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 [ID1175]

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 [ID1175]

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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

Single technology appraisal

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

Document B

Company evidence submission

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ALK	Anaplastic lymphoma kinase
APF12	Proportion of patients alive and progression-free at 12 months from randomisation
APF18	Proportion of patients alive and progression-free at 18 months from randomisation
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BSC	Best supportive care
CD	Cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CI	Confidence interval
CR	Complete response
CRT	Chemoradiation therapy
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTx	Chemotherapy
DCO	Data cut-off
DoR	Duration of response
EAP	Early Access Program
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
ERG	Evidence Review Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-C30	EORTC 30-item core quality of life questionnaire
EORTC-QLQ-LC13	EORTC quality of life questionnaire and lung cancer module
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Hazard ratio

Abbreviation	Definition
HRG	Healthcare resource group
HRQL	Health-related quality of life
HSU	Health state utility
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDMC	Independent data monitoring committee
imAE	Immune-mediated adverse event
ITT	Intention to treat
IV	Intravenous
KM	Kaplan–Meier
LCSS	Lung Cancer Symptom Scale
LOCF	Last observation carried forward
MAA	Marketing authorisation application
mg	Milligram
MHC	Major histocompatibility complex
MIMS	Monthly Index of Medical Specialities
mITT	Modified intention-to-treat
MoA	Mechanism of action
n	Number (subset of sample)
N	Number (total sample size)
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reached
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OS12	Proportion of patients alive at 12-months
OS24	Proportion of patients alive at 24-months
PAS	Patient access scheme
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PFS2	Time to second progression or death
PFS12	Proportion of patients alive and progression-free at 12-months

Abbreviation	Definition
PFS18	Proportion of patients alive and progression-free at 18-months
PPS	Post-progression survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
RT	Radiotherapy
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer
SoC	Standard of care
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology appraisal
TCR	T-cell receptor
TFST	Time to first subsequent therapy or death
TSST	Time to second subsequent therapy or death
TNM	Tumour-Node-Metastasis
TTD	Time to treatment discontinuation
TTDM	Time to death or distant metastasis
TTP	Time to progression
ULN	Upper limit of normal
WHO	World Health Organization

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the full marketing authorisation for durvalumab (IMFINZI™) monotherapy for the treatment of adults with locally advanced, unresectable NSCLC whose tumours express PD-L1 on ≥ 1% of tumour cells (TC) and whose disease has not progressed following platinum-based CRT.[1] The decision problem that the submission addresses is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose disease has not progressed after platinum-based chemo-radiation therapy (CRT)	Adults with locally-advanced, unresectable, Stage III NSCLC whose tumours express PD-L1 on ≥ 1% of tumour cells (TCs) and whose disease has not progressed following platinum-based CRT	The submission will focus on locally advanced (Stage III), unresectable NSCLC patients, whose tumours express PD-L1 on ≥ 1% of TCs, to reflect the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)[§], and the anticipated Marketing Authorisation for durvalumab in this indication
Intervention	Durvalumab	Durvalumab (10mg / kg every two weeks [Q2W] via intravenous [IV] infusion)	N/A
Comparator(s)	Best supportive care	Best supportive care (referred to as "active follow-up" throughout)	N/A
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates	• PFS (primary endpoint) – Secondary endpoints:	Time from randomisation to second progression or death (PFS2) and time

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Health-related quality of life (HRQL) • Adverse effects of treatment	proportion of patients alive and progression free at 12 and 18 months (PFS12 and PFS18) – Supportive summary analysis: time to first subsequent therapy or death (TFST) • PFS2* – Supportive summary analysis: time to second subsequent therapy or death (TSST) • Post-progression survival (PPS; *post-hoc* analysis) • OS (primary endpoint) – Secondary analysis: proportion of patients alive at 24 months (OS24) – *Post-hoc* analysis: impact of subsequent immunotherapy use • Response rates • TTDM* • HRQL (EORTC QLQ-C30 and EORTC QLQ-LC13) • Adverse effects of treatment	to death or distant metastasis (TTDM) endpoints are relevant given the earlier disease setting (Stage III) relative to previous immunotherapy appraisals in NSCLC (stage IV metastatic setting). They provide important information about the benefits of treatment beyond delaying disease progression: • PFS2 is an intermediate endpoint between PFS and OS and reflects real-life treatment decisions and patient experience. Its use is recommended by the EMA to capture potential negative impacts on next-line therapy and to demonstrate that any potential tolerability concerns are outweighed by treatment benefit.[2] • TTDM captures the value of maintaining local control and delaying progression to more-advanced metastatic disease stage

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a National Health Service (NHS) and Personal Social Services perspective.	As per National Institute for Health and Care Excellence (NICE) reference case. A lifetime time horizon is appropriate in this setting to capture all differences in costs or outcomes between the technologies being compared.	N/A

Key: CHMP, Committee for Medicinal Products for Human Use; CRT, chemoradiation therapy; EMA, European Medicines Agency; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer quality of life questionnaire and lung cancer module; HRQL, health-related quality of life; IV, intravenous; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; OS24, proportion of patients alive at 24 months; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PFS12, proportion of patients alive and progression free at 12 months; PFS18, proportion of patients alive and progression free at 18 months ; PFS2, time from randomisation to second progression or death; PPS, post-progression survival; TC, tumour cell; TFST, time to first or subsequent therapy or death; TSST, time to second subsequent therapy or death; TTDM, time to death or distant metastasis.
Notes: *Different from draft scope.
§On 26 July 2018, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product durvalumab (IMFINZI™) as monotherapy for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of TCs and whose disease has not progressed following platinum-based CRT.[3]

B.1.2. Description of the technology being appraised

Details of the technology being appraised in this submission are summarised in Table 2. The final summary of product characteristics (SmPC) and European Public Assessment Report (EPAR) are not available at the present time (24 August 2018); draft versions of both documents are provided in Appendix C.

Table 2: Technology being appraised

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.[1, 4] In doing so, it releases the inhibition of immune responses in the tumour microenvironment, resulting in prolonged T-cell activation and anti-tumour activity.[1] Further information on the mechanism of action of durvalumab and the rationale for use after CRT is available in Appendix L.
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.[3] The European Commission decision (marketing authorisation) is expected at the end of September 2018; however, exact timing is subject to change. Durvalumab is already available in the United Kingdom (UK) under an Early Access Program (EAP). [redacted][5]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Anticipated indication, based on CHMP opinion:[3] *Durvalumab (IMFINZI™) as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of TCs and whose disease has not progressed following platinum-based CRT*

Method of administration and dosage	• Treatment must be initiated and supervised by a physician experienced in the treatment of cancer.[1] • The recommended dose of durvalumab is 10 mg/kg administered as an intravenous (IV) infusion over 60 minutes every two weeks (Q2W), until disease progression or unacceptable toxicity, or a maximum of 12 months. • Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be required, based on individual safety and tolerability. Guidelines for management of immune mediated adverse reactions are described in Table 1 of the SmPC (Appendix C.1).
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.
List price and average cost of a course of treatment	£592 per 120mg vial £2,466 per 500mg vial Total mean cost of treatment: [redacted]
Key: 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; FDA, Food and Drug Administration; IgG, immunoglobulin; IV, intravenous; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; Q2W, every 2 weeks; SmPC, summary of product characteristics.	

B.1.3. Health condition and position of the technology in the treatment pathway

Disease overview

Lung cancer is a malignant tumour characterised by uncontrolled cell growth in tissues of the lung.[6] It is the **third most-common cancer in the UK**.[7] In 2016, lung cancer accounted for 12.7% of all new UK cancer cases (~39,038 confirmed cases in England and Wales)[8] and was the **leading cause of cancer-related death** (age-standardised mortality rate = 69 lung cancer deaths for every 100,000 males, and 47 every for every 100,000 females).[9]

Smoking is the most common cause of lung cancer; however, familial history, immunodeficiency, and exposure to pollutants or radiation have also been implicated in the disease aetiology.[10, 11] Patients with lung cancer may present either symptomatically or incidentally following chest imaging. Symptoms can vary, depending on the location of the primary local invasion, compression of adjacent thoracic structures, presence of distant metastases, and / or paraneoplastic phenomena[a].[6] Commonly-reported symptoms include cough, difficulty in breathing (dyspnoea), weight loss, chest pain, and recurring infections (such as bronchitis and pneumonia).[13] The non-specific and heterogeneous nature of symptoms make diagnosis difficult; majority of cases are identified at an advanced stage.[8]

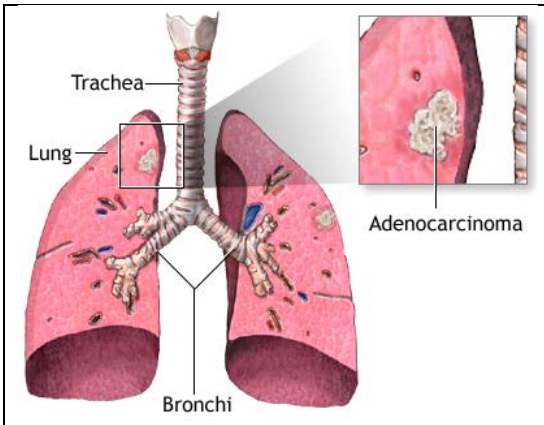
Lung cancer has two major histological sub-types, namely NSCLC and small cell lung cancer (SCLC).

NSCLC is the most common form of lung cancer

In 2016, **NSCLC accounted for 88.5% of all lung cancer cases in England and Wales**.[8] NSCLC arises from the epithelial cells of the lung from the central bronchi to the terminal alveoli, and has three main sub-types, namely, adenocarcinoma (most common), squamous cell carcinoma (SCC) and large cell carcinoma (Figure 1).[14]

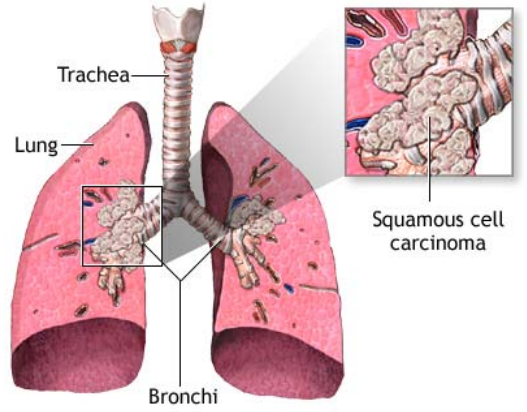
[a]Phenomena / symptoms arising from tumour secretion of hormones, peptides, or cytokines, or from immune cross-reactivity between malignant and normal tissues.[12]

Figure 1: Histological subtypes of NSCLC



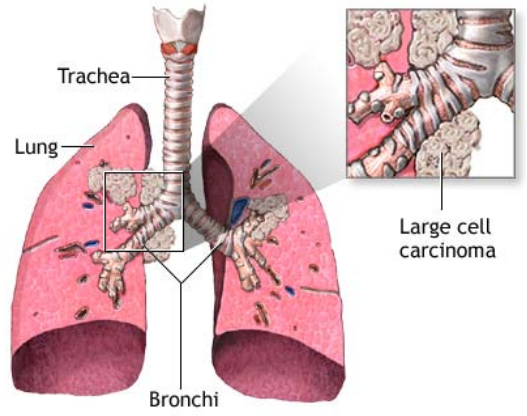
Adenocarcinoma

- Most common: **36%** of all lung cancers diagnosed in England & Wales (2016)*, [8]
- Arises from bronchi, bronchioles, and alveolar walls[6]
- Usually peripherally located; may occur at sites of pre-existing scars, wounds, or pneumonia[15]
- Most common histological sub-type among women and non-smokers[15]



Squamous cell carcinoma

- **22%** of all lung cancers diagnosed in England & Wales (2016)*, [8]
- Arises from large central bronchi[14]
- Most common histological sub-type among men and correlates with smoking / history of smoking[16, 17]



Large cell carcinoma

- **≤11%** of all lung cancers diagnosed in England & Wales (2016)*, [8]
- Usually appears as a large peripheral mass on chest radiography
- High tendency to spread to distant sites[16]

Key: NSCLC, non-small cell lung cancer
Notes: * 36% had "not pathologically confirmed" disease, with 11% having "other" histological sub-types (e.g. large cell carcinoma).
Source: Adapted from Our Health Page, 2015.[18]

The severity of NSCLC is captured by disease stage

NSCLC is staged according to the Tumour-Node-Metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC), and is based on the size of the

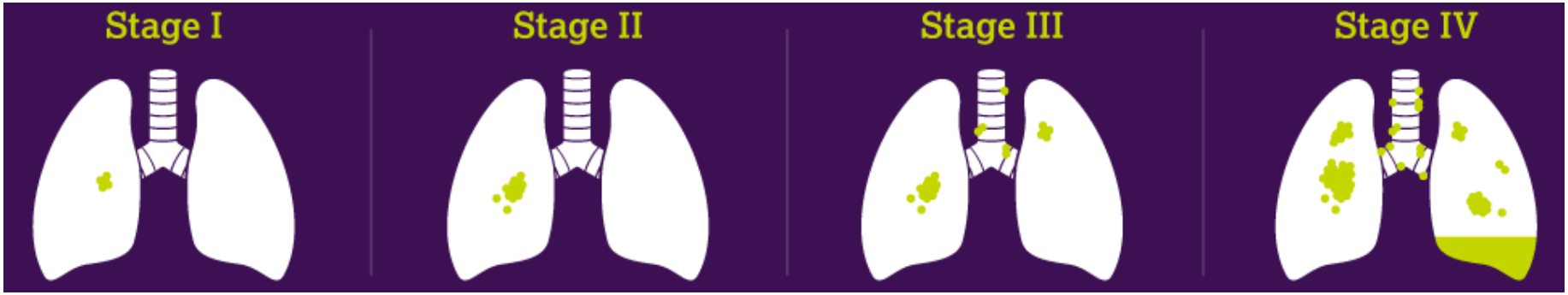
primary tumour (T), regional lymph node involvement (N), and presence / absence of distant metastases (M).[19] These three components are combined to assign patients with an overall disease stage of 0, I, II, III or IV (Figure 2).[20] Further details of the TNM classification for each stage (8th edition) are presented in Appendix L.[b20]

Stage III NSCLC, the focus of this submission, represents a **highly-heterogeneous** disease stage and is further classified into IIIA–C sub-stages (with IIIC being the most severe sub-stage).[20] A description of the three sub-stages and associated TNM status is illustrated in Appendix L.

The correct staging of NSCLC is crucial and largely determines treatment pathway / decision-making. Importantly, **treatment intent is usually curative in pre-metastatic disease stages (i.e. stage I–III)**. However, this is lost upon disease progression to metastatic state, and patients face significantly worse health-related quality of life (HRQL) and prognosis.

[b] It should be noted that the PACIFIC study used the 7th Edition of the AJCC TMN classification system.

Figure 2: The AJCC / UICC stage classification for lung cancer (8th edition) and the UK population of patients



Stage I	Stage II	Stage III	Stage IV
• An invasive cancer has formed, but has not spread to lymph nodes or to distant sites (**N0, M0**)	• The invasive cancer has either not spread to lymph nodes (**N0**) or spread to local nodes only (i.e. within the lung and / or around the area where the bronchus enters the lung [hilar lymph nodes]) on the same side as the cancer (**N1**; not shown) • The cancer has not spread to distant parts of the body (**M0**)	• The cancer may have spread to: – Lymph nodes around the carina (i.e. the point where the trachea splits into the left and right bronchi) or the mediastinum (space between the lungs), on the same side as the main tumour (**N2**), or – Lymph nodes near the collarbone on either side of the body and / or hilar or mediastinal lymph nodes on the other side of the body from the main tumour (**N3**) • The cancer has not spread to distant parts of the body (**M0**)	• The cancer can be any size (any T) and may or may not have reached nearby lymph nodes (**any N**). In addition, it has either spread to the other lung / in the fluid around the lung or heart, or outside the chest (**M1**)
			
• **~19%** of patients in England and Wales have stage I disease at diagnosis*	• **~8%** of patients in England and Wales have stage II disease at diagnosis*	• **~20%** of patients in England and Wales have Stage III disease at diagnosis*	• **~50%** of patients in England and Wales have stage IV disease at diagnosis*

Key: AJCC, American Joint Committee for Cancer; TNM, Tumour-Node-Metastasis; UICC, Union for International Cancer Control.
Notes: TNM classification and staging from AJCC/UICC 8th edition; further details are presented in Appendix L.
Source: Detterbeck et al. 2017[20]

Patients with metastatic disease experience a high symptom burden, significant deterioration in HRQL, and poor prognosis

