, a state transition modelling approach provides two additional advantages over a partitioned survival analysis that should be considered in the context of this appraisal: o All clinically plausible extrapolated OS and PFS curves produced logical inconsistencies where the curves crossed. As a partitioned survival analysis does not impose any fundamental structural relationship between PFS and OS, this curve crossing would be associated with significant limitations which cannot be overcome by simply selecting alternative extrapolated survival curves. By adapting a STM approach this logical inconsistency is avoided, which is demonstrated in the modelled and continuously separated PFS and OS curves in Figure 1 below (Company's base case analysis). o Evidence from the PACIFIC trial suggests that the prolongation of PFS is the main benefit of durvalumab and PPS is similar between both arms. Therefore, the data lends itself better to deriving OS from PFS and PPS data (semi-Markov approach, explicitly modelling the relationship between each health state) than independently extrapolating data for PFS and OS (as with the partitioned survival approach).

		• The state transition modelling structure therefore **produces clinically plausible and robust long-term outcomes that is aligned to UK clinical practice, confirming its appropriateness for this appraisal's cost-effectiveness analysis**.  **Key:** BSC: best supportive care; PFS: progression-free survival; OS: overall survival

		Assuming similar PPS across both treatment arms remains an appropriate assumption for the economic analysis; different modelling approaches for PPS have little to no impact on the results • In line with the accepted model structure and approach in the original submission, post-progression survival from PACIFIC DCO5 was pooled across both arms to increase the sample size and thereby the certainty of the parametric models' fit to the data. • The Company acknowledges that questions remain on the appropriateness of assuming that PPS is the same across treatment arms, particularly given the differences between arms in use of subsequent treatments, and whether this leads to a bias in the results. • However, when comparing the KM data for PPS from PACIFIC DCO5 as presented in the Company's response to the ERG clarification question B.1.B., there is no clear separation between the durvalumab and placebo-treated patients for the first few years of the study. • Furthermore, when comparing the pooled and treatment-stratified PPS data, it is clear that all curves are generally comparable, with only small [redacted] differences in extrapolated survival at 5 and 10 years. Extrapolated PPS data in the durvalumab arm performs slightly better when compared to extrapolated placebo PPS data, which confirms that using pooled PPS in the Company base-case analysis is a **conservative assumption**. • This can be demonstrated by conducting a scenario analysis in which extrapolated stratified instead of pooled PPS data from PACIFIC is used to inform the cost-effectiveness analysis (Table 2 below). In this scenario, the cost-effectiveness of durvalumab improves vs. the current base case by £1,168.

- This minor impact on the economic outcomes of changing the modelling of PPS can be explained by the fact that prolongation of PFS is the main benefit of durvalumab and therefore the key driver of the outcomes of the economic analysis; varying the modelling approach for PPS thus has little to no impact on the base case ICERs.
- Table 2 presents another method for extrapolating PPS, in which a PPS curve is generated based on the published data from the KEYNOTE-024 study instead of survival data from PACIFIC, as explained in the Company's original submission. Even in this scenario the impact on the base case ICER is minimal, and the cost-effectiveness of durvalumab vs. placebo only decreases by £267.
- Finally, the Company would like to note that the error identified by the NICE technical team that changing the distribution for pooled PPS in the 'Controls' tab has no effect on the model has now been corrected. It should be noted that the base case ICERs with any of the top 4 parametric survival models (log-logistic, lognormal, Gompertz or generalised gamma) for pooled PPS are almost identical, further highlighting that PPS is not a key driver of the model.

It can thus be concluded that regardless of the approach taken to extrapolate PPS in the economic model, the **impact on the final base case ICERs is negligible**. The Company's approach of assuming similar PPS for both treatment arms thus remains appropriate and even generates slightly conservative base case ICERs.

Table 2: PPS scenario analyses

	ICER
Base case	£11,507
Scenario 1: applying stratified PPS	£10,339

		Scenario 2: generating PPS curves using data from the KEYNOTE-024 study: £11,774 **Key:** ICER: incremental cost-effectiveness ratio; PPS: post-progression survival **UK clinicians confirm that the generalised gamma model produces the most clinically plausible PFS extrapolations, whereas the log-normal model produces the least clinically plausible PFS extrapolations for the durvalumab arm of the PACIFIC population with PD-L1 expression on ≥1% of tumour cells** • Expert clinical insights regarding expectations of long-term survival data were sought from 5 clinicians via 1:1 teleconference interviews held between 7th-11th March 2022. • When presented with the long-term PFS estimates for the durvalumab treated PD-L1 ≥1% group generated with the generalised gamma, Gompertz and log-normal models over a 20-year time horizon, all clinicians commented that both the generalised gamma or Gompertz curves models seemed clinically plausible at 10- and 20 years [redacted] respectively). • In contrast, it was noted that the long-term PFS estimations with the lognormal model seemed overly pessimistic ([redacted] at 10- and 20-years respectively). Physicians commented that they do not expect PFS events to occur in the high quantity or with the frequency predicted by the lognormal model in the PACIFIC population when they have reached 5 years without disease progression, which further rules out this model as an appropriate option for modelling PFS. • Clinicians also noted that once patients reach 5 years without experiencing disease progression, regardless of if they are treated with cCRT or cCRT +

<table>
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<td>durvalumab, they are extremely unlikely to experience disease progression due to their primary diagnosis of locally advanced unresectable NSCLC.
▪ As NSCLC is considered an aggressive disease, PFS events are expected to occur within the first 3-5 years.
▪ However, clinicians did acknowledge that a small proportion of patients would experience progression and therefore would expect a slight downward trend in the PFS curve in the 5–20-year time period, which is reflected in both the generalised gamma and Gompertz extrapolations.
Based on this feedback and in line with previous KEE insights (n=9, Nov-Dec 2021), the generalised gamma is the most appropriate parametric survival model for both arms in the economic analysis. However, sensitivity analysis was conducted using the Gompertz model for the durvalumab arm, which only shows a minor increase in the base case ICER by £1,070 (Table 3), giving further confidence in the robustness of the results.