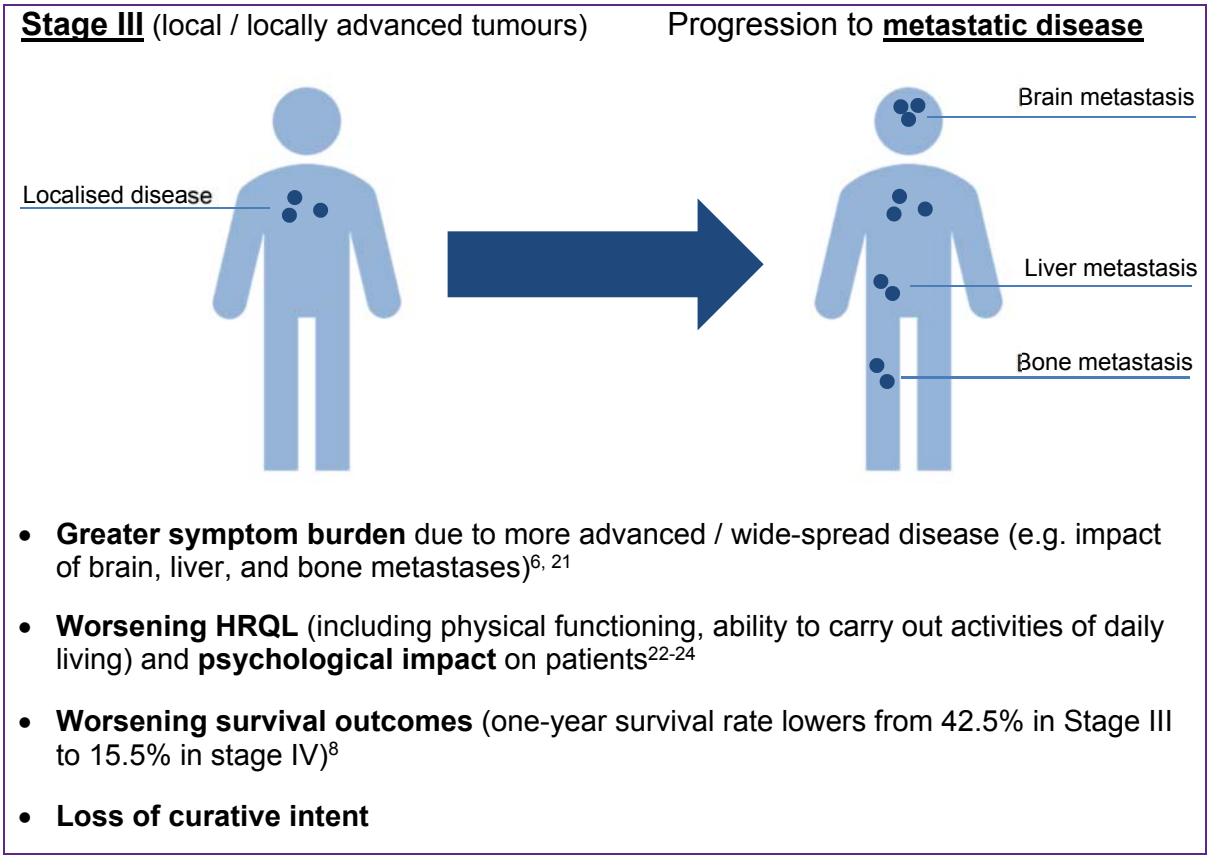
Patients in pre-metastatic disease stages (i.e. up to Stage III) mainly experience localised symptoms, such as persistent and / or worsening cough, wheezing, difficulty / pain when breathing (dyspnoea), hoarse or altered voice, and chest pain.[13] Some patients may also have blood in their saliva and mucous, and / or with cough (haemoptysis), causing significant discomfort and anxiety.[13] **Once a patient experiences disease progression to a metastatic state, the symptom burden of NSCLC normally increases substantially**. For instance, patients with skeletal metastases experience severe bone pain (especially in the spin or pelvis), while those with central nervous system or brain metastases may develop severe headaches, dizziness and / or difficulty in balancing, weakness / numbness in an arm or leg, seizures, and personality changes.[6, 21] This is coupled with growing fatigue, loss of appetite, weight loss and weakness, resulting in significant negative impact on patients' HRQL.

Consistent with greater symptom burden, **patients with metastases have significantly lower utilities** (measured using the EQ-5D questionnaire), relative to those without metastases (*P*=0.027 and 0.038 for self-classifier and VAS versions, respectively).[22] They also have significantly lower scores for the '*physical functioning*' and '*bodily pain*' domains of the SF-36 questionnaire (*P*=0.009 and 0.016, respectively), as well as lower physical component summary scores (*P*=0.015).[22]

Disease-specific instruments, such as the Lung Cancer Symptom Scale (LCSS), that capture the HRQL impact of lung cancer symptoms specifically, further highlight the significantly greater burden in metastatic stage IV patients versus those with locally-advanced Stage IIIB disease (*P*<0.001 for mean and overall symptom scores, as well as '*impact of symptoms from lung cancer*' and '*ability to carry out normal daily activities*' summary scores).[23] Ability to self-care and pain significantly correlate with self-reported depression in NSCLC patients, and underscore the significant psychological burden associated with this condition.[24] Further information on these studies is provided in Appendix L.

Patients who have metastatic, Stage IV NSCLC at diagnosis, or experience disease progression to Stage IV can no longer be treated with curative intent. Just **15.5%** of patients with stage IV disease in England and Wales are alive at one year from diagnosis[8], despite the availability of multiple new and often targeted treatment options.[25-39] This is substantially lower than patients with locally-advanced Stage III disease, who have average one-year survival rates of **42.5%**.[8] This emphasises the importance of treating patients early, before they become metastatic, when a curative outcome is still possible, or at the very least, by delaying progression to metastatic disease.

Figure 3. The impact of disease progression to metastatic NSCLC



Key: HRQL, health-related quality of life; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer.
Source: Cancer research UK 2017[21]; NCI 2017[6]; Trippoli et al. 2001[22]; Iyer et al. 2014[23]; Shi et al. 2015[24]; NLCA 2017[8].

Clinical pathway of care

Treatment intent is curative (termed "radical") for stage I–III NSCLC patients. NICE guidelines recommend treating patients based on surgical suitability and fitness, with lobectomy being specified as treatment of first choice.[40] Lung parenchymal-

sparing operations (segmentectomy or wedge resection) are recommended for patients with borderline fitness and smaller tumours (i.e. T1a–b, N0, M0), only if complete resection can be achieved. More extensive surgery (e.g. bronchoangioplastic surgery, bilobectomy, and pneumonectomy) is only recommended in those instances where deemed necessary to obtain clear margins. NICE guidelines **do not** recommend neo-adjuvant chemotherapy in patients who are suitable for surgery outside of a clinical trial.

In the latest National Lung Cancer Audit (NLCA), **81% of patients diagnosed with stage I–II disease** (between 1st January and 31st December 2016) and a World Health Organization (WHO) performance status (PS) of 0–2 **received curative-intent treatment.** The majority of patients (60%) underwent surgical resection, while the remaining (21%) received radical radiotherapy. Both strategies achieve good outcomes in stage I and II patients. Although recent five-year survival data by disease stage is not available for the UK specifically, data from the IASLC database (8th edition of the TNM classification for lung cancer) show that **68%–92% of stage I patients and 53%–60% of stage II patients remain alive at five years**.[41]

In contrast to stage I and II, only a minority of Stage III NSCLC patients receive curative intent treatment

Significant proportions of Stage III patients in England and Wales receive no treatment for their cancer. In the latest National Lung Cancer Audit (NLCA), approximately 36% of Stage III patients received best supportive care (BSC) only.[8, 42] Furthermore, almost half of all Stage IIIB patients (45.5%) and over a quarter (26.4%) of Stage IIIA were treated with palliative intent.[c] **Just 40% and 16% of Stage IIIA and IIIB patients, respectively (or 30% of all Stage III NSCLC patients), received treatment with curative intent.**

This emphasises that while curative treatment is still possible in Stage III NSCLC, more advanced disease (relative to stage I and II) may mean that many patients are

[c] The audit was based on the 7th classification system, hence included stage IIIA and IIIB only.

not fit, healthy, and / or willing to receive these therapies. Time-dependent variables such as deterioration in PS, significant weight loss, and tumour progression on imaging, as well as time-independent factors, such as comorbidities, poor lung function, and patient choice are commonly-cited reasons for not treating with curative intent in this setting.[43]

Surgery is suitable for a small proportion of Stage III patients

Treatment plans for Stage III NSCLC patients in the UK are generally determined by a multi-disciplinary team (MDT), typically including (but not limited to) a chest physician (who is the diagnosing physician and often MDT chair), a clinical oncologist, a medical oncologist, a thoracic surgeon, a radiologist, a histopathologist, and a specialist oncology nurse. The decision to use surgery (either alone, or part of a multi-modality treatment plan) is primarily driven by the thoracic surgeon.[44, 45] Nodal status is considered an important determinant of surgical suitability, with some surgeons preferring not to operate in instances where there is indication of N2 disease (i.e. metastasis in ipsilateral mediastinal and/or sub-carinal lymph node[s]).[44, 45] This is consistent with the ESMO Clinical Practice Guidelines for early and locally-advanced NSCLC, which recommends concurrent (i.e. overlapping) chemotherapy and definitive radiotherapy in patients with multi-station N2 disease (at staging).[46, 47]

In the latest NLCA, just 13% of Stage III patients in England and Wales underwent surgery (Figure 5).[8, 42] Rates of surgery were particularly low (1.8%) amongst those diagnosed with more advanced Stage IIIB NSCLC (relative to 20.1% in those with Stage IIIA disease).[8, 42]

CRT is standard-of-care for Stage III NSCLC patients who are not suitable for surgery

NICE guidelines specify that all patients who are considered as not being suitable for surgery should be offered an assessment by a clinical oncologist specialising in thoracic oncology for radiotherapy with curative intent (either alone or in combination with chemotherapy).[40]

Radical (curative) radiotherapy is recommended in unresectable Stage III NSCLC patients, who have good PS (WHO 0, 1) and whose disease can be encompassed

within a radiotherapy treatment volume without undue risk of normal tissue damage.[40] Definitive radiotherapy and chemotherapy combinations (hereafter chemoradiation therapy, CRT) provide better outcomes relative to radiotherapy alone, and are preferred in patients with unresectable Stage III disease.[47, 48] The goal of radiotherapy administered as part of a CRT regimen is to achieve local control. The addition of chemotherapy to radiotherapy serves two purposes: firstly, its acts as a radio-sensitising agent, thus increasing the therapeutic index of radiotherapy; secondly, it helps to prevent metastatic disease spread.[49, 50] Concurrent CRT (i.e. one or more overlapping cycles of chemotherapy and definitive radiotherapy) provides significantly improved OS outcomes than sequential protocols (five-year survival rates of 15.1% and 10.6%, respectively), and is specified as "treatment of choice" for unresectable Stage III patients in the ESMO Clinical Practice Guidelines for early and locally-advanced NSCLC (Figure 5).[46, 47, 51] Sequential approaches of induction chemotherapy followed by definitive radiotherapy are recommended as an alternative if overlapping protocols are not possible for any reason (Figure 5).[46, 47]

The latest NCLA reported that 65% of Stage III patients who received curative intent radiotherapy had CRT, but did not distinguish between sequential and overlapping protocols (Figure 5).[8, 42] However, a subsequent analysis of this data showed that (of those patients for whom complete radiotherapy and chemotherapy dates were available), 34% received treatment with overlapping CRT, while 66% received sequential CRT (personal communication with Dr Susan Harden [20 June 2018]; data to be presented at the 19th World Conference on Lung Cancer, Toronto, 23rd–26th September 2018).

NICE guidelines specify that Stage III NSCLC patients who are eligible for radical radiotherapy and who cannot tolerate / do not wish to have CRT, should be offered the Continuous Hyper-fractionated Accelerated RadioTherapy (CHART) regimen[d].[40] However, this is only available at select centres and is used in a minority of cases. An UK audit of 45 centres (between 14 October 2013 and 6 December 2013) showed that just 8% of patients who received radical radiotherapy for their NSCLC, were treated

[d] The CHART regimen gives thirty-six small fractions of 1·5 Gy, three times per day, to give 54 Gy over 12 consecutive days including weekends, with a minimum inter-fraction interval of 6 hours.[52]

with the CHART regimen.[53] If CHART is not available, then conventionally fractionated radiotherapy to a dose of 64–66 Gy in 32–33 fractions over 6.5 weeks, or 55 Gy in 20 fractions over 4 weeks, is recommended.[40]

It is worth highlighting that additional national (e.g. Royal College of Radiologists, British Thoracic Society) and regional guidelines (e.g. London Cancer Alliance) exist for the management of Stage III NSCLC patients in the UK.[54-56] There is a strong correlation between these and NICE / ESMO Clinical Practice guidelines, highlighting a consensus agreement on the optimal management of these patients.

There are no active treatment options after CRT, despite significant numbers of investigational studies

Several targeted and chemotherapy regimens have been evaluated in unresectable Stage III patients whose disease has not progressed following treatment with concurrent (i.e. overlapping) CRT, the standard-of-care (SoC) in this setting. However, none of these trials could consistently demonstrate a significant survival benefit, combined with good tolerability.

A pooled analysis of data from 41 Phase II and III studies (published before 31st December 2011) **showed no evidence that consolidation chemotherapy achieved significant OS benefit in this setting** (predicted HR of consolidation therapy versus no consolidation therapy was 0.94; $P = 0.40$).[57] Similar findings were reported in more recent studies, such as the PROCLAIM[e, 58] or RTOG[f, 59] studies. Further details of the design of these Phase III RCTs are presented in Appendix L.

Several targeted therapies (including the anti-EGFR antibody cetuximab, the EGFR TKI gefitinib, and the anti-VEGF antibody bevacizumab), have also been evaluated as consolidation / maintenance regimens following CRT. Cetuximab was evaluated both as part of CRT and as an addition to consolidation chemotherapy in a Phase II RCT,

[e] Pemetrexed-cisplatin or etoposide-cisplatin plus radiotherapy, followed by consolidation chemotherapy.

[f] Standard- versus high-dose radiotherapy with concurrent and consolidation carboplatin-paclitaxel ± cetuximab.

but showed modest efficacy.[60] The toxicity of gefitinib and bevacizumab were deemed unacceptable for integration into consolidation / maintenance treatment post-CRT in respective early-stage studies.[61, 62] Further details of the design of these studies is presented in Appendix L.

Thus, **despite numerous clinical trials, no new treatments have been approved for unresectable Stage III patients in over a decade**.[40, 63] Current ESMO Clinical Practice Guidelines for early and locally-advanced NSCLC recommend active surveillance and BSC after completion of CRT (referred to as active follow-up throughout).[46, 47] Surveillance visits, including history, physical examination, and chest CTs are recommended every six months for the first two years and annually thereafter, to detect second primary tumours.[46, 47] Patients are strongly encouraged to quit smoking and / or participate in smoking cessation programmes.[46, 47]

In the absence of active treatment, most unresectable Stage III patients experience disease progression following completion of CRT

Only a small sub-set of patients with unresectable Stage III NSCLC achieve good outcomes following overlapping CRT, the SoC in this setting, with two- and five-year survival rates of 35.6% and 15.1%, respectively[g].[51] Survival rates are lower still amongst patients treated with sequential CRT approaches, with just 30.3% and 10.6% remaining alive two- and five-years from starting therapy, respectively.[51] The uncertainty of knowing whether CRT will provide long-term benefit causes great psychological stress and anxiety in patients, which, in turn, is associated with lung cancer mortality.[64]

The majority of patients experience disease progression within a year of receiving CRT in the absence of active treatment (59.6% and 62.1% for overlapping and sequential approaches, respectively).[51] Just 9.4%−11.6% of patients remain alive and progression-free at five years.[51] Nearly two-thirds of patients have a systemic relapse, with one-third developing brain metastases. Moreover, brain as the sole of site of relapse occurs in approximately 20% of patients and represents a major cause of morbidity and mortality in this patient population.[65] Outcomes are especially poor in

[g] Meta-analysis included data from six trials and 1,205 patients.

patients who are diagnosed with / develop brain metastases, with a median OS of ~4 months from the date of diagnosis in those treated with whole brain radiotherapy or a programme of stereotactic radiosurgery[h].[66]

Patients who relapse with distant metastatic disease are typically treated as stage IV patients with first-line (1-L) systemic drug therapies including platinum-based doublet chemotherapy, molecular targeted therapies, or immunotherapy with PD-1 / PD-L1 inhibitors if their disease-free period is >12 months (AstraZeneca data on file).[44] Otherwise, patients are eligible to be treated with second-line (2-L) single agent chemotherapies, molecular targeted therapies, or immunotherapy agents.[44] However, due to rapid deterioration, many patients do not receive any therapy upon disease progression. Insights from UK clinical experts (N=13) suggest that ~18% of Stage III patients do not receive any subsequent therapy upon disease progression following CRT and have a median OS of just seven months (AstraZeneca data on file).[44] The same clinician survey revealed that ~7% of patients receive a targeted therapy (such as an EGFR tyrosine kinase inhibitor [TKI] or an ALK inhibitor) following disease progression after CRT, while ~30% of patients receive anti PD-1 / PD-L1 immunotherapy. Most patients (~41%) are still treated with chemotherapy upon progression after CRT, with median OS of just 15 months. Radiotherapy is used in a small proportion of patients (~5%) who have suffered local disease recurrence as it is often not feasible to re-irradiate previously irradiated tissue[i]. It is important to emphasise that treatment intent is palliative in the metastatic setting, regardless of type of therapy, and a significant unmet medical need exists for new treatment strategies that can improve the chances of cure and prolong the initial benefit achieved with CRT, when treatment intent remains curative.

Positioning of durvalumab in the treatment pathway

Prior to the PACIFIC study, PD-1 / PD-L1 immune checkpoint inhibitors, which have marked a step-change in the treatment of metastatic NSCLC patients, had not been

[h] Data from cohort of 91 NSCLC patients treated at a tertiary cancer centre in Canada during 2005−2007 (whole brain radiotherapy) and from 167 NSCLC patients treated at the same centre during 2010−2012 (stereotactic radiosurgery).

[i] In the majority of cases, radiotherapy is delivered with palliative intent (although SABR is used in a small minority of centres for re-treatment with curative intent).

evaluated in the **locally advanced (Stage III)** setting. The first suggestive evidence that an immunotherapy-based approach might be effective in this setting was presented by Butts *et al* 2014, who demonstrated that administration of a vaccine (tecemotide) after CRT in patients with locally-advanced NSCLC led to a modest survival gain (25.6 months with tecemotide versus 22.3 months with placebo; *P*=0.123). The study also reported a greater survival benefit in patients who were treated with overlapping, rather than sequential, CRT protocols, although this could not be replicated in the subsequent Phase I / II EMR 63325-009 study of tecemotide versus placebo in Japanese patients[j].

The positioning of durvalumab after CRT is supported by the immune-priming effects of radiotherapy

Multiple preclinical studies have shown that anti−PD-1 / PD-L1 antibodies can augment the immune-stimulatory effects of radiotherapy, thus improving local disease control (further discussed in Appendix L).[68] Furthermore, clinical data (from the KEYNOTE-001 study and individual case reports in the metastatic NSCLC setting) suggest that radiotherapy can sensitise tumours to immunotherapy, promoting tumour shrinkage and improving survival outcomes (described in Appendix L).[69-71]

The use of anti−PD-1 / PD-L1 immunotherapy immediately after CRT and prior to disease progression offers a strategy to reinvigorate T-cells at a time when the volume of tumour burden is at its lowest. Indeed, lower tumour volume was associated with improved clinical response / outcomes with the anti−PD-1 antibody pembrolizumab in both melanoma[72] and metastatic NSCLC,[73] providing further rationale for immunotherapy immediately after CRT in the pre-metastatic Stage III NSCLC setting.

[j] The clinical development program for tecemotide was terminated globally by Merck Group, following the results of the Phase I / II EMR 63325-009 study.[67]

Durvalumab is the first and only immunotherapy to show statistically-significant and clinically meaningful PFS and OS benefit in locally-advanced, unresectable, Stage III NSCLC patients who have completed CRT[k]

Enrolment in the pivotal Phase III PACIFIC RCT of durvalumab versus placebo was not restricted by PD-L1 expression on TCs and durvalumab demonstrated a statistically-significant PFS and OS benefit versus placebo in the full intention-to-treat (ITT) population.[74-77] Based on these data, the Food and Drug Administration (FDA) approved durvalumab for patients with locally-advanced, unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based CRT on 16 February 2018.[78] Durvalumab has been also approved by Health Canada (04 May 2018),[79] Swiss Medic (11 June 2018),[80] and the Pharmaceutical and Medical Devices Agency (PMDA, Japan; 02 July 2018)[81] for the treatment of unresectable Stage III NSCLC patients, regardless of TC PD-L1 expression levels.

On 27 July 2018, the CHMP of the EMA adopted a positive opinion, recommending marketing authorisation for durvalumab monotherapy for the treatment of locally advanced, unresectable NSCLC in **adults whose tumours express PD-L1 on ≥1% of TCs** and whose disease has not progressed following platinum based CRT.[3] The reasoning behind the CHMP decision to restrict Marketing Authorisation by PD-L1 expression is briefly explained in Figure 4.

Given that marketing authorisation for durvalumab is expected in patients with PD-L1 expression on ≥1% TCs, this group (hereafter PD-L1 ≥1%; N=303) will be the focus of this submission. Although randomisation in the PACIFIC study was not stratified based on PD-L1 status, similar proportions of patients in durvalumab and placebo groups had pre-CRT PD-L1 expression on ≥1% of TCs (44.5% and 38.4%, respectively). In addition, baseline characteristics in terms of major prognosis factors (i.e. age, histology, stage, smoking status, and performance status) were all well-balanced between durvalumab and placebo arms of the PD-L1 ≥1% group (described in Section B.2.3; Baseline characteristics). Treatment with durvalumab achieved a **robust, consistent, and statistically-significant benefit versus placebo in the PD-L1 ≥1%**

[k] A statistically-significant PFS and OS benefit for durvalumab versus placebo was also observed in patients with PD-L1 expression on ≥1% of tumour cells (TCs). See Table 6 for further details.

group in terms of PFS and OS, demonstrating clinically-meaningful benefit in the intended patient population.

Figure 4: Background to the CHMP opinion

The PACIFIC study was designed to evaluate the efficacy and safety of durvalumab in all locally-advanced, unresectable, Stage III NSCLC patients, regardless of PD-L1 expression levels on tumour cells (TCs).

The rationale for an "all comers" study design was as follows:

- At the time of study design, there was limited understanding of the predictive value of PD-L1 expression in NSCLC, particularly in Stage III, and no biomarker had ever been used to guide therapeutic decisions in this setting;
- Biopsy of tumour tissue that has been treated with CRT is clinically not feasible; therefore, it is not possible to measure PD-L1 expression just prior to randomisation.
- CRT may increase PD-L1 expression on TC in any case, based on preclinical data (page 28 and Appendix L; Mechanism of action of durvalumab).

Consistent with its "all comers" design, PD-L1 testing was not made mandatory; instead PD-L1 expression was tested retrospectively using archival tumour tissue obtained at the time of diagnosis (if available). Questions around the PD-L1 status and outcomes were addressed based on pre-CRT PD-L1 status, as part of exploratory subgroup analysis[§].

As part of the regulatory review process, the EMA requested an exploratory *post-hoc* analysis to justify the use of durvalumab in patients whose tumours express PD-L1 on <1% TCs. This exploratory post-hoc PACIFIC ITT population included 148 patients with PD-L1 expression on <1% TCs, 303 patients with PD-L1 expression on ≥1% TCs, and 262 patients of unknown PD-L1 status*. A PFS benefit with durvalumab versus placebo was observed in both PD-L1 <1% and PD-L1 ≥1% groups, as well as in patients whose PD-L1 status was not known, supporting the use of durvalumab after CRT in all patients (Appendix E; Figure 6). OS benefit, in favour of durvalumab, was observed in the PD-L1 ≥1% group and in patients with "unknown" expression. However, the HR for OS in the PD-L1 <1% TC group was more than 1.0, with a wide 95% CI that included 1 (Appendix E; Figure 9).

Although inconclusive and based on an analysis in a small number of patients (148 of 713), the CHMP determined that an OS benefit of durvalumab over placebo in the PD-L1 <1% group had not been shown and recommended restricting Marketing Authorisation to those patients who express PD-L1 on ≥1% of TCs.[3] While AstraZeneca do not agree with this decision, the proposed indication was nonetheless accepted in the interest of providing rapid access to durvalumab for the majority of locally-advanced, unresectable Stage III NSCLC patients in Europe.

Key: CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; CRT, chemoradiation therapy; EMA, European Medicines Agency; HR, hazard ratio; ITT, intention to treat; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; TC, tumour cell.

Notes: [§]Based on data from Study1108[82-84] that became available during the course of the PACIFIC study, a PD-L1 TC expression ≥25% (i.e. 25% or more TCs expressing PD-L1 at any intensity) was established as optimal in the durvalumab NSCLC programme in the metastatic setting. Therefore, the Statistical Analysis Plan for the PACIFIC study planned a subgroup analysis of durvalumab efficacy (PFS and OS) using the PD-L1 TC 25% cut-off (i.e. PD-L1 expression on <25% and ≥25% of TCs). *Tumour tissue collection was not mandatory for inclusion and was only available for 545 (76%) of patients. 451 (63%) of patients had evaluable tumour tissue that could be tested for PD-L1 expression.

PD-L1 testing is routinely performed in the UK in the metastatic NSCLC setting, prior to initiating treatment with pembrolizumab (first-line: TA531[85]; second-line: TA428[26]) and nivolumab (second-line [non-squamous]: TA484[86]). The Final Appraisal Determination (FAD) for pembrolizumab in untreated PD-L1−positive metastatic NSCLC (TA531) noted a comment from the NHS England Clinical Lead stating that "*all lung cancer centres should be able to offer testing for PD-L1 status*".[87] Furthermore, the committee concluded that "*PD-L1 testing could be standardised quickly and, with training, implemented as standard clinical practice in the NHS*".[87] Based on this, it is anticipated that PD-L1 testing for eligible unresectable Stage III NSCLC patients can be conducted within the existing infrastructure of the NHS. As it is technically very challenging to obtain samples from tissue that has been irradiated, it is expected that PD-L1 testing will be conducted on biopsies obtained prior to CRT, as part of standard staging and diagnostic workup. PD-L1 testing can be conducted in parallel to CRT / during the recovery period after CRT and therefore, should not cause any delays in starting durvalumab treatment following completion of CRT (if appropriate). A number of PD-L1 immunohistochemistry (IHC) assays are commercially available and routinely used to assess PD-L1 expression in the advanced metastatic Stage IV NSCLC setting, including the D-L1 IHC 28-8 pharmDx (28-8), PD-L1 IHC 22C3 pharmDx (22C3), and Ventana PD-L1 SP263 (SP263; used in the PACIFIC study). 28-8, 22C3, and SP263 assays show high concordance when assessing PD-L1 expression on TCs membranes, and are considered interchangeable in their use in NSCLC.[88]

In the PACIFIC study, patients were required to start durvalumab treatment within 42 days of completing CRT to maximise potential benefits derived from the immune-priming effects of CRT (although, patients could start durvalumab within [redacted] months of completing CRT in the EAP).[5] This recovery period should allow time for resolution of radiation-related toxicities and for centres to organise delivery of durvalumab therapy. It is highly unusual for patients to experience disease progression immediately after CRT. Insights from UK clinical experts (N=5) suggest that only a small minority of patients (<5%) show evidence of disease progression at the three-monthly CT scan that is routine in current clinical practice.[89] Although a chest X-ray is

commonly conducted approximately four to six weeks after CRT is completed[I], the results can be misleading due to the acute radiation-induced changes typically seen affecting the lungs immediately after treatment. Signs of clinical progression may be a more reliable indicator of relapse in the initial period following CRT. Given current follow-up protocols, we do not anticipate that additional scans will be needed prior to initiation of durvalumab therapy in UK clinical practice.

Based on available data from the latest NLCA and the following assumptions, we estimate that **~367 patients will be eligible to receive treatment with durvalumab in England and Wales** (Figure 5):

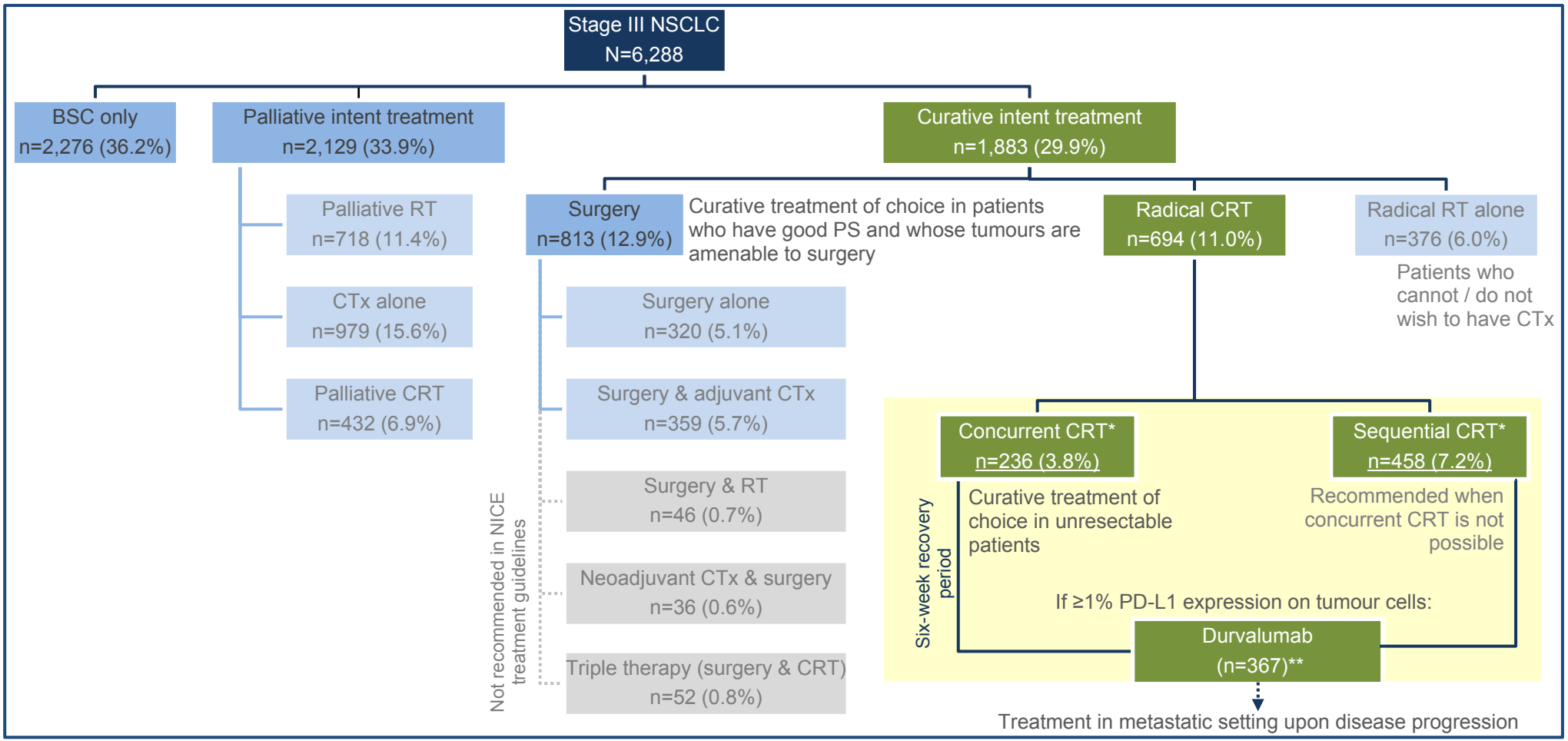
- ~95% of unresectable Stage III patients will not have experienced disease progression in the recovery period following curative-intent CRT;[89]
- Of these, 82.8% of patients will have evaluable tissue for PD-L1 testing (PACIFIC RCT; data on file);
- Of these, 67.2% will have tumours with ≥1% PD-L1 expression (PACIFIC RCT; data on file).

B.1.4. Equality considerations

No equality issues related to the use of durvalumab have been identified or are foreseen.

[I] There are few agreed guidelines and follow-up imaging practice may vary across the UK.

Figure 5: Treatment of Stage III NSCLC



Key: BSC, best supportive care; CRT, chemoradiation therapy; CTx, chemotherapy, 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[8, 42]; *, Personal communication with Dr Susan Harden (20 June 2018; data to be presented at the 19th World Conference on Lung Cancer; Toronto, 23−26 September, 2018), relative proportion of sequential versus overlapping CRT use applied to full dataset (i.e. n=694); **, Assumes that 95% of patients will not have experienced disease progression within six weeks or 42 days of completing CRT.[44, 89] Of these, 82.8% will have evaluable tissue for PD-L1 testing, and that 67.2% will have tumours with ≥1% PD-L1 expression.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was performed to identify published clinical trial data on the efficacy and safety of durvalumab versus active follow-up, the current SoC in locally-advanced, unresectable, Stage III NSCLC patients whose disease has not progressed after CRT (to reflect the population, intervention, and comparator specified in the decision problem). Full details of the methodology and results of the SLR are provided in Appendix D.1.

The SLR identified six clinical trials that evaluated either durvalumab and / or active follow-up in this treatment setting. Of these, **only one (the Phase III PACIFIC RCT) directly compared the efficacy and safety of durvalumab versus placebo (active follow-up). This clinical trial will form the basis of this submission**.

The remaining five studies evaluated investigational maintenance / consolidation therapies versus active follow-up, and are thus not relevant to this appraisal. A brief overview of these studies is nonetheless provided in Appendix D.1.

Data from the largest of these studies, the Phase III START RCT, was also used to validate assumptions of long-term survival on active follow-up for health economic-modelling purposes (discussed further in section B.3.1).

B.2.2. List of relevant clinical effectiveness evidence

As stated above, the randomised, double-blind, placebo-controlled, multicentre, international, Phase III, PACIFIC study is the only clinical trial that directly compared durvalumab versus placebo (active follow-up); this study is the focus of this submission. A summary of the PACIFIC RCT is presented in Table 3; further details are provided in Section B.2.3.

Table 3: Clinical effectiveness evidence

<table>
<tr><td>Study</td><td colspan="5">PACIFIC; NCT02125461[74, 75]</td></tr>
<tr><td>Study design</td><td colspan="5">PACIFIC is an ongoing, randomised, double-blind, placebo-controlled, multi-centre, international, Phase III study</td></tr>
<tr><td>Population</td><td colspan="5">Patients with locally-advanced, unresectable, Stage III NSCLC whose disease has not progressed following two or more overlapping cycles of definitive, platinum-based CRT</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Durvalumab (n=476)</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo (n=237)</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">PACIFIC presents the pivotal regulatory clinical evidence in support of durvalumab in the population directly relevant to the decision problem</td></tr>
<tr><td>Reported outcomes specified in the decision problem
Note: outcomes used in the economic model are in bold</td><td colspan="5">• PFS
– PFS12, PFS18, TFST
• OS
– OS24
• Response rates
• Adverse effects of treatment
• HRQL
– EQ-5D
– EORTC</td></tr>
<tr><td>All other reported outcomes
Note: outcomes used in the economic model are in bold</td><td colspan="5">• PFS2
– TSST
• PPS
• TTDM
• Time to treatment discontinuation</td></tr>
<tr><td colspan="6">Key: AE, adverse event; CRT, chemoradiation therapy; CSR, clinical study report; EQ-5D, EuroQol 5-dimension; EORTC, European Organisation for Research and Treatment of Cancer; HRQL, health-related quality of life; OS, overall survival; OS24, proportion of patients alive at 24 months; PFS12, proportion of patients alive and progression free at 12 months; PFS18, proportion of patients alive and progression free at 18 months; PFS2, time to second progression or death; PPS, post-progression survival; TFST, time to first or subsequent therapy or death; TSST, time to second subsequent therapy or death; TTDM, time to death or distant metastasis.
Source: Antonia et al., 2017[74] and PACIFIC CSR.[75]</td></tr>
</table>

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Trial design

An overview of the PACIFIC study design is shown in Figure 6. Eligible patients (who had unresectable histologically- or cytologically-documented Stage III NSCLC, and complete response [CR], partial response [PR], or stable disease [SD] following two or more overlapping cycles of definitive, platinum-based CRT), were randomised within one to 42 days of receiving the last radiotherapy dose[m].[74, 75] Details of eligibility criteria are provided in the next sub-section.