Table 3: Base case results and scenario analysis using the Gompertz model for PFS
<table>
<tr><th></th><th>ICER</th></tr>
<tr><td>Base case*</td><td>£11,507</td></tr>
<tr><td>Scenario analysis: Gompertz model for PFS</td><td>£12,577</td></tr>
</table>
Key: ICER: incremental cost-effectiveness ratio; PFS: progression-free survival</td>
</tr>
<tr>
<td>Issue 5 – Appropriateness of assumptions on the duration of treatment effect</td>
<td>Yes/No</td>
<td>There is no clinical rationale to support the implementation of a treatment waning effect for durvalumab in this curative intent setting
• Clinician insights confirmed that patients with locally advanced unresectable NSCLC who are treated with concurrent CRT, i.e., are treated with curative</td>
</tr>
</table>

		intent, who reach 5-years without disease progression are considered are generally discharged • As durvalumab treatment is administered after initial cCRT therapy, there is no clinical rationale to apply a treatment waning effect when no treatment waning effect is observed for patients who reach 5 years without disease progression following just cCRT • Clinicians described durvalumab treatment of increasing the proportion of patients who are able to reach 5-years with no disease progression and hence can be discharged • The consistent PFS HRs at the 2-year (PFS HR: 0.44 [95% CI: 0.31, 0.63])[1] and 5-year (PFS HR: 0.47 [95% CI: 0.34, 0.64])[4] landmark analysis also demonstrate the lack of treatment waning effect. • The PFS and OS Kaplan-Meier curves for the PACIFIC PD-L1 ≥1% group (Figure 1 and 2 in the CS, respectively) demonstrate the treatment effect over time, with curves remaining separate beyond 60 months of follow-up, which is maintained and in favour of durvalumab. A treatment waning effect after 5 years is therefore not appropriate considering the available data. • However, to provide further confidence on the range of possible ICERs when questioning the long-term treatment effect of durvalumab in this clinical setting, the Company has provided a scenario analysis where a treatment waning effect is applied at 7.5 and 10 years. By doing so, it is assumed that from the start of treatment waning, the probability of progression/death for durvalumab is the same as the BSC arm, i.e., the hazard ratio is equal to 1. • The results of these scenario analyses are presented in Table 4 below and clearly demonstrate that incorporating a treatment waning effect does not have a large impact on the base case ICERs.

<table>
<tr>
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<td></td>
<td>Table 4: Treatment waning effect of durvalumab scenario analyses
<table>
<tr><th></th><th>ICER</th></tr>
<tr><td>Base case*</td><td>£11,507</td></tr>
<tr><td>Scenario 1: base case + treatment waning at 7.5 years</td><td>£13,442</td></tr>
<tr><td>Scenario 2: base case + treatment waning at 10 years</td><td>£12,139</td></tr>
<tr><td>Scenario 3: Gompertz model for PFS extrapolations + treatment waning at 7.5 years</td><td>£14,773</td></tr>
<tr><td>Scenario 4: Gompertz model for PFS extrapolations + treatment waning at 10 years</td><td>£13,246</td></tr>
</table>
Notes: * base case adapts the generalised gamma model to extrapolate lifetime PFS
Key: PFS: progression-free survival; ICER: incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>Issue 6 – Subsequent treatments included in the model</td>
<td>No</td>
<td>The proportion of patients in the durvalumab arm receiving subsequent IO therapy was relatively small and duration of treatment was shorter than the placebo arm

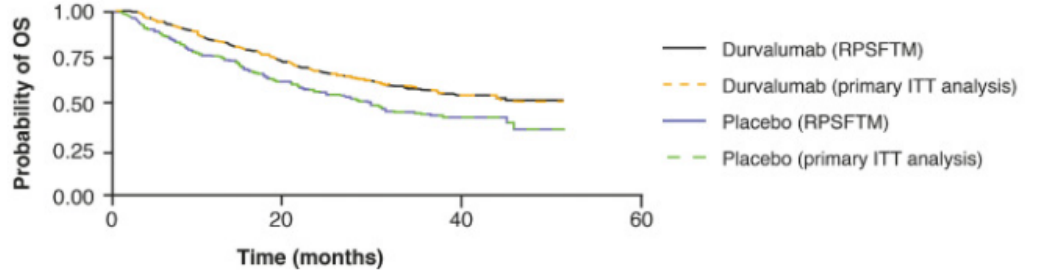
As described in the CS (table 7), only [redacted] of patients in the durvalumab arm received subsequent IO therapy, compared to [redacted] in the placebo arm
Also as described in the CS (section A.6.4.1), the mean duration of immunotherapy use was greater in the placebo arm ([redacted]) compared with the durvalumab arm ([redacted])

A previously conducted analysis removing the treatment effect of subsequent immunotherapy in the durvalumab arm demonstrated minimal impact on OS</td>
</tr>
</table>