Randomisation was performed in a 2:1 ratio to durvalumab or matching placebo. Durvalumab was administered 10mg/kg intravenously every two weeks (Q2W) for up to 12 months (maximum of 26 doses, last dose at Week 50).[74, 75] A central Interactive Voice Response System (IVRS) / Interactive Voice and Web Response System (IWRS) was used to allocate patients to the two treatment groups. A blocked randomisation was generated, and all centres used the same list to minimise any imbalance in the number of patients assigned to each treatment group. Patients were stratified at randomisation based on their age (<65 versus ≥65 years), sex, and smoking history (current or former smoker versus never smoked).[74] Initially, randomisation was required to have occurred within 14 days[75]; however, the study protocol was amended to increase this to 42 days to allow time for resolution of CRT-related toxicities.[74, 75] The first patient was randomised into the study on 09 May 2014, and the last patient on 22 April 2016.

The study was conducted in a double-blind manner. Patients, investigators, and study centre staff were all blinded to the study drug allocation. The study centre pharmacist was unblinded and prepared the durvalumab solution / matching placebo for patients, as specified by the randomisation scheme and IVRS. The reconstituted durvalumab solution and its matching placebo were identical in colour. The identity of the study

[m] Defined as the day of the last radiation treatment session.

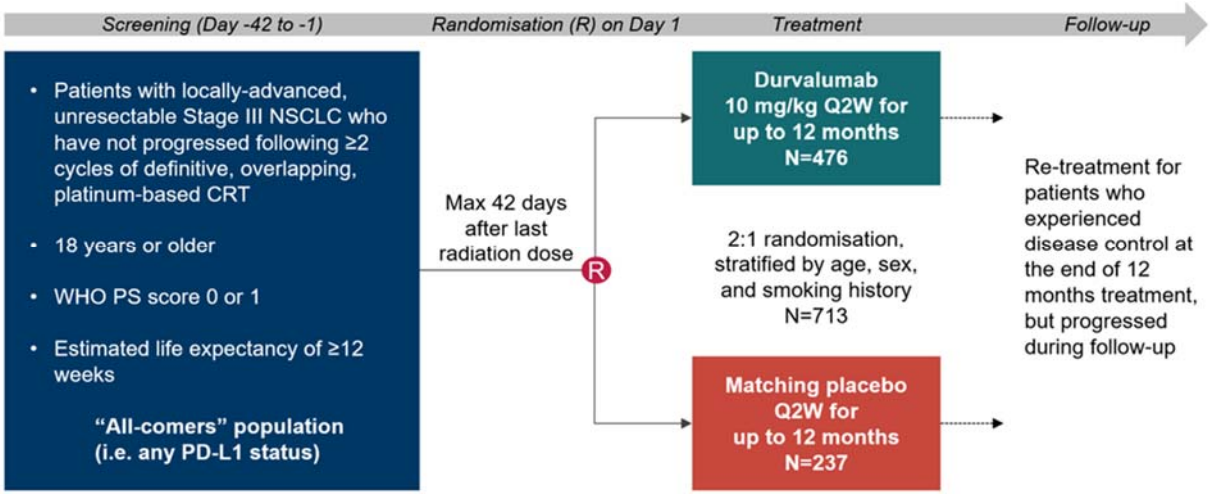
drug was blinded using an opaque sleeve over the IV bag, fastened with tamper-evident tape.

Administration of the study drug commenced on Day 1 following randomisation, once eligibility to participate was confirmed. Treatment was discontinued upon confirmed disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, or withdrawal of patient consent.[74] Patients who achieved and maintained disease control (i.e. CR, PR, or SD) through to the end of the 12-month treatment period entered follow-up.[75]

Patients who experienced disease progression (according to RECIST 1.1) during follow-up could restart study treatment for up to an additional 12 months. No crossover between treatment groups (i.e. placebo → durvalumab, or vice-versa) was permitted at any stage.[75]

At the time of the primary OS analysis (22 March 2018 DCO), median duration of follow-up was 26.9 months (range 0.5−40.5) and 21.1 months (range 0.5−41.0) in durvalumab and placebo arms, respectively (PD-L1 ≥1% group). Patients continue to be followed for survival and an additional analysis of OS will be performed at the end of the study to address regulatory requirements / post marketing commitments.

Figure 6: PACIFIC study design schematic



Key: CRT, chemoradiation therapy; CSR, clinical study report; PD-L1, programmed cell death ligand 1; Q2W, every 2 weeks; WHO PS, World Health Organization performance status.
Source: PACIFIC CSR.[75]

Eligibility criteria

Key inclusion and exclusion criteria for the PACIFIC study are shown in Figure 6 and in Appendix D.1 (pages 25–26). Full details are available in the PACIFIC CSR (page 34–39).[75]

Importantly, enrolment in the PACIFIC study was not restricted by PD-L1 expression on TCs. The ITT population included a mixture of patients with / without PD-L1 expression on TCs, as well as patients whose PD-L1 expression status was not known (described in Section B.2.4). The rationale for an "all comers" study design, regardless of pre-CRT PD-L1 expression on TCs is explained in Figure 4. Further details are available in the Clinical Study Protocol (Section 3.2.3.3.; page 53−54). Questions around the PD-L1 status and outcomes were addressed based on pre-CRT PD-L1 status, as part of exploratory subgroup analysis, based on pre-CRT PD-L1 expression cut-off of 25%[n].

Settings and locations where the data were collected

The PACIFIC study is currently being conducted in 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, UK, United States (US), and Vietnam.[75]

The study included eight UK patients across three centres (all eight were randomised to durvalumab treatment).[75]

Trial drugs and concomitant medications

Patients were assigned to receive either durvalumab 10mg/kg via a 60-minute IV infusion or matching placebo (saline IV infusion) Q2W, for up to 12 months.[75]

Investigators could prescribe concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care.[75] Details of active

[n] Based on data from Study1108 that became available during the course of the PACIFIC study, a PD-L1 TC expression ≥25% (i.e. 25% or more TCs expressing PD-L1 at any intensity) was established as optimal in the durvalumab NSCLC programme in the metastatic setting. Therefore, the Statistical Analysis Plan for the PACIFIC study planned a subgroup analysis of durvalumab efficacy (PFS and OS) using the PD-L1 TC 25% cut-off (i.e. PD-L1 expression on <25% and ≥25% of TCs).

treatments that were not permitted during the study are provided in Appendix D.1 (pages 26–27).

Discontinuation of study treatment / withdrawal from study

Patients could discontinue treatment or withdraw from the study (treatment and evaluations) at any time, without prejudice to further treatment.[90] Further information on discontinuations and withdrawals is provided in Appendix D.1 (pages 27–28).

At the time of the 22 March 2018 DCO, 395 patients in the ITT population and 160 patients in the PD-L1 ≥1% group had discontinued treatment. The most commonly cited reasons for discontinuation included worsening of the condition under investigation (ITT: 265 patients; PD-L1 ≥1% group: 103 patients) and AEs (ITT: 96 patients; PD-L1 ≥1% group: 41 patients) (see patient disposition in Appendix D.4, Figure 3 and Figure 3).

Primary, secondary and exploratory objectives

The RECIST version 1.1 criteria were used to evaluate tumour responses at each visit, to determine if / when a patient experienced disease progression, and their best objective response.[91] Further information on tumour assessments, including the frequency of scans and the derivation of RECIST visit responses is provided in Appendix D.1 (pages 28–29) and the Statistical Analysis Plan (pages 25–35).[91]

To **primary objective** of the PACIFIC study was to assess the efficacy of durvalumab treatment compared with placebo in terms of OS and PFS (using BICR assessments according to RECIST 1.1). TFST was derived as a supportive summary to PFS.

Key secondary objectives of the study were:

- To further assess the efficacy of durvalumab compared with placebo in terms of:
  - PFS12, PFS18, ORR, DoR, TTDM (using BICR assessments according to RECIST 1.1);
  - OS24;
  - PFS2 (as defined by local standard clinical practice). TSST was derived as a supportive summary to PFS2.
- To assess the safety and tolerability profile of durvalumab compared with placebo.

- To assess symptoms and HRQL in patients treated with durvalumab compared with placebo using EORTC QLQ-C30 and EORTC QLQ-LC13.

Further information on key endpoints, including definitions, are provided in Appendix D.1 (pages 28-31). A full list of secondary and exploratory objectives of the PACIFIC RCT are available in the Statistical Analysis Plan (pages 14–16).

All efficacy endpoints were evaluated in the ITT population (Section B.2.6), which included patients regardless of PD-L1 expression on TCs. Efficacy and tolerability of durvalumab in the PD-L1 ≥1% group was analysed in exploratory *post-hoc* analyses.

Baseline characteristics

Nine hundred and eighty-three patients were enrolled from 235 centres across 26 countries. Of these, 713 patients were randomised in 2:1 ratio to receive either durvalumab 10 mg/kg Q2W (N=476) or placebo (N=237). This constituted the ITT population or full analysis set (FAS) for the PACIFIC study. Further information on analysis sets is provided in Section B.2.4 (page 46); information on participant flow in the PACIFIC study is provided in Appendix D.2.

Molecular phenotypes (PD-L1 expression on tumour cells prior to CRT and *EGFR* mutation status), where known, were well matched between the two groups (Table 4). The prevalence of *EGFR* mutations (6.0% positive, 67.6% negative, 26.4% not known in the ITT population) was as expected, considering patient demographics and tumour histology (i.e. predominantly smokers, 70.1% male, 69.3% White, and 45.7% squamous histology). PD-L1 status was retrospectively analysed in patients with available samples, obtained prior to CRT. Of the 713 patients, 76.4% had biopsies available (biopsies were missing for remaining patients since tumour tissue collection was not mandated for inclusion in the study). Of the patients with available tumour tissue, 82.8% had samples that were evaluable for PD-L1 expression status. In total, 303 (42.5%) patients in the ITT population (212 [44.5%] in the durvalumab group and 91 [38.4%] in the placebo group) had ≥1% PD-L1 expression on TCs.

Patients with ≥1% PD-L1 expression in durvalumab and placebo arms were well balanced in terms of demographics (as shown in Table 4). 69.0% were male and most were either current or past smokers (17.2% and 73.9%, respectively). Mean weight at

baseline was 71.1kg. 68.0% of patients were White, 28.1% were Asian, and 3.0% were Black or African American. Median age at randomisation was 64.0 years (range: 36−90 years) and approximately half of the patients (49.2%) were between 50 and 64 years.

Patients with ≥1% PD-L1 TC expression in durvalumab and placebo arms were also well balanced in their disease characteristics. Similar proportions of patients in the two groups had Stage IIIA / IIIB disease at baseline (IIIA: 55.7% [durvalumab] and 52.7% [placebo]; IIIB: 42.0% [durvalumab] and 46.2% [placebo], per AJCC 7th Edition). The same was true for WHO PS (0 or 1) and tumour histology (squamous versus non-squamous), as shown in Table 4. Similar proportions of patients in durvalumab and placebo groups had pre-CRT PD-L1 expression on <25% or ≥25% of TCs, despite no stratification by PD-L1 status. This cut-off was selected based on data from Study1108 that became available during the course of the PACIFIC study.[82-84]

99.7% of patients had received ≥2 overlapping cycles of definitive, platinum-based, CRT prior to randomisation, as intended in the study protocol. All patients received radiotherapy (mean total dose of 62.5 Gy in both durvalumab and placebo groups); all sites of known disease were included in the radiation field. All patients also received at least one chemotherapy regimen (per local protocol) prior to randomisation; 23.1% of patients in both durvalumab and placebo groups also received neo-adjuvant (induction) chemotherapy prior to definitive CRT. Similar proportions of patients in durvalumab and placebo groups had CR, PR, and SD following CRT (Table 4).

A summary of patient demographics, disease characteristics at baseline, and prior anti-cancer therapies for the PD-L1 ≥1% group is provided in Table 4. Baseline characteristics for the full ITT population are also shown alongside for completeness, and illustrate the consistency / similarity between PD-L1 ≥1% group of patients and the ITT population. Generalisability of the PACIFIC RCT to UK clinical practice is discussed in Section B.2.13.

Table 4: Patient demographics, baseline disease characteristics, and prior anti-cancer therapies

Characteristic	ITT			PD-L1 ≥1% group		
	Durvalumab (n=476)	Placebo (n=237)	Total (n=713)	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)
Demographics						
Age, mean (SD)	63.0 (8.7)	62.6 (9.6)	62.9 (9.0)	63.0 (8.4)	63.1 (8.8)	63.1 (8.5)
Age, median (range) [years]	64 (31−84)	64 (23−90)	64 (23−90)	64 (36−83)	64 (41−90)	64 (36−90)
Age groups (years), n (%)						
<50	30 (6.3)	22 (9.3)	52 (7.3)	12 (5.7)	6 (6.6)	18 (5.9)
≥50−<65	231 (48.5)	108 (45.6)	339 (47.5)	104 (49.1)	45 (49.5)	149 (49.2)
≥65−<75	178 (37.4)	88 (37.1)	266 (37.3)	81 (38.2)	34 (37.4)	115 (38.0)
≥75	37 (7.8)	19 (8.0)	56 (7.9)	15 (7.1)	6 (6.6)	21 (6.9)
Sex, n (%)						
Male	334 (70.2)	166 (70.0)	500 (70.1)	144 (67.9)	65 (71.4)	209 (69.0)
Female	142 (29.8)	71 (30.0)	213 (29.9)	68 (32.1)	26 (28.6)	94 (31.0)
Race						
White	337 (70.8)	157 (66.2)	494 (69.3)	146 (68.9)	60 (65.9)	206 (68.0)
Black / African American	12 (2.5)	2 (0.8)	14 (2.0)	8 (3.8)	1 (1.1)	9 (3.0)
Asian	120 (25.2)	72 (30.4)	192 (26.9)	58 (27.4)	27 (29.7)	85 (28.1)
Native Hawaiian or Other Pacific	1 (0.2)	1 (0.4)	2 (0.3)	0	1 (1.1)	1 (0.3)
American Indian or Alaska Native	4 (0.8)	5 (2.1)	9 (1.3)	0	2 (2.2)	2 (0.7)
Other	1 (0.2)	0	1 (0.1)	0	0	0
Missing	1 (0.2)	0	1 (0.1)	0	0	0
Weight, mean (SD) [kg]	71.9 (17.39)	69.4 (15.73)	71.1 (16.88)	72.6 (17.88)	67.4 (15.4)	71.1 (17.3)
Weight, median (range) [kg]	69 (34−175)	69 (38−128)	69 (34−175)	69 (34−133)	65 (43−128)	69 (34−133)

Characteristic	ITT			PD-L1 ≥1% group		
	Durvalumab (n=476)	Placebo (n=237)	Total (n=713)	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)
Weight group (kg), n (%)						
<70	243 (51.1)	124 (52.3)	367 (51.5)	107 (50.5)	54 (59.3)	161 (53.1)
≥70-≤90	174 (36.6)	93 (39.2)	267 (37.4)	77 (36.3)	31 (34.1)	108 (35.6)
>90	58 (12.2)	19 (8.0)	77 (10.8)	28 (13.2)	6 (6.6)	34 (11.2)
Missing	1 (0.2)	1 (0.4)	2 (0.3)	0	0	0
Smoking status, n (%)						
Current smoker	79 (16.6)	38 (16.0)	117 (16.4)	39 (18.4)	13 (14.3)	52 (17.2)
Former smoker	354 (74.4)	178 (75.1)	532 (74.6)	153 (72.2)	71 (78.0)	224 (73.9)
Never smoked	43 (9.0)	21 (8.9)	64 (9.0)	20 (9.4)	7 (7.7)	27 (8.9)
Disease characteristics						
Disease Stage, n (%)						
IIIA	252 (52.9)	125 (52.7)	377 (52.9)	118 (55.7)	48 (52.7)	166 (54.8)
IIIB	212 (44.5)	107 (45.1)	319 (44.7)	89 (42.0)	42 (46.2)	131 (43.2)
Other[a]	12 (2.5)	5 (2.1)	17 (2.4)	5 (2.3)	1 (1.1)	6 (2.0)
WHO performance-status score, n (%)[b]						
0	234 (49.2)	114 (48.1)	348 (48.8	105 (49.5)	45 (49.5)	150 (49.5)
1	240 (50.4)	122 (51.5)	362 (50.8)	106 (50.0)	46 (50.5)	152 (50.2)
Not reported	2 (0.4)	1 (0.4)	3 (0.4)	1 (0.5)	0	1 (0.3)
Tumour histological type, n (%)						
Squamous	224 (47.1)	102 (43.0)	326 (45.7)	109 (51.4)	41 (45.1)	150 (49.5)
Non-squamous	252 (52.9)	135 (57.0)	387 (54.3)	103 (48.6)	50 (54.9)	153 (50.5)
PD-L1 status, n (%)[c]						

Characteristic	ITT			PD-L1 ≥1% group		
	Durvalumab (n=476)	Placebo (n=237)	Total (n=713)	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)
TC <25%	187 (39.3)	105 (44.3)	292 (41.0)	97 (45.8)	47 (51.6)	144 (47.5)
TC ≥25%	115 (24.2)	44 (18.6)	159 (22.3)	115 (54.2)	44 (48.4)	159 (52.5)
Unknown[d]	174 (36.6)	88 (37.1)	262 (36.7)	N/A	N/A	N/A
EGFR mutation status, n (%)						
Positive	29 (6.1)	14 (5.9)	43 (6.0)	17 (8.0)	4 (4.4)	21 (6.9)
Negative	317 (66.6)	165 (69.6)	482 (67.6)	180 (84.9)	84 (92.3)	264 (87.1)
Unknown[d]	130 (27.3)	58 (24.5)	188 (26.4)	15 (7.1)	3 (3.3)	18 (5.9)
Prior anti-cancer therapy						
Previous radiotherapy, n (%)[e]						
<54 Gy	3 (0.6)	0	3 (0.4)	2 (0.9)	0	2 (0.7)
≥54 to ≤66 Gy	442 (92.9)	217 (91.6)	659 (92.4)	193 (91.0)	86 (94.5)	279 (92.1)
>66 to ≤74 Gy	30 (6.3)	19 (8.0)	49 (6.9)	17 (8.0)	5 (5.5)	22 (7.3)
Missing[f]	1 (0.2)	1 (0.4)	2 (0.3)	0	0	0
Previous chemotherapy, n (%)[g]						
Adjuvant	3 (0.6)	1 (0.4)	4 (0.6)	2 (0.9)	0	2 (0.7)
Induction	123 (25.8)	68 (28.7)	191 (26.8)	49 (23.1)	21 (23.1)	70 (23.1)
Concurrent with radiation therapy	475 (99.8)	236 (99.6)	711 (99.7)	211 (99.5)	91 (100.0)	302 (99.7)
Best response to previous CRT, n (%)[h]						
Complete response	9 (1.9)	7 (3.0)	16 (2.2)	3 (1.4)	2 (2.2)	5 (1.7)
Partial response	232 (48.7)	111 (46.8)	343 (48.1)	106 (50.0)	45 (49.5)	151 (49.8)
Stable disease	222 (46.6)	114 (48.1)	336 (47.1)	100 (47.2)	43 (47.3)	143 (47.2)
Progression	2 (0.4)	0	2 (0.3)	1 (0.5)	0	1 (0.3)
Non-evaluable	9 (1.9)	4 (1.7)	13 (1.8)	2 (0.9)	1 (1.1)	3 (1.0)

Characteristic	ITT			PD-L1 ≥1% group		
	Durvalumab (n=476)	Placebo (n=237)	Total (n=713)	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)
Not applicable	2 (0.4)	1 (0.4)	3 (0.4)	0	0	0

Key: CRT, chemoradiation therapy; CSR, clinical study report; DCO, data cut-off; EGFR, epidermal growth factor receptor; ITT, intention to treat; N/A, not applicable; PD-L1, programmed cell death ligand 1; SD, standard deviation; TC, tumour cell; WHO, World Health Organization.
Notes: The PD-L1 subgroup has been defined using the re-scored PD-L1 data.
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 performance-status 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 2 patients in the durvalumab group changed from unknown to negative between the 13 February 2017 and 22 March 2018 DCOs, as the results for these 2 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, For the two patients with missing data, the biologically effective radiotherapy dose could not be calculated, primarily because their radiotherapy treatment planning data were neither collected nor accessible; g, Patients may have received previous chemotherapy in more than one context; h, best response to prior therapy is based on the last therapy prior to entering the study.
Source: Antonia et al., 2017[74], PACIFIC 13 February 2017 DCO CSR[75], PACIFIC 22 March 2018 DCO CSR (for updated disease characteristics)[77] and PACIFIC PD-L1 data.[92]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

All analyses were performed in accordance with a comprehensive Statistical Analysis Plan (SAP), detailing analyses to be conducted, summaries produced, and the analysis sets upon which they would be based.[91]

The main hypothesis evaluated in the PACIFIC study was that durvalumab 10mg/kg Q2W via IV infusion achieves improved efficacy (assessed through primary endpoints of PFS and OS) compared to placebo, in locally-advanced, unresectable, Stage III NSCLC patients, whose disease did not progress following two or more overlapping cycles of definitive, platinum-based CRT. The study would have met this objective if a statistically significant PFS and / or OS benefit of durvalumab was demonstrated.

All efficacy and HRQL data were analysed using the full analysis set (FAS), which included all randomised patients on an intention-to-treat (ITT) basis (i.e. based on treatment assigned at randomisation, regardless of whether treatment was received).[91] **Summaries of safety and tolerability assessments were based on the safety analysis set**, which included all patients who received at least one dose of randomised study medication.[91] Full details of participant flow in the PACIFIC clinical trial are provided in Appendix D.2. Statistical and analytical methods used and determination of sample size for the ITT analyses are provided in Appendix D.1 (pages 32–37).

As stated previously, **the evaluation of efficacy of durvalumab versus placebo in the PD-L1 ≥1% group was not pre-specified in the PACIFIC study**. The recent positive CHMP opinion recommending marketing authorisation for durvalumab in locally-advanced, unresectable NSCLC patients whose tumours express PD-L1 on ≥ 1% of TCs was based on exploratory *post-hoc* analysis of OS and PFS by different pre-CRT PD-L1 expression cut-offs.

Interim analyses

Three interim analyses were planned- one for PFS and two for OS.

Interim analysis of PFS (13 February 2017 DCO)

The interim analysis of PFS was planned for when approximately 367 PFS events had occurred (52% maturity) (CSR; page 139).[90] This analysis was conducted on 13 February 2017 (10 months after the completion of recruitment), based on the recommendation of an independent data monitoring committee (IDMC) (CSR page 54).[75]

At the time of DCO for this interim analysis, 371 PFS events (based on BICR assessments per RECIST 1.1) had occurred. Based on the review of data from this analysis, the IDMC concluded that the PACIFIC study had achieved statistically significance for PFS.[75] The OS data remained blinded and follow-up for OS continued until the target number of death events (discussed below) were reached.

Data from this interim analysis (for the ITT population) are fully described in the CSR.[75]

Interim analysis of OS (22 March 2018 DCO)

The planned interim analysis of OS was conducted after 299 (61%) of the target 491 deaths were observed (DCO: 22 March 2018). Based on the review of that interim analysis, the study was unblinded for OS. Since the study achieved statistical significance in the full ITT population based on this DCO, these results are considered to be the final OS analysis. Data from this analysis for the ITT population are fully described in a CSR Addendum.[77] PFS and OS data for the PD-L1≥1% group are provided in Appendix E.[92] Full table listings for key secondary endpoints in the PD-L1≥1% group are provided in a separate document.[92] Patients continue to be followed for survival and an additional analysis of OS will be performed at the end of the study in order to address regulatory requirements / post marketing commitments.

At the time of DCO, 232 patients (49.0%) in the durvalumab group and 82 patients (34.6%) in the placebo group had completed the protocol-defined 12 months of treatment, while 241 (50.6%) and 154 (65.0%), respectively, had discontinued (ITT population; see Appendix D.2 for further details).

In the PD-L1 ≥1% group, 143 (47.2%) patients had completed 12 months of treatment at the time of DCO (109 [51.4%] in the durvalumab arm and 34 [37.4%] in the placebo arm). 160 (52.8%) patients had discontinued study treatment (103 [48.6%] in durvalumab arm and 57 [62.6%] in the placebo arm). Further details are available in Appendix D.2.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The PACIFIC study was designed by representatives of AstraZeneca / MedImmune and academic advisors. The study protocol and amendments (detailed in the CSR, pages 54−63) were approved by relevant ethics committees, and the study was performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice (GCP) and the Declaration of Helsinki.[75] Quality of data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures (as detailed in the Clinical Study Protocol, page 48).[90] In addition, an Independent Data Monitoring Committee (IDMC) was created to assess the safety of the study on a regular basis.[75]

The PACIFIC was study was conducted in a double-blind manner. Patients, Investigators, and study centre staff were all blinded to the study drug allocation, thus reducing the risk of bias in assessment of key outcomes such as PFS and OS.

A complete quality assessment, in accordance with the NICE-recommended checklist for RCT assessment of bias, is presented in Appendix D; a summary of results is presented in Table 5. The risk of bias in the PACIFC study confirmed as being low.

Table 5: Quality assessment results for PACIFIC

Question	Applicable to PACIFIC study?
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes

Question	Applicable to PACIFIC study?
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
Source: Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.	

B.2.6. Clinical effectiveness results of the relevant trials

As stated previously, the Phase III PACIFIC RCT is the only study that directly compared the clinical effectiveness of durvalumab 10mg/kg Q2W versus active follow-up, the current SoC in locally-advanced, unresectable Stage III NSCLC patients whose disease did not progress following CRT. Inclusion in the study was not restricted by PD-L1 expression status prior to CRT and the ITT population included 303 patients with PD-L1 expression on ≥1% of TCs, 148 patients with PD-L1 expression on <1% of TCs, and 262 patients of unknown PD-L1 expression status. As explained in Figure 4, the CHMP requested exploratory *post-hoc* subgroup analyses based on pre-CRT, PD-L1 expression as part of the regulatory review process. This analysis was performed on both PFS and OS, and was discussed at an oral explanation. While a PFS benefit with durvalumab versus placebo was observed in both PD-L1 <1% and PD-L1 ≥1% groups, as well as in patients whose PD-L1 status was not known (Appendix E; Figure 6), the HR for OS in the PD-L1 <1% TC group was more than 1.0, with a wide 95% CI that included 1 (Appendix E; Figure 9). An OS benefit, in favour of durvalumab, was observed in the PD-L1 ≥1% group and in patients with "unknown" expression.

Based on these results, the CHMP determined that a survival benefit of durvalumab over placebo in the PD-L1 <1% group had not been shown. On 27 July 2018, the CHMP adopted a positive opinion, recommending 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 and whose disease has not progressed following platinum based CRT.[3]

Given that marketing authorisation for durvalumab is expected for patients with PD-L1 expression on ≥1% TCs, data for this subgroup will be the focus of this submission. Efficacy and safety analyses for the full PACIFIC ITT population are available in the CSR (13 February 2017 DCO; PFS interim analysis) / CSR addendum (22 March 2018 DCO; OS interim analysis). Top-line efficacy and safety data for the ITT population are also described below for information. Importantly, treatment with durvalumab resulted in a statistically-significant and clinically meaningful PFS and OS benefit versus placebo in both the ITT population and the PD-L1 ≥1% group (Table 6). Durvalumab treatment also resulted in statistically-significant improvements in key secondary endpoints versus placebo (Table 6).

Table 6: Key efficacy outcomes for durvalumab versus placebo from the PACIFIC RCT (ITT and PD-L1 ≥1% group; 22 March 2018 DCO)

Endpoint	ITT		PD-L1 ≥1%	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=212)	Placebo (N=91)
Primary endpoints				
PFS (13 February 2017 DCO; BICR) Median (95% CI) [months]	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)	17.8 (16.9, NR)	5.6 (3.6, 11.0)
HR (95% CI); *P*-value	0.52 (0.42, 0.65); *P*<0.001		0.44 (0.30, 0.64); *P*<0.0001	
OS (22 Mar 2018 DCO) Median (95% CI), [months]	NR (34.7, NR)	28.7 (22.9, NR)	NR (NR, NR)	29.1 (17.7, NR)
HR (95% CI); *P*-value	0.68 (0.53, 0.87); *P* =0.003		0.54 (0.35, 0.81); *P*=0.003	
Updated PFS and secondary endpoints (at the time of OS interim analysis; 22 March 2018 DCO)				
PFS (BICR) Median (95% CI) [months]	17.2 (13.1, 23.9)	5.6 (4.6, 7.7)	23.9 (17.2, NR)	5.6 (3.6, 11.0)
HR (95% CI); *P*-value	0.51 (0.41, 0.63); *P*<0.0001		0.44 (0.31,0.63); *P*<0.0001	
TFST Median (95% CI) [months]	21.0 (16.6, 25.5)	10.4 (8.3, 12.5)	25.8 (18.7, 37.8)	10.0 (7.0, 17.0)
HR (95% CI); *P*-value	0.58 (0.47, 0.72); *P* <0.0001		0.51 (0.36, 0.73); *P*=0.0002	
PFS2 Median (95% CI) [months]	28.3 (25.1, 34.7)	17.1 (14.5, 20.7)	33.8 (26.7, NR)	16.5 (10.3, 22.1)
HR (95% CI); *P*-value	0.58 (0.46, 0.73); *P* <0.0001		0.44 (0.30, 0.64); *P*<0.0001	
TSST	29.3 (26.0, 34.9)	18.6 (14.8, 23.9)	34.7 (28.8, NR)	17.9 (12.7, 26.2)

Endpoint	ITT		PD-L1 ≥1%	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=212)	Placebo (N=91)
Median (95% CI) [months] HR (95% CI); *P*-value	0.63 (0.50, 0.79); *P* <0.0001		0.49 (0.33, 0.71); *P*=0.0002	
Response rate ORR, % (95% CI)	30.0 (25.8, 34.5)	17.8* (13.0, 23.7)	32.5 (26.0, 39.5)	16.5 (9.3, 26.1)
P-value	*P* <0.001		*P*<0.005	
TTDM Median (95%CI)	28.3 (24.0, 34.9)	16.2 (12.5, 21.1)	NR (26.2, NR)	17.1 (9.2, 20.6)
HR (95% CI); *P*-value	0.53 (0.41, 0.68); *P* <0.0001		0.40 (0.26, 0.61); *P*<0.0001	

Key: BICR, blinded independent central review; CI, confidence interval; CRT, chemoradiation therapy; CSR, clinical study report; HR, hazard ratio; DCO, data cut-off; ITT, intent-to-treat; NR, not reached; ORR, objective response, OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria In Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death; TTDM, time to death or distant metastasis.
Notes: *, may reflect residual effect from prior CRT. The analysis of time to event endpoints 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.
Source: Antonia *et al*., 2017[74]; PACIFIC 13 February DCO CSR[75] and PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO[92]

Progression-free survival (BICR assessment per RECIST 1.1)

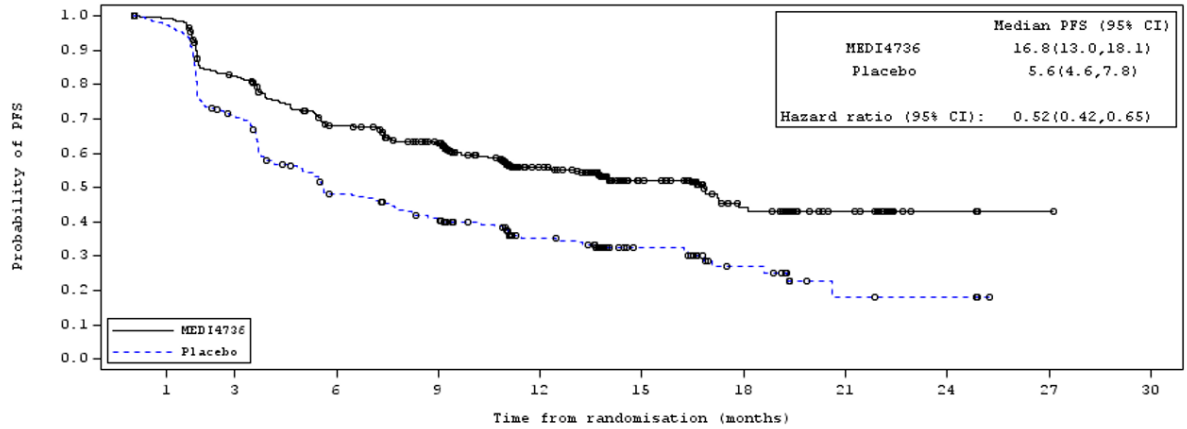
Primary PFS analysis (co-primary endpoint, 13 February 2017 DCO); PACIFIC ITT and PD-L1 ≥1% group

Durvalumab met the PFS primary endpoint in the ITT population, **demonstrating a statistically-significant and clinically meaningful benefit versus placebo** (HR=0.52; 95% CI: 0.42, 0.65; *P*<0.001), based on BICR assessments according to RECIST 1.1.[74, 75] The Kaplan–Meier (KM) estimate of median duration of PFS was 16.8 months (95% CI: 13.0, 18.1) in the durvalumab group versus 5.6 months (95% CI: 4.6, 7.8) in the placebo group[o].[74, 75] Median PFS of 16.8 months in the ITT population is remarkable, considering that 60% of unresectable Stage III NSCLC experience disease progression within a year of ***starting*** CRT.[93] A PFS gain of this

[o] Median PFS of 5.6 months in the placebo arm is comparable to the UK-specific Phase II SOCCAR clinical trial (median PFS of ~12 months from start of CRT; assuming treatment duration of three months for overlapping / concurrent CRT, plus 1.5 months recovery time, estimated PFS from a comparable time-frame to start of durvalumab treatment in the PACIFIC trial will be 6.5 months).

magnitude is also unprecedented for any immunotherapy approved in NSCLC[p].[73, 94-98] The PFS benefit was even greater in the PD-L1 ≥1% group (HR=0.44; 95% CI: 0.30, 0.64; *P*<0.0001; BICR assessments per RECIST 1.1). Median PFS duration was 17.8 months (95% CI: 16.9, NR) in the durvalumab arm versus 5.6 months (95% CI: 3.6, 11.0) in the placebo arm. Durvalumab treatment produced a sustained benefit, evident from the early and consistent separation of PFS KM-curves (both in the ITT and the PD-L1 ≥1% group; shown in Figure 7 and Figure 8).