		• A study assessing the influence of subsequent immunotherapy on overall survival in patients with unresectable stage III NSCLC from the PACIFIC study demonstrated that adjustments for subsequent IO therapy were consistent with the 3-year ITT analysis[15]
		• For reference, the observed HRs in the primary and updated 3-year ITT analysis of the PACIFIC trial (i.e. PD-L1 all comers) were 0.68[16] and 0.69[17] respectively
		• Two statistical methods were implemented to examine the influence of subsequent IO on OS; a rank preserving structural time failure model (RPSFTM) and a modified 2-stage method (M2SM)
		• The RPSFTM was used to examine a number of hypothetical scenarios. The most relevant scenarios for this appraisal were:
		  ○ Removal of subsequent IO use from the durvalumab arm and proportion of IO use in the placebo arm set to 27%, as per the PACIFIC trial resulted in an OS HR of 0.70 (95% CI: 0.55, 0.88) by log-rank test (Figure 1)
		  ○ Removal of subsequent IO use from the durvalumab arm and proportion of IO use in the placebo arm set to 40% (i.e. an over estimation of IO use in the placebo arm compared to the population for appraisal) resulted in an estimated OS HR of 0.69 (95% CI: 0.55, 0.87)

Figure 1: Rank Preserving Structural Failure Time Model: Observed and adjusted Kaplan-Meier curves for overall survival (PACIFIC 3-year ITT)

	Durvalumab	Placebo	HR (95% CI)
Median OS (95% CI), months			
RPSFTM	NR (37.0–NR)	29.1 (22.1–35.1)	0.70 (0.55–0.88)
Primary ITT analysis[9,13]	NR (34.7–NR)	28.7 (22.9–NR)	0.68 (0.53–0.87)



Notes: Assumes patients in the placebo arm received subsequent immunotherapy as prescribed in the trial, and that patients in the durvalumab arm received no subsequent immunotherapy (based on the log-rank test)

Key: CI: confidence interval; HR, hazard ratio; ITT, intention to treat; OS, overall survival; NR, not reached, RPSFTM, rank preserving structural failure time model

Source: Ouwens et al. 2019[15]

		• The M2SM was also used to examine a number of scenarios. The most relevant scenario for this appraisal was adjustment of the durvalumab arm to receive no subsequent IO, which resulted in an OS HR of 0.69 • Overall, the estimated OS HRs produced by both of these methods were comparable to the OS HR observed in the primary and updated 3-year ITT analysis of the PACIFIC trial. These data therefore suggest that subsequent immunotherapy, received after disease progression on either placebo or durvalumab, had minimal influence on OS compared with the benefit already conferred by earlier treatment with durvalumab. It can be concluded that removing subsequent IO treatments in the durvalumab arm of the PACIFIC trial would not significantly impact the OS, however, the cost of subsequent therapies would be reduced, as previously demonstrated in the response to ERG clarification question B6. Therefore, our base case is conservative, especially given the small proportion of patients receiving subsequent IO in the durvalumab arm and the key model driver being PFS, which is not influenced by subsequent therapy.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
The Company has no additional issues to raise.			

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 3 – No additional quality of life data was collected since durvalumab entered the CDF	The NICE technical team identified an error in the economic model, i.e., the model adopts a lower health state utility value (HSUV) for the progressed disease state for the durvalumab (0.769) vs. the placebo arm (0.793), which should not be the case (HSUV for the PD state should be equal across both arms).	• The reason that the HSUV for progressed disease for the durvalumab arm was lower than the placebo arm is because a treatment related decrement was applied to reflect that the incidence of adverse events was higher in the durvalumab arm (0.793 – 0.0024 = 0.769). • However, considering that it is reasonable to assume that the impact of AEs on	Correcting this error has led to a small improvement in the base case ICER from £11,719 to £11,507 (see Table 5 below). As the impact is less than £200, the Company felt it was reasonable to not re-run all of the sensitivity and scenario analyses, as the conclusion(s) of the economic analysis remain the same.

		patients who received durvalumab in the PF state will not apply indefinitely over time, the HSUV for the PD state has now been adjusted to be equal across both arms at 0.793.	

Table 5: Updated Company's base case analysis

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Durvalumab	[redacted]	[redacted]			
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	£11,507

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Clinical expert statement and technical engagement response form

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on durvalumab in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (Section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

Deadline for comments by **5pm** on **17 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

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Part 1: Treating non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Patricia Margaret Fisher
2. Name of organisation	Weston Park Hospital, Sheffield Teaching Hospitals Foundation Trust
3. Job title or position	Consultant Clinical Oncologist with Thoracic Oncology practice
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with non-small-cell lung cancer? ☐ A specialist in the clinical evidence base for non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NIL

Clinical expert statement

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

8. What is the main aim of treatment for non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	In the context of locally advanced disease, which is the indication for the technology under assessment, the aim of treatment is cure / long term control combined with maintaining quality of life. For those patients who do relapse the aim is to delay development of recurrent disease for as long as possible. Again maintaining quality of life is important.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	The overall treatment plan would aim to result in at least radiological stabilisation of disease – we know from studies where surgery takes place after chemoradiotherapy treatment that radiology scans can significantly underestimate the response to treatment in a significant proportion of patients. However, many patients will have a marked reduction in the volume of their disease during the chemoradiotherapy component of their treatment. Maintenance Durvalumab is then intended to maintain that response, be it a partial response or stable disease, for as long as possible. For some patients these responses can then be maintained for very long periods of time suggesting the residual CT abnormality is post radiotherapy change rather than residual cancer.
10. In your view, is there an unmet need for patients and healthcare professionals in non-small-cell lung cancer?	Yes – previously patients undergoing chemoradiotherapy would have outcomes inferior to those undergoing surgery. The addition of Durvalumab means outcomes of a nonsurgical treatment strategy are now at least comparable if not better than surgical outcomes.
11. How is non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are multiple guidelines available for the management of lung cancer, however, National Lung Cancer Audit data demonstrates that there is a large degree of variation in the management of patients with Stage III NSCLC. Many patients receive no active treatment or palliative treatment with radiotherapy plus or minus chemotherapy only. In the UK, sequential chemoradiotherapy has to date been used more than concurrent chemoradiotherapy due to patient fitness / comorbidities and the limitations of older radiotherapy techniques and large radiotherapy fields. However