Figure 7: BICR assessment of PFS (per RECIST 1.1); PACIFIC ITT population (13 February 2017 DCO)



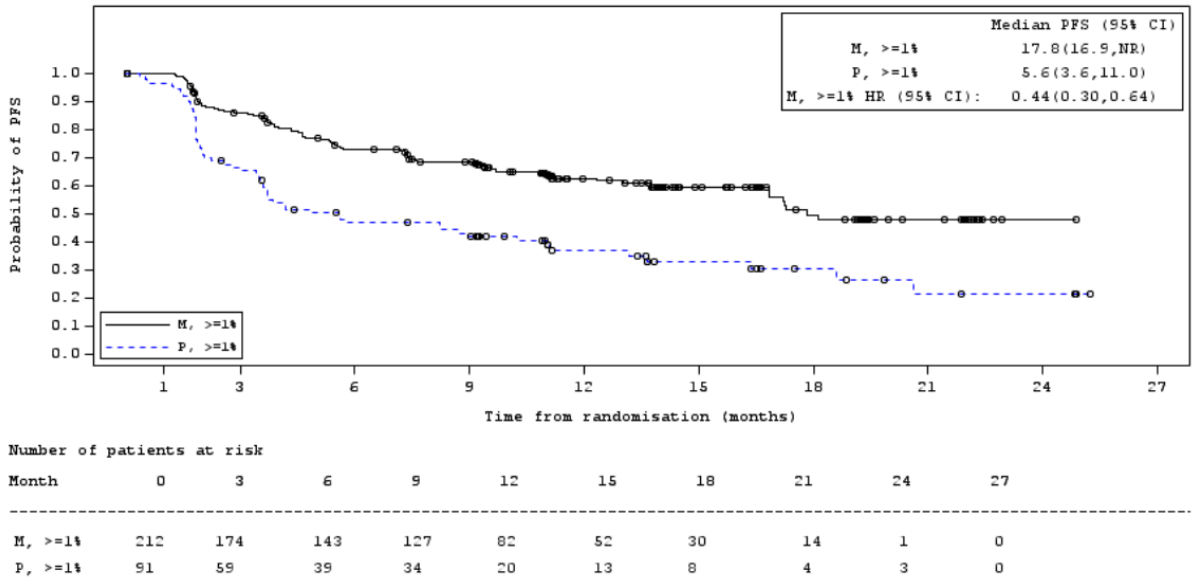
Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30
MEDI4736	476	377	301	264	159	86	44	21	4	1	0
Placebo	237	163	106	87	52	28	15	4	3	0	0

Key: BICR, Blinded Independent Central Review; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; ITT, intention to treat; MEDI4736, durvalumab; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumors Version 1.1; SmPC, summary of product characteristics. **Note:** Circles indicate a censored observation. **Source:** PACIFIC 13 February 2017 DCO CSR[75]; SmPC[1]

[p] Pembrolizumab first-line metastatic PD-L1 ≥50% NSCLC (KEYNOTE-024): median PFS (95% CI): pembrolizumab arm = 10.3 months (6.7, NR); standard of care arm = 6.0 months (4.2, 6.2)
Pembrolizumab second-line advanced PD-L1 ≥1% NSCLC (KEYNOTE-010): median PFS (95% CI): pembrolizumab arm = 3.9 months (3.1, 4.1); docetaxel arm = 4.0 months (3.1, 4.2).
Nivolumab second-line, advanced, squamous NSCLC (CHECKMATE-017): median PFS (95% CI): nivolumab arm = 3.5 months (2.1, 4.9); docetaxel arm = 2.8 months (2.1, 3.5).
Nivolumab second-line, advanced or metastatic, non-squamous NSCLC (CHECKMATE-057): median PFS (95% CI): nivolumab arm = 2.3 months (2.2, 3.3); docetaxel arm = 4.2 (3.5, 4.9).
Atezolizumab second-line advanced or metastatic NSCLC (OAK): median PFS (95% CI): atezolizumab arm = 4.0 months (3.3, 4.2); docetaxel arm = 2.8 (2.6, 3.0).
Atezolizumab second-line advanced or metastatic NSCLC (POPLAR): median PFS (95% CI): atezolizumab = 2.7 months (2.0, 4.1); docetaxel arm = 3.4 (2.8, 4.1).

Figure 8: BICR assessment of PFS (per RECIST 1.1); PACIFIC PD-L1 ≥1% group (13 February 2017 DCO)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27
M, >=1%	212	174	143	127	82	52	30	14	1	0
P, >=1%	91	59	39	34	20	13	8	4	3	0

Key: BICR, Blinded Independent Central Review; CI, confidence interval; DCO, data cut-off; MEDI4736, durvalumab; 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; SmPC, summary of product characteristics.
Notes: Circles indicate a censored observation.
Source: PACIFIC PD-L1 subgroup analysis[92]

A sustained treatment benefit of durvalumab versus placebo in the PD-L1 ≥1% group is also supported by 12-month PFS rates (62.7% versus 37.1%) and 18-month PFS rates (49.8% and 30.7%).[74, 75] A summary of PFS analysis in the PD-L1 ≥1% group (13 February 2017 DCO) is provided in Table 7.

Table 7: Summary of PFS analyses (BICR assessments, per RECIST 1.1); PACIFIC PD-L1 ≥1% group (13 February 2017 DCO)

Progression status	Durvalumab (N=212)	Placebo (N=91)
Total events, n (%)[a]	**84 (39.6)**	**59 (64.8)**
RECIST 1.1 progression	73 (34.4)	51 (56.0)
Death in absence of progression	11 (5.2)	8 (8.8)
Censored patients, n (%)	**128 (60.4)**	**32 (35.2)**
Censored RECIST 1.1 progression[b]	0	0
Censored death[c]	3 (1.4)	1 (1.1)
Progression-free at time of analysis	117 (55.2)	28 (30.8)
Lost to follow-up	0	0
Withdrawn consent	6 (2.8)	2 (2.2)
Discontinued study	2 (0.9)	1 (1.1)

Progression status	Durvalumab (N=212)	Placebo (N=91)
Median PFS, months[d] (95% CI)	17.8 (16.9, NR)	5.6 (3.6, 11.0)
Hazard ratio (95% CI)[e]; two-sided *P*-value	0.44 (0.30, 0.64); *P*<0.0001	
PFS rate at 12 months, %[d] (95% CI)	62.7 (55.4, 69.1)	37.1 (26.7, 47.6)
PFS rate at 18 months, %[d] (95% CI)	49.8 (40.1, 58.6)	30.7 (20.1, 41.8)

Key: BICR, Blinded Independent Central Review; CI, confidence interval; DCO, data cut-off; MEDI4736, durvalumab; 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 did not experience disease progression or had died, or those who experienced disease progression or died after ≥2 missed visits, were censored at the latest non-missing RECIST 1.1 assessment. Patients who had no non-missing visits or no baseline data were censored on day 1, unless they died within 2 visits of baseline
[b], RECIST 1.1 progression event occurred after ≥2 missed visits or within 2 visits of baseline, where the patient had no non-missing visits or no baseline assessment
[c], Death, which occurred after ≥2 missed visits in the absence of RECIST 1.1 progression
[d], Calculated using the Kaplan–Meier technique
[e], 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.
Source: PACIFIC PD-L1 subgroup analysis[92]

BICR assessments (per RECIST 1.1) showed a lower frequency of new lesions in the durvalumab arm of the PD-L1 ≥1% group, relative to placebo (16.5% versus 35.2%, respectively). These analyses were updated at the time of the OS interim analyses (22 March 2018 DCO) and are described in further detail below (page 54).

Updated PFS analysis (22 March 2018 DCO); PACIFIC PD-L1 ≥1% group

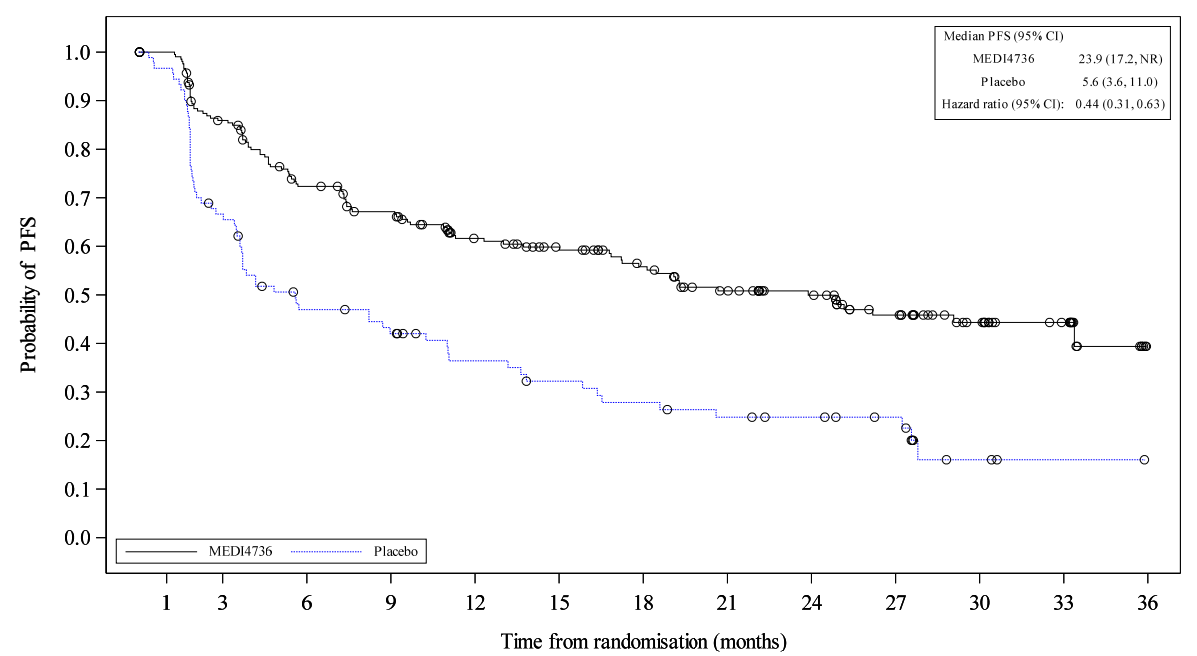
Although the primary endpoint of PFS was statistically met at 13 February 2017 DCO (for both ITT population and PD-L1 ≥1% group), PFS data were updated at the time of the primary OS analysis (22 March 2018 DCO). Briefly, these data confirmed the PFS benefit of durvalumab versus placebo both in the ITT (Table 6; see CSR Addendum for details) and the PD-L1 ≥1% group (HR=0.44, 95% CI: 0.31, 0.63, two-sided *P*<0.0001; BICR assessments per RECIST 1.1). The KM estimate of median PFS increased to 23.9 months (95% CI: 17.2, NR) in the durvalumab arm in this more mature dataset, versus 5.6 months (95% CI: 3.6, 11.0) for placebo (data maturity at both DCOs is shown in Table 6). These updated PFS data were used to inform the health economic modelling described in Section B.3 (full details of analyses are available in the CSR Addendum[77, 92]).

Durvalumab treatment produced a sustained benefit, evident from the early and consistent separation of PFS KM-curves (Figure 9). This is also supported by the proportion of patients alive and progression-free at 12 months (PFS12) and 18 months (PFS18):

- PFS12: 61.6% in durvalumab arm (95% CI 54.4, 68.0) versus 36.4% in placebo arm (95% CI 26.2, 46.7)
- PFS18: 55.8% in durvalumab arm (95% CI 48.3, 62.6) versus 27.8% in placebo arm (95% CI 18.4, 38.0)

A clear benefit for durvalumab versus in supported by non-overlapping CIs for both PFS12 and PFS24.

Figure 9: BICR assessment of PFS (per RECIST 1.1); PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)



Key: BICR, Blinded Independent Central Review; CI, confidence interval; DCO, data cut-off; MEDI4736, 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.
Notes: Circles indicate a censored observation. Note that HR is different in the SmPC since that was based on the unstratified Cox regression model versus the stratified log rank test.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

BICR assessments (per RECIST 1.1) of new lesions was consistent with previous analyses (13 February 2017 DCO) and PFS data, and showed a lower frequency of new lesions in the durvalumab group relative to placebo (Table 8). These data highlight an important benefit of durvalumab in preventing / delaying local recurrence, as well as controlling systemic disease spread. Furthermore, noticeably fewer instances of burdensome and difficult-to-treat lesions (such as brain metastases) in the durvalumab group are likely to contribute towards the substantial OS and HRQL benefits achieved with durvalumab versus placebo (pages 66 and 75, respectively).

Table 8: Incidence of new lesions in the PACIFIC interim analysis (BICR assessments according to RECIST 1.1); PD-L1 ≥1% group (22 March DCO)

New lesion site, n (%)[a]	Durvalumab (N=212)	Placebo (N=91)
Patients with no new lesions	**173 (81.6)**	**58 (63.7)**
Any new lesion	**39 (18.4)**	**33 (36.3)**
Lung	19 (9.0)	16 (17.6)
Lymph nodes	15 (7.1)	10 (11.0)
Brain	10 (4.7)	11 (12.1)
Liver	3 (1.4)	3 (3.3)
Bone	2 (0.9)	4 (4.4)
Adrenal	1 (0.5)	3 (3.3)
Other	2 (0.9)	2 (2.2)

Key: BICR, blinded independent central review; DCO, data cut-off; ITT, intention-to-treat; PD-L1, programmed cell death ligand 1; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: [a], A patient may have had more than one new lesion site.
Source: PACIFIC PD-L1 subgroup analyses.[92]

TFST data were derived as a supportive summary to PFS, and updated at the 22 March 2018 DCO. These data are briefly described below.

Time to first subsequent therapy or death (TFST); PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Consistent with the PFS benefit, durvalumab treatment resulted in a statistically-significant extension in TFST relative to placebo in the PD-L1 ≥1% group (HR: 0.51; 95% CI: 0.36, 0.73; *P*=0.0002). Median TFST was over twice as long in the durvalumab group compared to the placebo group (25.8 months versus 10.0 months;

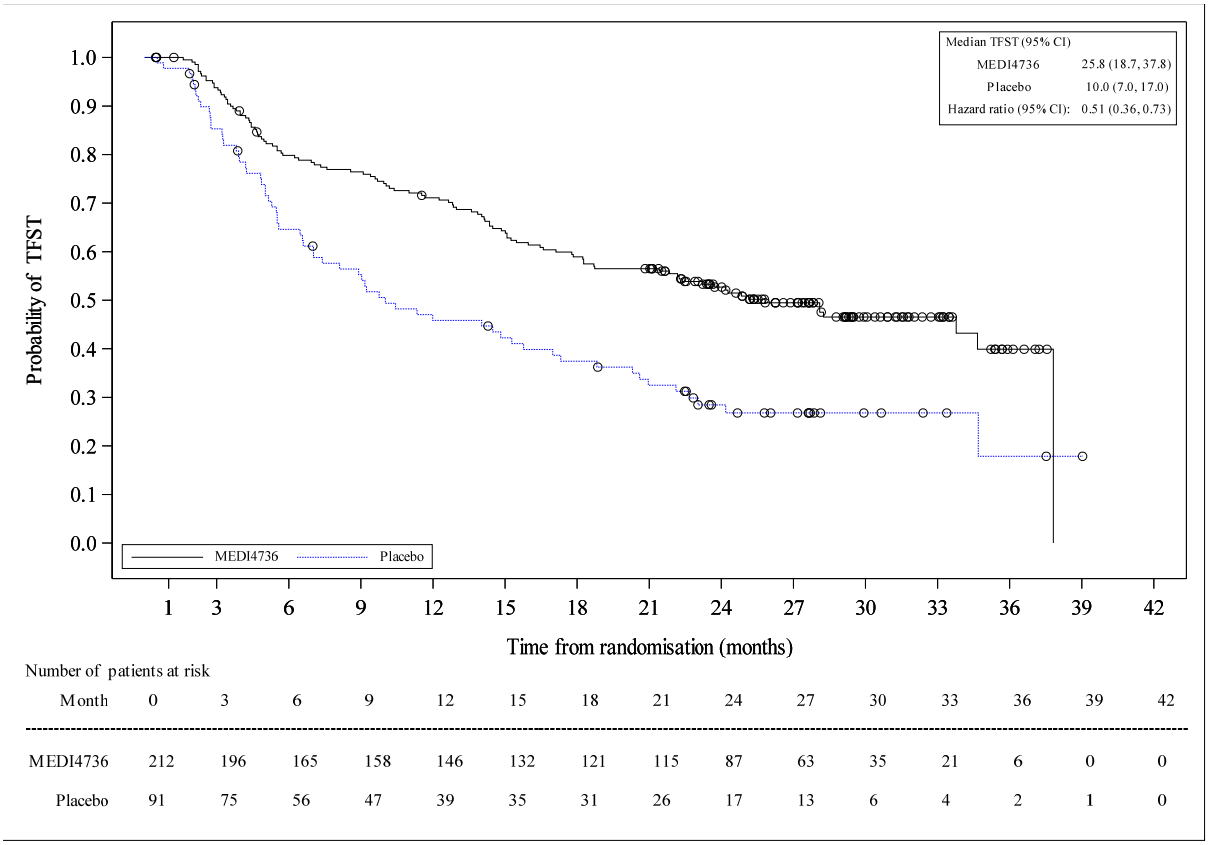
Table 9). Separation in the KM curves between durvalumab and placebo groups occurred early and was sustained over the treatment period (as shown in Figure 10). TFST in the PD-L1 ≥1% group was consistent with results in the ITT population, which demonstrated statistically significant and clinically meaningful extension in TFST in the durvalumab group, relative to placebo (HR: 0.58, *P*<0.0001; further details available in the CSR Addendum).

Table 9: Summary of TFST analyses (BICR assessment per RECIST 1.1); PACIFIC ITT population (22 March 2018 DCO)

	Durvalumab (N=212)	Placebo (N=91)
Total events, n (%)[a]	**108 (50.9)**	**63 (69.2)**
Subsequent therapy	81 (38.2)	51 (56.0)
Death	27 (12.7)	12 (13.2)
Censored patients	104 (49.1)	28 (30.8)
Median TFST, months[b] (95% CI)	25.8 (18.7, 37.8)	10.0 (7.0, 17.0)
Hazard ratio (95% CI)[c]; two-sided *P*-value[c]	0.51 (0.36, 0.73); *P*=0.0002	

Key: BICR, blinded independent central review; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; ITT, intention to treat; PFS, progression-free survival; TFST, time to start of first subsequent therapy or death.
Notes: [a], Patients with TFST. TFST is defined as the time from randomisation to the start of the first subsequent therapy after discontinuation of treatment, or death.
[b], Calculated using the Kaplan–Meier technique.
[c], 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.
Source: PACIFIC 22 March 2018 CSR[77]

Figure 10: KM plot of TFST (BICR assessment per RECIST 1.1); PACIFIC ≥1% PD-L1 group (22 March 2018 DCO)



Key: BICR, blinded independent central review; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; ITT, intention-to-treat; KM, Kaplan–Meier; MEDI4736, durvalumab; PD-L1, programmed death-ligand 1; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TFST, time to first subsequent therapy, or death.
Note: Each circle indicates a censored observation.
Source: PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO.[92]

At the time of the 22 March 2018 DCO, 81 (38.2%) patients who received durvalumab and 50 (54.9%) patients who received placebo in the PD-L1 ≥1% group, had received post-discontinuation, disease-related anticancer therapy (Table 10).