• What impact would durvalumab have on the current pathway of care?	sequential chemoradiotherapy, whilst being better tolerated, has inferior outcomes to concurrent chemoradiotherapy. Since the initial PACIFIC results were published there has already been a significant shift to more concurrent chemoradiotherapy to enable an increasing number of patients to have access to maintenance Durvalumab due to the magnitude of improvement in outcomes.
12. Will durvalumab be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between durvalumab and current care? • In what clinical setting should durvalumab be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce durvalumab? (for example, for facilities, equipment, or training)	Durvalumab is already in use extensively in the UK due to its availability on the Cancer Drugs Fund. It is given intravenously every 4 weeks for 12 months in total. Durvalumab is only be prescribed by clinical and medical oncologists who are based in secondary care. However, it can be administered in non-hospital settings including people's homes as it is a low-risk infusion of short duration. There is no specific investment required other than the need to ensure that treatment administration units have sufficient capacity (both physical space and workforce) to deliver as there are significant capacity restraints in most if not all services currently. No training requirements as thoracic oncology teams already use many other immunotherapy drugs.
13. Do you expect durvalumab to provide clinically meaningful benefits compared with current care? • Do you expect durvalumab to increase length of life more than current care? • Do you expect durvalumab to increase health-related quality of life more than current care?	Yes, the updated 5-year survival outcomes from PACIFIC clearly demonstrate a clinically very meaningful improvement in overall survival with median survival of 63 months Vs 29 months i.e., the addition of Durvalumab added almost 3 years of additional life. No previous study of different approaches to the multimodality management of Stage III NSCLC has shown an improvement of anything like this magnitude. Long term control of lung cancer would be expected to improve QoL and even for those patients who do ultimately relapse, deferring the need to use further lines of oncology treatments should also result in improved QoL.

14. Are there any groups of people for whom durvalumab would be more or less effective (or appropriate) than the general population?	The magnitude of benefit that patients with tumours expressing <1% PDL1 remains a controversial subject not least as this was not a pre specified analysis. However, all other subsets of PDL1 derive clear benefit. Some patients do not recover sufficiently from their initial chemoradiation to be able to receive Durvalumab in a timely fashion, plus a small proportion of patients have autoimmune conditions or other pre-existing health conditions that are contra-indications to treatment with immunotherapy including Durvalumab.
15. Will durvalumab be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Durvalumab is already the current standard of care in the UK. It is delivered as a short IV infusion (1 hour) every 4 weeks x12 i.e., for 12 months. Due the wide range of potential toxicities patients require regular monitoring and the panel of blood tests done is wider than that used for monitoring chemotherapy. As treatment lasts longer there is also an increased need for CT scanning which is generally performed every 3 months whilst patients are on treatment.
16. Will any rules (informal or formal) be used to start or stop treatment with durvalumab? Do these include any additional testing?	I would anticipate that the rules for use of Durvalumab will remain as per the current CDF indications as, with the exception of the PDL1 cut-off of 1%, they conform to the evidence base. PDL1 testing is now the standard of care for patients with NSCLC as there are multiple potential indications for treatment with immunotherapy agents depending on stage of disease. PDL1 testing is therefore often performed reflexly by thoracic pathologists as part of the routine battery of immunohistochemical and molecular testing for lung cancer specimens.
17. Do you consider that the use of durvalumab will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.

• Do the instruments that measure quality of life fully capture all the benefits of durvalumab or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider durvalumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is durvalumab a 'step-change' in the management of the condition? • Does the use of durvalumab address any particular unmet need of the patient population?	Yes, an improvement in overall survival of approaching 3 years definitely represents a step change and is unprecedented in trials of multimodality treatment for stage III NSCLC. This is a very significant improvement in survival for people unable to have surgery due to the distribution of their disease or their comorbidities – whereas previously this group would have had a significantly worse outcome than patients undergoing surgery, they now have comparable if not better survival rates.
19. How do any side effects or adverse effects of durvalumab affect the management of the condition and the patient's quality of life?	Whilst there is a wide range of potential toxicities, most people tolerate Durvalumab very well and significantly better than chemotherapy type treatments. Severe pneumonitis and non-pneumonitis immune mediated adverse events are very rare with less than 2% of patients experiencing side effects in each category. One of the most common and long-lasting immune toxicities is that of thyroid dysfunction which may require lifelong medication / monitoring but have a minimal impact on patients QoL once controlled. Other side effects are managed with the administration of systemic corticosteroids and / or treatment interruption with only occasional need for additional treatments to counteract the side effects such as infliximab or mycophenolate. A very small number of people treated with immunotherapy will have long lasting effects from having required very high dose steroids for extended periods of time to manage this toxicity.

20. Do the clinical trials on durvalumab reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes – therefore next question not relevant. Overall survival is the most important outcome in the context of a trial investigating a curative treatment strategy. As OS was reported in the PACIFIC study the question on surrogate outcome measures is also not relevant. Quality of life outcomes are also important. No.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
23. How do data on real-world experience compare with the trial data?	I am aware of 2 real world data sets. Outcomes from PACIFIC-R were presented at ESMO (the European Society of Medical Oncology Annual Meeting) in 2021. 1399 patients received treatment with Durvalumab on an Early Access to Medicine scheme of which 54 were from the UK. In some countries sequential chemoradiotherapy was permitted and therefore only 76% of the patients received concurrent chemoradiotherapy before receiving maintenance Durvalumab. The median progression free survival for patients with a PDL1 of 1% or greater was 22.4 months which is comparable to the PACIFIC trial median PFS of 24.9 months for patients with a PDL1 of 1% or greater. The SACT data set confirms my clinical experience in that despite the inclusion of older (median age 67 Vs 64 years) and less fit (14% PS2 Vs 0.5%, only 27% PS0

	Vs 49.5%) patients than those in the PACIFIC trial, the overall survival rate at 24 months was 68% for PDL1 positive patients in the SACT data set compared with 72.9% for PDL1 positive patients receiving Durvalumab in the PACIFIC study
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	No.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1 – Differences in PD-L1 status between the PACIFIC trial population and the SACT cohort Does the number of patients with PD-L1 status unknown having durvalumab in the SACT data (12%) correspond to your clinical experience? How would the efficacy of durvalumab compare with that in patients with PD-L1 1% or more?	PDL1 testing was not embedded in clinical practice at the time of the study and was not mandated in the PACIFIC trial – it is important to note that 36% of patients in the study were PDL1 status unknown. Lung cancer biopsies are often comprised of limited tissue due to the difficulty in safely accessing the tumour, particularly in people with poor lung function who may not be able to withstand a pneumothorax. These biopsy specimens are then subject to an increasing range of testing for molecular targets as well as PDL1 meaning that the pathologists have insufficient tissue to run all the additional tests in some cases. Therefore sometimes we need to perform more than one biopsy in an individual patient to get all the information we require

Clinical expert statement

	to make a personalised treatment plan. However, it's not always possible to safely do more than one biopsy. There are also sometimes technical failures within pathology laboratories although these are rare. Approximately 1 in 10 patients without PDL1 status is a little higher than that in my own clinical practice but not out of keeping with UK clinical practice. The actual PDL1 status of those patients with that information missing would be expected to break down into the same proportions as the overall population of NSCLC in the UK i.e., around 25 – 30% of them would be PDL1 <1% and therefore the magnitude of benefit from Durvalumab would potentially be less. In a patient with an unknown PDL1 status it would be preferable to offer a highly effective and very tolerable treatment rather than deny them this opportunity on a 1 in 3 chance that they may derive less benefit. This also ensures equity of access.
Issue 2 – Differences between the dosing used in the trial (weight based 10mg/kg, Q2W) and the fixed dose (1500mg, Q4W) given to some SACT patients To what extent is the fixed dose of durvalumab now used in UK clinical practice? Would the efficacy of	The fixed dose was introduced as an option as part of the interim CDF treatment changes in April 2020 to reduce the frequency hospital attendance during the COVID pandemic. The vast majority of UK centres have since continued to deliver treatment Q4W due to a) increased convenience for people on treatment b) capacity issues in chemotherapy day case units. The introduction of the Q4W dosing was approved by the EMA in January 2021 for this indication as, based on modelling and simulation of exposure there were no anticipated clinically significant differences in efficacy and safety between Durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks in locally advanced NSCLC. The exception

durvalumab be affected by the dosing regimen?	being that patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to Durvalumab 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg. Note this exception still allows Q4W dosing and patients below 30 kg are extremely rare in an adult oncology practice. Lung cancer is also extremely rare in a paediatric population. Finally, there are many instances of other immunotherapy drugs widely used in the UK for the treatment of NSCLC switching to longer treatment intervals at the same time and for the same reasons which have also remained standard practice in the UK – pembrolizumab Q6W instead of Q3W, atezolizumab Q4W instead of Q3W for example.
Issue 3 – No additional quality of life data was collected since durvalumab entered the CDF **Are the utility values used in the appraisal appropriate?** **Durvalumab arm – Progression free = 0.803** **Durvalumab arm – Progressed disease = 0.769** **Standard of care arm – Progression free = 0.827** **Standard of care arm – Progressed disease = 0.793**	Whilst I'm not an expert in this area, those values seem not unreasonable.

Issue 4 – Internal consistency between modelled survival and observed trial data was lacking Do the modelled estimates of survival for the two arms match what you would expect to see in clinical practice? Total life years gained was 8.1 for durvalumab and 5.0 for standard of care.	Yes. However, my clinical experience with Durvalumab is limited to the 3 years it's been available via the CDF. Nevertheless, we are seeing people with durable responses / stable disease many months post completion of Durvalumab and our experience with other immunotherapy drugs used in patients with NSCLC is that responses that are maintained at 2 to 3 years post treatment are highly likely to be maintained in the longer term.
Issue 5 – Appropriateness of assumptions on the duration of treatment effect To what extent do you expect the treatment effect of durvalumab would wane over a patient's lifetime?	I would expect there to be only minor waning of the treatment effect of Durvalumab once patients are 2 years out from completion of treatment. Firstly, this is biologically plausible as Durvalumab releases inhibition of immune responses in the tumour microenvironment, resulting in prolonged T cell activation. Secondly, we now have significant knowledge from other immunotherapy studies and extensive clinical experience, and know that the responses seen with this class of drugs are durable and maintained at 5 years and longer.
Issue 6 – Subsequent treatments included in the model Do the subsequent therapies and their durations represent UK clinical practice?	PACIFIC was an international trial and recruitment took place in Europe, the Americas and Asia as well as the UK. Consequently, some of the subsequent therapies are not those used in clinical practice in the UK i.e., Irinotecan, Ramucirumab and the Tegafur / Gimeracil / Oteracil combination.

	Also, further treatment with immunotherapy would not be permitted under the CDF rules for those patients in the Durvalumab arm of PACIFIC, whilst those on the placebo arm would not only be allowed but very much expected to receive immunotherapy as a subsequent line of treatment. Some other malignancies treated with immunotherapy, in particular malignant melanoma, do have an evidence base for re-treating patients with further immunotherapy when patients experience progression off treatment. However in lung cancer the trials are on-going and therefore the magnitude of any potential benefit to this treatment strategy difficult to quantify. With those provisos, yes subsequent therapies represent current UK clinical practice.
Are there any important issues that have been missed in ERG report?	No.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The updated 5-year survival outcomes from PACIFIC clearly demonstrate a clinically very meaningful improvement in overall survival with median survival of 63 months Vs 29 months i.e., the addition of Durvalumab added almost 3 years of additional life - no previous study of different approaches to the multimodality management of Stage III NSCLC have shown an improvement of anything like that magnitude.