More patients in the placebo group received immunotherapy in any subsequent line of therapy (22 [24.2%], versus 18 [8.5%] in the durvalumab group). Greater use of immunotherapy in the placebo arm relative to the durvalumab arm can extend post-progression survival (PPS) in the subgroup of patients who received these treatments, and underestimate the OS benefit of durvalumab versus placebo (although this is reflective of real-world treatment practice). This is discussed further below (PPS: page

64; OS: page 66). Level of subsequent immunotherapy use in the placebo arm is broadly comparable to UK clinical practice (~30%; AstraZeneca data on file).[44] Lower use of subsequent immunotherapy in the durvalumab is expected and consistent with UK clinical expert opinion (AstraZeneca data on file).[44]

Use of other anticancer therapies was more similar between the two groups, although greater subsequent therapy usage was consistently reported in the placebo group across all treatment classes (Table 10). Full details of post-discontinuation disease-related anticancer therapies used in the PD-L1 ≥1% group (as of 22 March 2018 DCO) are available in the PD-L1 subgroup CSR Addendum[92] and are consistent with data from the ITT population (CSR addendum, Table 11.1.18).[77]

Table 10: Post-discontinuation disease-related anticancer therapy; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

	Durvalumab (N=212)	Placebo (N=91)
Patient with post-discontinuation disease-related anticancer therapy, n (%)	**81 (38.2)**	**50 (54.9)**
Radiotherapy, n (%)	31 (14.6)	20 (22.0)
Immunotherapy, n (%)	18 (8.5)	22 (24.2)
Cytotoxic chemotherapy, n (%)	54 (25.5)	29 (31.9)
Systemic therapy (e.g. EGFR TKIs ALKi), n (%)	24 (11.3)	13 (14.3)

Key: ALKi, anaplastic lymphoma kinase inhibitor; DCO, data cut-off; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death ligand 1; TKI, tyrosine kinase inhibitor.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

Time from randomisation to second progression or death (PFS2); PD-L1 ≥1% group (22 March 2018 DCO)

As stated above, the use of multiple subsequent therapies after disease progression can underestimate the survival benefit of new interventions. Intermediate clinical endpoints, such as PFS2 and TSST provide information about the long-term benefits of a treatment and reflect real-life treatment decisions and patient experience.

Treatment with durvalumab significantly extended PFS2 versus placebo in both the ITT population (Table 6; see CSR Addendum for details) and the PD-L1 ≥1% group (Table 11). The HR for PFS2 (0.44; 95% CI 0.30, 0.64; *P*<0.0001) was consistent with the HR for 22 March 2018 analysis of PFS (HR 0.44; 95% CI 0.31, 0.63; *P*<0.0001) in

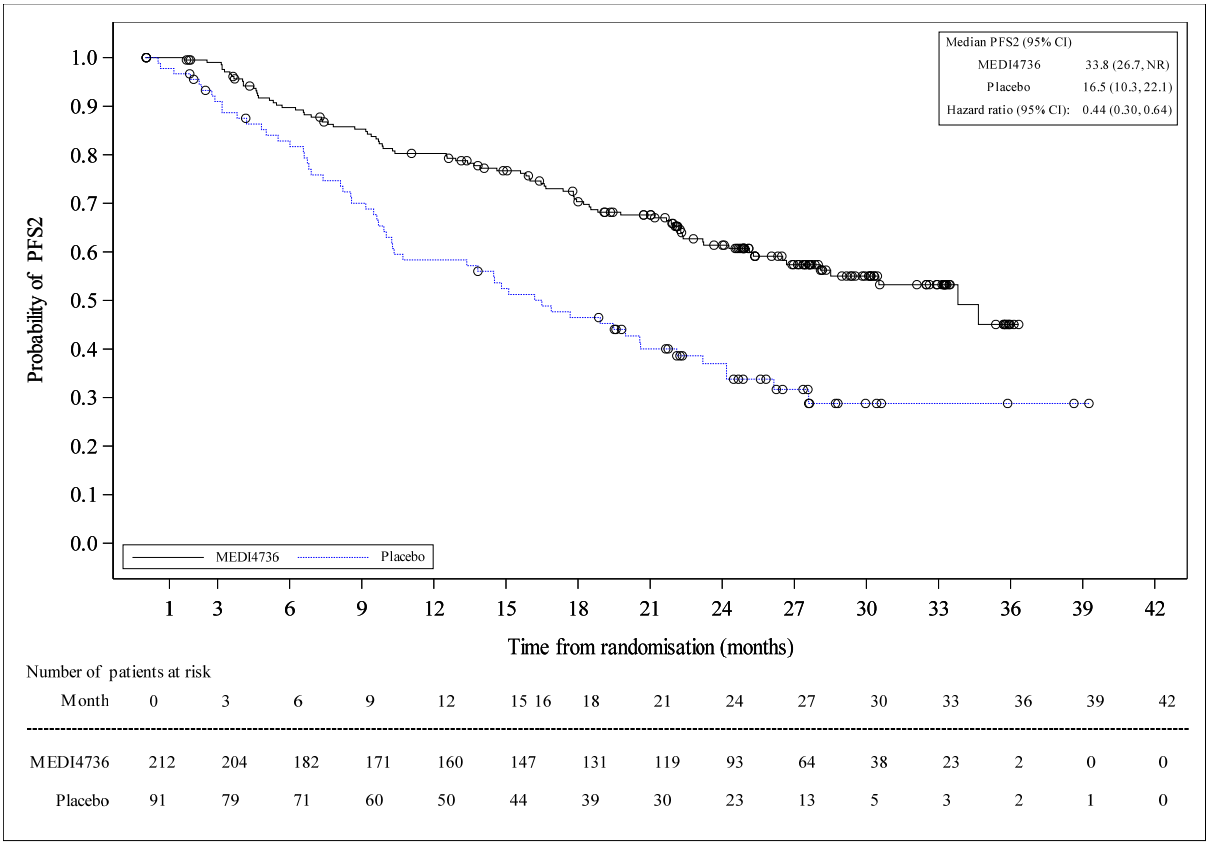
the PD-L1 ≥1% group. The KM-plot for PFS2 shows clear and early separation of the curves in favour of durvalumab (Figure 11). The benefit of durvalumab also supported by a much greater median duration of PFS2 (33.8 months; 95% CI 26.7, NR) versus placebo (16.5 months; 95% CI 10.3, 22.1).

Table 11: Time to second progression or death (PFS2); PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Progression status	Durvalumab (N=212)	Placebo (N=91)
Total events, n (%)[a]	**84 (39.6)**	**57 (62.6)**
Second progression	42 (19.8)	36 (39.6)
Objective progression by RECIST 1.1	28 (13.2)	24 (26.4)
Symptomatic progression	1 (0.5)	9 (9.9)
New or worsening of soft tissue / visceral or bone metastases	12 (5.7)	3 (3.3)
Other	1 (0.5)	0
Death in absence of second progression	42 (19.8)	21 (23.1)
Censored patients, n (%)	**128 (60.4)**	**34 (37.4)**
Censored second progression[b]	0	0
Censored death[c]	0	0
Alive and progression free	76 (35.8)	15 (16.5)
No second progression	42 (19.8)	14 (5.4)
Lost to follow-up	0	0
Withdrawn consent	10 (4.7)	5 (5.5)
Discontinued study	0	0
Median PFS2, months[b] (95% CI)	33.8 (26.7, NR)	16.5 (10.3, 22.1)
Hazard ratio[e] (95% CI); two-sided *P*-value	0.44 (0.30, 0.64); *P*<0.0001	

Key: CI, confidence interval; DCO, data cut-off; NR, not reached; PD-L1, programmed cell death ligand 1; PFS2, time to second progression or death; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1.
Notes: [a], Progression is determined by investigator assessments. Patients who have not progressed the second time or died, or who progress the second time or die after two or more missed visits, are censored at the latest evaluable second progression assessment, or day 1 if there are no evaluable visits. Patients with a second progression within two visits of baseline who do not have any evaluable visits or do not have a baseline assessment are censored at day 1.
[b], Second progression event occurred after two or more missed visits or within two visits of baseline where the patient has no evaluable visits or does not have a baseline assessment.
[c], Death which occurred after two or more missed visits in the absence of second progression.
[d], Calculated using the Kaplan–Meier technique.
[e], 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.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO[92]

Figure 11: KM plot of time to second progression or death (PFS2); PD-L1 ≥1% group (22 March 2018 DCO)



Key: CI, confidence interval; DCO, data cut-off; KM, Kaplan–Meier; MEDI4736, durvalumab; NR, not reached; PD-L1, programmed cell death ligand 1; PFS2, time to second progression or death.
Notes: Circles indicate a censored observation.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

It is worth noting that greater use of anti PD-1 / PD-L1 therapies in subsequent lines of treatment in the placebo group (Table 10) may underestimate the benefit of durvalumab (as the difference between the two arms is reduced by patients in the placebo group benefiting from subsequent immunotherapy), although this is generally reflective of real-world treatment practice.

Time to second subsequent therapy or death (TSST); PD-L1 ≥1% TC group (22 March 2018 DCO)

These analyses were consistent with the observed PFS2 results in the PD-L1 ≥1% group and showed significant extension of TSST in patients who received durvalumab versus placebo (HR 0.49; 95% CI 0.33, 0.71; *P*=0.0002; Table 12 and Figure 12). Importantly, the median duration of TSST in the durvalumab group (34.7 months; 95% CI 28.8, NR) was nearly twice as long compared to the placebo group (17.9 months;

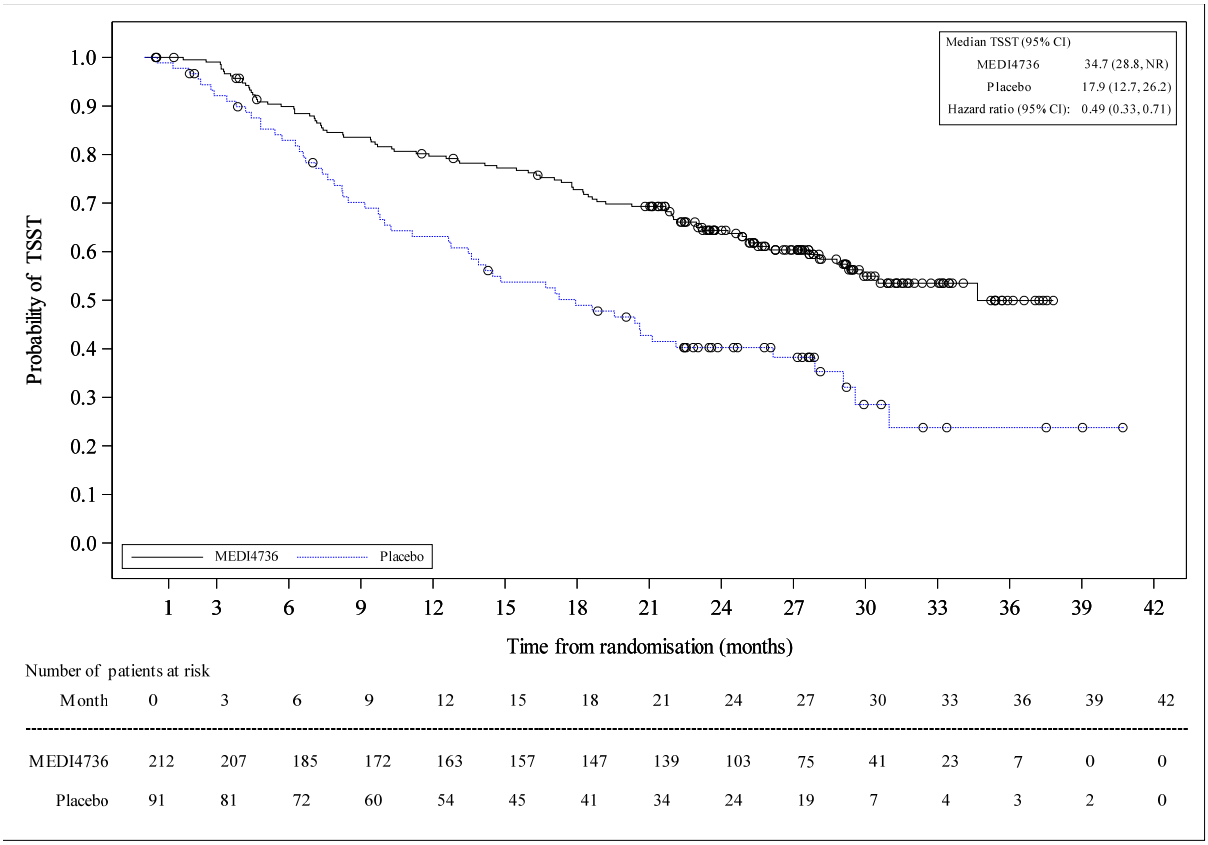
95% CI 12.7, 26.2), indicating meaningful extension in the time between subsequent lines of therapy.

Table 12: Summary of TSST analyses; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

TSST	Durvalumab (N=212)	Placebo (N=91)
Total events, n (%)[a]	**85 (40.1)**	**56 (61.5)**
Second subsequent therapy	37 (17.5)	26 (28.6)
Death	48 (22.6)	30 (33.0)
Censored patients, n (%)	127 (59.9)	35 (38.5)
Median TSST, months[b] (95% CI)	34.7 (28.8, NR)	17.9 (12.7, 26.2)
Hazard ratio (95% CI); two-sided *P*-value[c]	0.49 (0.33, 0.71); *P*=0.0002	

Key: CI, Confidence interval; DCO, data cut-off; NR, not reached; PD-L1, programmed cell death ligand 1; TSST, time to subsequent therapy or death.
Notes: [a], Patients with second subsequent therapy or death (TSST). TSST is defined as the time from randomisation to the earlier of the second subsequent cancer therapy start date following study treatment discontinuation, or death
[b], Calculated using the Kaplan–Meier technique
[c], 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.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

Figure 12: KM plot of TSST; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)



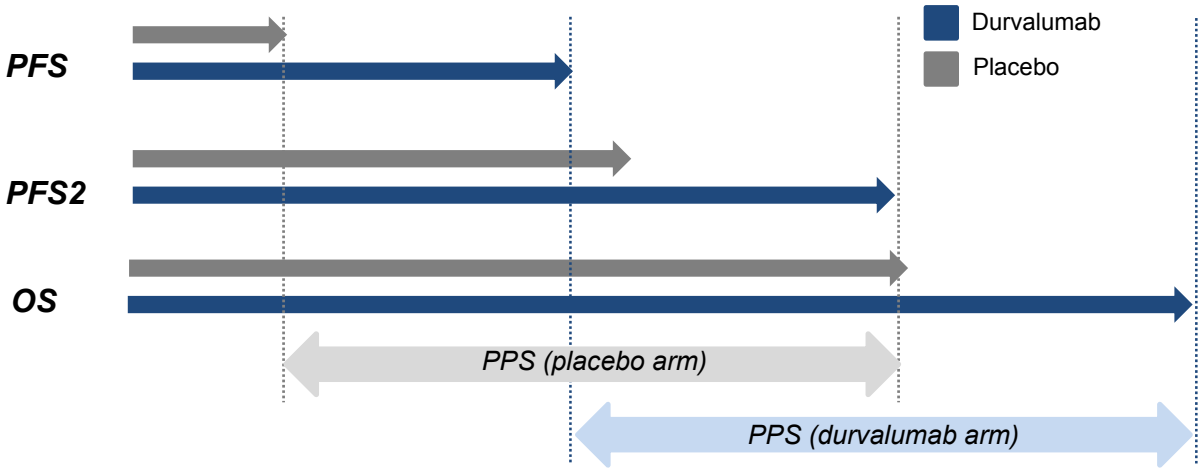
Key: CI, confidence interval; DCO, data cut-off; KM, Kaplan–Meier; MEDI4736, durvalumab; NR, not reached; PD-L1, programmed cell death ligand 1; TSST, time to second subsequent therapy, or death.
Notes: Circles indicate a censored observation.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

At the time of the primary OS analysis (22 March 2018 DCO), 8.5% of patients in the durvalumab group and 24.2% of patients in the placebo group with ≥1% PD-L1 expression on TCs had received subsequent immunotherapy upon disease progression. Significant extension of TSST in the durvalumab group versus placebo, despite greater subsequent immunotherapy use in the latter, emphasises the overall benefit of early immunotherapy use in controlling / delaying the development of burdensome metastatic disease, and highlights the important benefit to patients of delaying the need to use potentially more toxic subsequent palliative therapies.

Post-progression survival (PPS; BICR); *post-hoc* analysis (PD-L1 ≥1% group; 22 March 2018 DCO)

PPS was determined using a semi-parametric analysis and defined as the time from first progression until death due to any cause. The relationship between PFS, PFS2, PPS, and OS endpoints is illustrated in Figure 13.

Figure 13: Relationship between PFS, PFS2, OS and PPS endpoints



Key: OS, overall survival; PFS, progression-free survival; PFS2, time to second progression or death; PPS, post-progression survival. **Note: For illustration only; does not reflect actual PFS, PFS, and OS benefit reported in the PACIFIC study.**

The PPS analysis in the PD-L1 ≥1% group was based on 86 patients in the durvalumab arm and 57 patients in the placebo arm who had confirmed disease progression before death (based on BICR assessments, per RECIST 1.1) at the time of the 22 March 2018 DCO (one patient in the placebo arm who had disease progression, died on the same day this was confirmed; this patient was excluded from PPS analysis).