This very significant improvement in survival for people unable to have surgery due to the distribution of their disease or their comorbidities means that whereas previously this group would have had a significantly worse outcome than patients undergoing surgery, they now have comparable if not better survival rates.

Both of the PACIFIC-R and the SACT data sets are in line with my clinical experience i.e. despite the inclusion of older and less fit patients, as well as some patients who received sequential chemoradiotherapy (which is inferior to concurrent chemoradiotherapy) the outcomes are broadly in keeping with those from the PACIFIC trial.

There is no evidence that extending the treatment interval reduces the efficacy of immunotherapy drugs and pharmacology studies have reassured the oncology community that this is very unlikely; many other immunotherapy drugs have also switched to extended intervals therefore this is not unique to Durvalumab.

I would expect there to be only minor waning of the treatment effect of Durvalumab once patients are 2 years out from completion of treatment.

Thank you for your time.

Your privacy

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

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

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

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

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Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (Section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

Deadline for comments by **5pm** on **17 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Treating non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Elizabeth Toy
2. Name of organisation	Somerset Foundation Trust
3. Job title or position	Consultant Clinical Oncologist and Co Lead for Lung Cancer GIRFT Workstream
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with non-small-cell lung cancer? ☐ A specialist in the clinical evidence base for non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

Clinical expert statement

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

8. What is the main aim of treatment for non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Within the context of this appraisal of an indication for patients with radically treatable disease the aims of treatment are; To improve rates of long-term survival Increase chance of cure Delay time to progression Maintenance of quality of life Overall improvement of quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement of symptoms e.g. reduced pain Delay in tumour progression of 6 months or greater Although we often see tumour shrinkage post radiotherapy and there can be ongoing shrinkage for a number of months afterwards on devolumab the amount of shrinkage is not a clinically significant measure per se.
10. In your view, is there an unmet need for patients and healthcare professionals in non-small-cell lung cancer?	Yes, despite significant improvements in imaging and radiotherapy techniques which have improved staging, improved accuracy of treatment delivery and reduced treatment related morbidity and mortality, the chance of long term survival for non-small cell lung cancer remains significantly lower than that of other tumour types of a similar stage e.g breast , prostate or colon.
11. How is non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	NICE Guidance (NG122) Lung Cancer Diagnosis and Management 2019 National Optimal Lung Cancer Pathway and associated diagnostic standards of care for lung cancer published by Lung Cancer Expert Reference Group Radiotherapy for Lung Cancer-RCR Consensus Statements 2020 The commissioned lung cancer pathway for the NHS is the national optimal lung cancer pathway which maps out each step of the diagnostic and treatment pathway.

• What impact would durvalumab have on the current pathway of care?	The main options are Surgery +/- adjuvant chemotherapy, Radical radiotherapy alone, sequential chemoradiotherapy and concurrent chemoradiotherapy. There is however variation across the country in surgical rates in addition to variation in the use of radical radiotherapy either as a single modality or in combination with platinum-based chemotherapy. Whilst patient choice and fitness will be factors in suitability for these radical treatments it is recognised in data collected through the national lung cancer audit that physician preferences also impact on the modality of treatment offered and indeed the intent of that treatment radical or palliative. This variation is greatest in stage three non-small cell lung cancer which in itself represents a very heterogeneous disease. There is currently significant work going on through the professional organisations e.g. Royal College of Radiologists, British Thoracic Oncology group and also the Cancer Alliances and the GIRFT (get it right first time) lung cancer workstream to address this variation and undoubtedly in recent years there has been an increase in the use of concurrent chemoradiation in preference to sequential chemo-radiotherapy or single modality radiotherapy. This change has been enabled due to three main factors: 1)IMRT (intensity modulated radiotherapy), motion management techniques and IGRT (Image guided radiotherapy) being more widely available in UK centres enabling treatment to be delivered more accurately to the cancer with less damage to surrounding tissues 2)Training of healthcare professionals to deliver multimodality therapies 3)The funding of Durvalumab via the CDF for patients who had received concurrent treatment. The clear clinical benefit over standard chemoradiotherapy alone, lead practitioners, who had been concerned about the excess toxicity of concurrent treatment over sequential treatment for only a 1-2% improvement in long term outcomes to switch to concurrent therapy in order to access adjuvant

	durvalumab therapy which has been regarded by the clinical community as a huge step forward in patient care. If Durvalumab were to be fully funded through NICE I believe concurrent chemoradiotherapy rates will increase still further as clinicians gain confidence in using multimodality therapies. Furthermore there may be a small number of patients who would currently be offered and elect to have surgery, who on discussion of mortality and morbidity and long term outcomes may elect to received concurrent chemoradiotherapy followed by durvalumab. Additionally as outcomes are reviewed at MDT, patients currently felt borderline either anatomically or due to fitness for surgery e.g those requiring a pneumonectomy may be offered the lower risk option of chemoradiotherapy + durvalumab as the MDT recommendation.
12. Will durvalumab be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between durvalumab and current care? • In what clinical setting should durvalumab be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce durvalumab? (for example, for facilities, equipment, or training)	The clinical community has already embraced the use of Durvalumab since CDF access being granted in 2019, it has rapidly become the standard of care. Clearly it represents an additional period (usually 12 months) of active treatment compared to the care delivered prior to May 2019. It should only be prescribed and delivered under the direction of clinical or medical oncologists and their teams who are experienced in the management of immune related toxicities. It may however be physically delivered in community settings e.g chemotherapy out reach clinics, outside the cancer centre or indeed in a persons own home by appropriately trained staff. Clearly the adjuvant nature of the treatment necessitates a greater number of hospital visits for treatment and clinical review than if the patient were on radiological follow up alone. This requires clinic capacity, appropriate workforce

	(oncologist and/ or immunotherapy nurse specialist), chair space on the chemotherapy unit and laboratory and pharmacy time. However, this is offset by the expectation that the majority of these patients would be offered 24 months of immunotherapy at the time of their relapse As with any new indication for therapy, the key investment required is an adequate appropriately trained workforce. However the expertise of delivering immunotherapy (durvalumab) is already business as usual for all oncology units.
13. Do you expect durvalumab to provide clinically meaningful benefits compared with current care? • Do you expect durvalumab to increase length of life more than current care? • Do you expect durvalumab to increase health-related quality of life more than current care?	Yes, this is described in the executive summary "Data from the SACT database confirms the benefit of durvalumab demonstrated in the PACIFIC trial as generalisable to the UK population. The OS rate at 24 months was 68% (95% CI: 62%, 74%) for the SACT PD-L1 ≥1% group (Appendix C, page 4) compared with 72.9% (95% CI: 66.2%, 78.4%) for the durvalumab treated PACIFIC PD-L1 ≥1% group. " This is in line with my personal experience of using Durvalumab. Likewise I would expect health related quality of life to increase with the use of durvalumab compared to radiotherapy/ chemoradiotherapy alone. The drug is very well tolerated and the improvements in PFS and OS spare patients the significant symptom burden/ physical/ psychological/ social/ financial/ emotional and spiritual morbidity that occurs with recurrent and often terminal cancer
14. Are there any groups of people for whom durvalumab would be more or less effective (or appropriate) than the general population?	Durvalumab would be relatively contraindicated in patients with a serious concomitant auto-immune disease. Caution should also be used in patients who have had a solid organ transplant.

15. Will durvalumab be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	See question 12. Treatment with Durvalumab is generally very acceptable to patients
16. Will any rules (informal or formal) be used to start or stop treatment with durvalumab? Do these include any additional testing?	It would be important to ascertain patients had not developed metastatic disease during their chemoradiotherapy treatment as Durvalumab would not be the licensed agent of choice in the metastatic setting where alternative immunotherapy agents are funded for up to 2 years. At the present time there is not a nationally agreed guideline for follow up imaging after chemoradiotherapy. Most centres would offer CT imaging at 2-4 monthly intervals for patients suitable for further systemic therapies or SABR for oligometastatic disease upon relapse. Evidence of progression on such a scan would inform a decision to stop durvalumab therapy. I note the agreed comparator for the review was for less frequent imaging. Centres would monitor patients for evidence of immune related toxicities throughout treatment and would investigate these appropriately as an when a potential toxicity arose. Examples of such tests would include additional blood tests, radiological investigations e.g MRI brain for suspected hypophysitis and endoscopic procedures e.g sigmoidoscopy for suspected immune related colitis. A high grade toxicity e.g. pneumonitis or nephritis which does not settle with steroid treament may preclude further treatment with durvalumab i.e a decision to stop. This would be decided in line with local departments guidelines for the management of immune related toxicities

17. Do you consider that the use of durvalumab will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of durvalumab or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No The instruments used for measuring quality of life are validated and would capture appropriate data. At
18. Do you consider durvalumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is durvalumab a 'step-change' in the management of the condition? • Does the use of durvalumab address any particular unmet need of the patient population?	The significant improvements in both PFS and OS are a huge improvement over SOC treatments and should be considered as step change in the management. Although the licensed indication id for inoperable patients t is likely that the role of surgery will be questioned for some patients in view of the superior outcomes for chemoradiotherapy + durvalumab compared to historic surgical series.
19. How do any side effects or adverse effects of durvalumab affect the management of the condition and the patient's quality of life?	In general durvalumab is extremely well tolerated however a significant subset (30.5 % G3/4 toxicities reported in the PACIFIC study) of patients will require acute management of their toxicities which may in some cases require a hospital admission although these are now usually managed as outpatients. For a small number of patients the effects may be chronic e.g pneumonitis which may adversely impact on QOL.
20. Do the clinical trials on durvalumab reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	Yes Most important outcomes are OS

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	PFS QOL These were all measured within the PACIFIC trial. I believe the data to now be clinically mature and therefore representative of long term outcomes. I am not aware of any new safety signals however recognise that in real world practice the rate of pneumonitis is somewhat higher in the real world population.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
23. How do data on real-world experience compare with the trial data?	Clinical trial populations will usually represent a fitter population than we see in a real world experience. Patients are often more motivated e.g to travel significant distances to participate in a clinical trial and have less comorbidity than the general population. In a clinical trial a number of potential patients will be excluded both pre and during screening. However the data from the SACT database confirms that the improvements in outcomes are applicable and generalisable to the UK population
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	No

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on durvalumab in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (Section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1 – Differences in PD-L1 status between the PACIFIC trial population and the SACT cohort Does the number of patients with PD-L1 status unknown having durvalumab in the SACT data (12%) correspond to your clinical experience? How would the efficacy of durvalumab compare with that in patients with PD-L1 1% or more?	I would expect a degree of inter-hospital variation in the patients with PDL1 unknown due to the variation in access to high quality EBUS , CT biopsy and Navigational bronchoscopy. In addition, we see variation in the individual MDTs enthusiasm for rebiopsy if there is inadequate tissue for full molecular testing. In my own Trust I believe the percentage of PDL1 unknown is less than 10% however the national figure of 12 % would be in line with expected variation in practice. Obviously, the cohort of PDL1 unknown will contain some patients who are PDL1 negative and therefore maybe less likely to derive maximal benefit from durvalumab therapy. These may be patients without mediastinal disease or with fewer lymph nodes involved resulting in difficulty in gaining sufficient representative tissue at EBUS for PDL1 testing i.e earlier stage disease, who may have a higher rate of disease control with chemoradiotherapy alone.
Issue 2 – Differences between the dosing used in the trial (weight based 10mg/kg, Q2W) and the fixed	Fixed dosing and less frequent dosing of all immunotherapy agents licensed for non-small cell lung cancer is now widely used across the UK in both the radical and palliative settings.

Clinical expert statement

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

dose (1500mg, Q4W) given to some SACT patients To what extent is the fixed dose of durvalumab now used in UK clinical practice? Would the efficacy of durvalumab be affected by the dosing regimen?	This approach has not raised new safety signals and is welcomed by both patients and healthcare providers due to the reduced time waiting for medication, reduced drug wastage and the reduction in hospital attendances. As a clinician I was very reassured when we first made such steps to see the rationale being supported by pharmacokinetic data. In line with our experience of other PDL1 / PD1 inhibitors I do not think the efficacy of Durvalumab is likely to be affected by this dosing regimen
Issue 3 – No additional quality of life data was collected since durvalumab entered the CDF Are the utility values used in the appraisal appropriate? (0.79 for the progression free state and 0.76 for the progressed disease state)	The assignment of Health Sate Utility Values lies outside my area of expertise
Issue 4 – Internal consistency between modelled survival and observed trial data was lacking Do the modelled estimates of survival for the two arms match what you	The choice of the optimal model lies outside my expertise however based on clinical practice these estimates look to be consistent with clinical experience

would expect to see in clinical practice? Total life years gained was 8.1 for durvalumab and 5.0 for standard of care.	
Issue 5 – Appropriateness of assumptions on the duration of treatment effect To what extent do you expect the treatment effect of durvalumab would wane over a patient's lifetime?	I would not expect to see the effect waning over time based on my experience with durvalumab and other immunotherapy agents. Prior to durvalumab being available via the CDF we saw the majority of patients relapsing within the first 2 years. I believe the more mature data now published supports the view that efficacy is unlikely to wane over time
Issue 6 – Subsequent treatments included in the model Do the subsequent therapies and their durations represent UK clinical practice?	The majority of the patients in the UK would not currently be eligible to receive a second immunotherapy agent. The most commonly used subsequent line agents in the UK would include radiotherapy, carboplatin, pemetrexed, gemcitabine, vinorelbine, docetaxel, osimertinib and no further treatment For small numbers of patients with driver mutations would receive, osimertinib, Alectanib (for ALK positive patients rather that crizotinib) or Crizotinib for Ros 1 mutations. A small number of patients will now undergo re biopsy for molecular analysis and may be eligible of molecularly targeted agents that were unavailable at that time. Examples would include BRAF or KRAS inhibitors.
Are there any important issues that have been missed in ERG report?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The improvement in progression free and overall survival is clinically very significant and is achieved with a very manageable toxicity profile.

The data from the PACIFIC trial is applicable in a real world UK population and represents a step change in treatment. Where previously clinicians were reluctant to consider cure of locally advanced NSCLC largely discussing long term control, the addition of durvalumab to concurrent chemoradiation allows this to be a realistic aim.

Availability of Durvalumab through the CDF has been rapidly adopted across the UK and has helped improve access to concomitant chemoradiation across the UK such that concurrent chemoradiation + durvalumab is now considered the best practice standard of care by Clinical Oncologists

The durvalumab dosing schedule is convenient for patients and clinical teams already have the necessary expertise to deliver the treatment safely

I would strongly support NICE guidance advocating the use of Durvalumab for patients treated with definitive chemoradiation who have not progressed on treatment with a PDL1 >1 or uncertain due to a lack of available tissue

Thank you for your time.

NICE National Institute for Health and Care Excellence

Your privacy

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

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

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

NICE National Institute for Health and Care Excellence

Technical engagement response form

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Deadline for comments by **5pm** on **17 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Technical engagement response form

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (CDF review of TA578) [ID3885]

NICE National Institute for Health and Care Excellence

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

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Roy Castle Lung Cancer Foundation
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1 – Differences in PD-L1 status between the PACIFIC trial population and the SACT cohort	Yes/No	
Issue 2 – Differences between the dosing used in the trial (weight based 10mg/kg, Q2W) and the fixed dose (1500mg, Q4W) given to some SACT patients	Yes/No	
Issue 3 – No additional quality of life data was collected since durvalumab entered the CDF	Yes/No	

Issue 4 – Internal consistency between modelled survival and observed trial data was lacking	Yes/No	
Issue 5 – Appropriateness of assumptions on the duration of treatment effect	Yes/No	
Issue 6 – Subsequent treatments included in the model	Yes/No	

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Importance of the technology		No	Roy Castle Lung Cancer Foundation is a UK charity, focused on improving outcomes for people affected by this often devastating disease. The Foundation has contact with patients/carers through its UK network of Lung Cancer Patient Support Groups, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline. We do not have any additional evidence to present, as part of this review. However, we would wish to express the views of our patient community, for consideration, as decisions are made on reviewing this technology. Durvalumab has been available through the CDF in recent years, in an adjuvant setting, after chemoradiation therapy, whilst data has been collected. Durvalumab in this setting has been confirmed as showing a significant survival benefit. From a patient perspective this is important for this group of patients, where overall survival has been disappointing and not improved, despite advances in chemotherapy an radiotherapy treatments. Patients have more chance of cure and of delayed recurrence. This marks a step change in the treatment of this disease. We would strongly support positive NICE guidance for the use of durvalumab following radical

			chemoradiation in unresectable NSCLC, as within the PACIFIC Trial.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]