The analysis showed a slightly longer median PPS of 18.6 months (95% CI 12.5, 26.5) in the durvalumab group versus placebo (median: 15.3 months; 95% CI 12.5, 18.5; Table 13). Consistent with this, durvalumab and placebo KM-curves separated between ~13 and 27 months, in favour of durvalumab (shown in Figure 14). It is possible that this apparent benefit is a result of lower overall disease burden in durvalumab patients at the point of disease progression. This is supported by fewer new lesions in the brain, lung, and lymph nodes in the durvalumab group versus placebo. It should be emphasised however, that these analyses are relatively

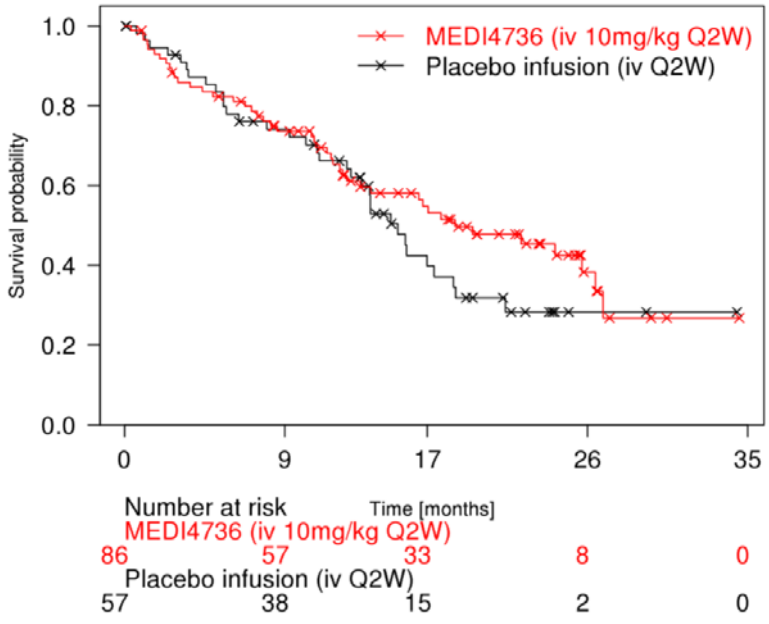
immature (51.2% and 57.9% maturity in durvalumab and placebo arms, respectively) and based on a small number of events; therefore, the apparent PPS benefit observed with durvalumab should be interpreted with caution. In light of this, a conservative scenario that assumes equal PPS benefit in durvalumab and placebo arms was used in the health economic modelling (presented in Section B.3.3).

Table 13: Semi-parametric analysis of PPS in patients with confirmed disease progression (BICR); PD-L1 ≥1% group (22 March 2018 DCO)

Post-progression survival	Durvalumab (N=86)	Placebo (N=57)
Total events, n (%)[a]	**44**	**33**
Ratio (durvalumab:placebo)	1.33	
Difference (durvalumab–placebo)	11	
Median time to event, months (95% CI)	**18.6 (12.5, 26.5)**	**15.3 (12.5, 18.5)**
Ratio (durvalumab:placebo)	1.21 (1.0, 1.4)	
Difference (durvalumab–placebo)	3.22 (0, 8)	

Key: BICR, blinded independent central review; CI, Confidence interval; DCO, data cut-off; ITT, intent to treat; PD-L1, programmed cell death ligand 1; PPS, post-progression survival.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO (from SIBYL report).[92]

Figure 14: Kaplan–Meier curve of PPS in patients with confirmed disease progression (BICR); PD-L1 ≥1% TC group (22 March 2018 DCO)



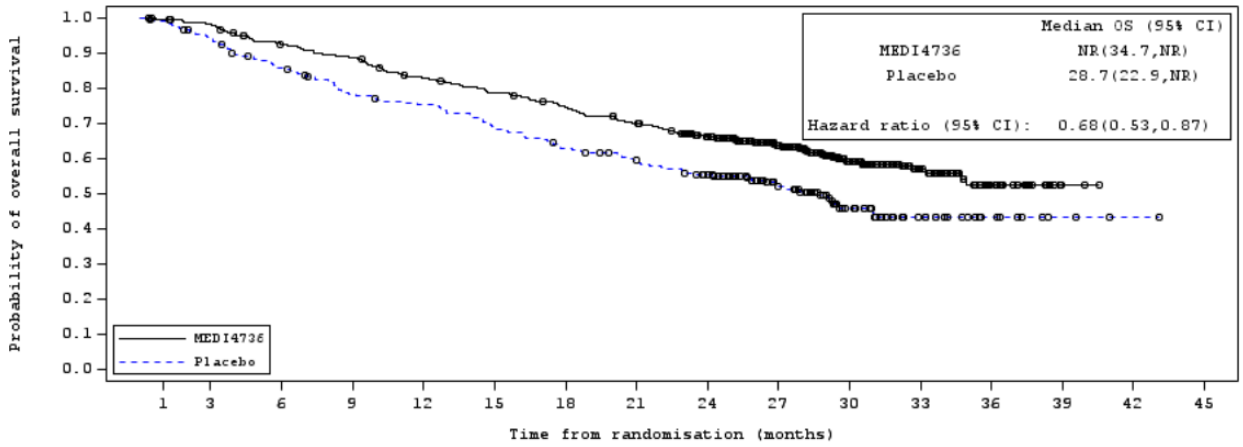
Key: BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; ITT, intention to treat; iv, intravenous; kg, kilogram; MEDI4736, durvalumab; mg, milligram; PD-L1, programmed cell death ligand 1; PPS, post-progression survival; Q2W, every 2 weeks; TC, tumour cell.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO[92]

Overall survival (OS, co-primary endpoint); PACIFIC ITT and PD-L1 ≥1% group (22 March 2018 DCO)

Treatment with durvalumab achieved a statistically-significant and clinically meaningful OS benefit versus placebo in the ITT population (HR=0.68; 95% CI: 0.53, 0.87; *P*=0.003). This is also illustrated in the early and consistent separation of OS KM-curves in favour of the durvalumab group (shown in Figure 15), and statistically-significantly greater 24-month OS rates in the durvalumab group versus placebo (66.3% vs 55.6%; *P*=0.005). The KM estimate of median duration of OS was 28.7 months (95% CI: 22.9, NR) in the placebo group; median OS was not reached in the durvalumab group (95% CI: 34.7, NR), although the lower bound of 95% CI indicates a OS benefit of at least six months versus placebo. Final analysis of OS will be conducted when 491 OS events have occurred (70% maturity).

Treatment with durvalumab also significantly extended OS relative to placebo in the PD-L1 ≥1% group (HR 0.54; 95% CI 0.35, 0.81; *P*=0.0034), with a greater benefit relative to the ITT. This is supported by the early and consistent separation of OS KM-curves in favour of the durvalumab group (shown in Figure 16). A summary of the OS analysis for the PD-L1 ≥1% group is provided in Table 14. The KM estimate of median duration of OS was 29.1 months (95% CI 17.7, NR) in the placebo group; median OS was not reached in the durvalumab group (95% CI NR, NR).

Figure 15: KM plot of OS (co-primary endpoint); PACIFIC ITT population (22 March 2018 DCO)

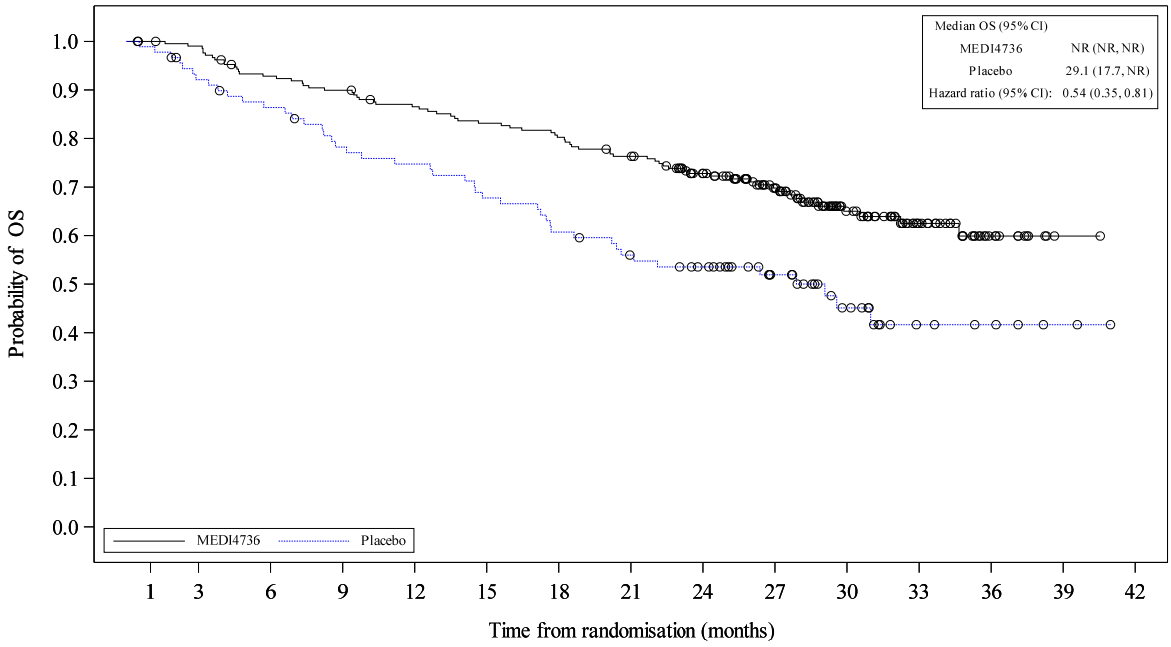


Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
MEDI4736	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Key: CI, confidence interval; DCO, data cut-off; ITT, intention to treat; KM, Kaplan–Meier; MEDI4736, durvalumab; NR, not reached; OS, overall survival. **Notes:** Circles indicate a censored observation. **Source:** PACIFIC 22 March 2018 DCO CSR; SmPC.[1]

Figure 16: KM plot of OS; PD-L1 ≥1% group (22 March 2018 DCO)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	32	33	36	39	42
MEDI4736	212	208	193	187	178	171	165	156	134	105	62		34	12	1	0
Placebo	91	81	75	67	64	58	52	46	41	29	17		7	5	2	0

Key: CI, confidence interval; DCO, data cut-off; KM, Kaplan–Meier; MEDI4736, durvalumab; NR, not reached; OS, overall survival; PD-L1, programmed-death ligand-1; **Notes:** Circles indicate a censored observation. Note that HR is different in the SmPC since that was based on the unstratified Cox regression model versus the stratified log rank test. **Source:** PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO[92]

Table 14: Summary of primary OS analysis; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Overall survival	Durvalumab (N=212)	Placebo (N=91)
Death, n (%)	70 (33.0)	45 (49.5)
Censored patients:	142 (67.0)	46 (50.5)
Still in survival follow-up[a]	130 (61.3)	40 (44.0)
Terminated prior to death[b]	12 (5.7)	6 (6.6)
Voluntary discontinuation by patient	12 (5.7)	6 (6.6)
Subject lost to follow-up	0	0
Other	0	0
Median OS, months (95% CI)[c]	**NR** (NR, NR)	**29.1** (17.7, NR)
Survival rate:		
12 months, % (95% CI)[c]	86.5 (81.1, 90.5)	74.7 (64.2, 82.6)
24 months, % (95% CI)[c]	72.8 (66.2, 78.4)	53.6 (42.5, 63.4)
Hazard ratio (95% CI)[e] ; two-sided *P*-value	**0.54** (0.35, 0.81); *P*= 0.0034	

Key: CI, confidence interval; CSR, clinical study report; DCO, data cut-off; ITT, intention to treat; NR, not reached; OS, overall survival.
Notes: [a], Includes patients known to be alive at data cut-off
[b], Includes patients with unknown survival status or patients who were lost to follow-up
[c], Calculated using the Kaplan–Meier technique
[d], 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.
Source: PACIFIC 22 March 2018 DCO CSR.[77]

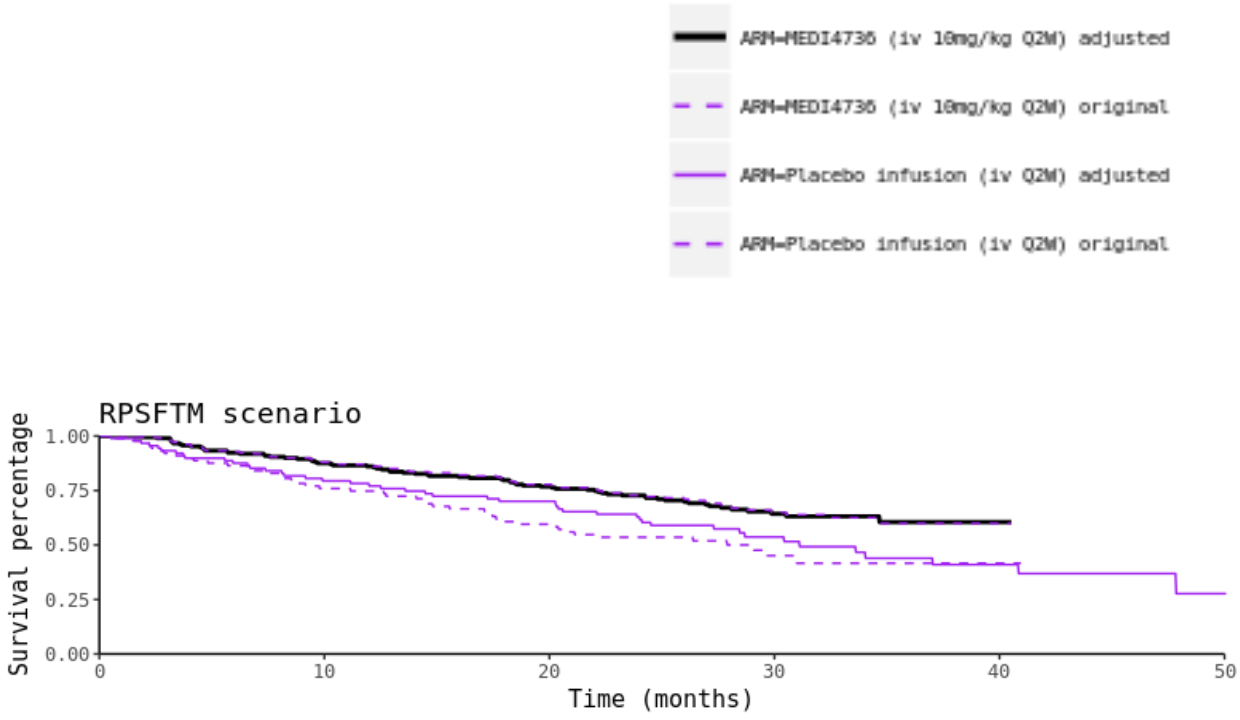
Given the intended patient population for durvalumab (i.e. patients with PD-L1 expression on ≥1% of TCs), it is likely that those patients who are well enough **will** go on to receive subsequent immunotherapy upon disease progression following CRT and active follow-up. To understand the relative benefit of treating patients with an immunotherapy earlier in the treatment pathway (i.e. with durvalumab immediately after CRT, in the curative-intent locally-advanced Stage III setting), as opposed to waiting and treating patients with immunotherapy upon disease progression (e.g. pembrolizumab or nivolumab in the palliative-intent advanced metastatic setting), the following scenario analysis was conducted: all placebo patients who received a subsequent anticancer treatment (~54.9%; Table 10) were assumed to have received

an immunotherapy at the initiation of their first subsequent treatment; in contrast, no subsequent immunotherapy was received by any of the durvalumab patients[q].

Rank Preserving Structural Failure Time (RPSFT) models were used to evaluate OS in durvalumab and placebo arms in this scenario (full description of rationale and methodology is provided in Appendix S.

Durvalumab treatment still reduced the overall risk of death by 34% versus placebo (HR 0.66; 95% CI 0.44, 1.00). The adjusted median OS estimates are 31.1 (95% CI 24.1, 47.8) and NR (95% CI NR, NR) in the placebo and durvalumab arms, respectively. Durvalumab and placebo survival curves separate early and remain consistently in favour of durvalumab, as shown in Figure 17.

Figure 17: OS in RPSFTM scenario where all patients in the placebo arm receive an immunotherapy at the initiation of their first subsequent treatment AND no patients in the durvalumab arm receive subsequent immunotherapy



Key: iv, intravenous; kg, kilogram; MEDI4736, durvalumab; mg, milligram; OS, overall survival; Q2W, every 2 weeks; RPSFTM, rank preserving structural failure time model.

[q] Note: A scenario where no subsequent immunotherapy was received by any patient from either treatment arm was also explored (described later).

There were only six patients in the placebo group with >35 months of follow-up. This explains why the observed KM-curve is horizontal from 30 months onwards, while the corresponding adjusted KM-curve is still decreasing (having increased the survival for patients with subsequent treatment). Overall, this analysis supports a clear benefit of treating patients with immunotherapy immediately after CRT in a curative-intent setting, rather than later in the treatment pathway upon disease progression to advanced metastatic NSCLC. It is important to reiterate that treatment switching from placebo → durvalumab (or vice versa) was not permitted in the PACIFIC study. The effect of subsequent immunotherapy in this scenario represents the use of pembrolizumab and nivolumab in the metastatic NSCLC setting.

RPSFT models were also used to analyse the impact of subsequent therapies on OS estimates for durvalumab versus placebo. When effect of subsequent immunotherapy is removed from both arms, the HR improves slightly (in favour of durvalumab) to 0.51 (versus 0.54 in the observed / unadjusted dataset). The adjusted median OS estimate is slightly lower in the placebo arm at 27.9 months (95% CI 17.6, NR); median OS was not reached in the durvalumab arm (95% CI NR, NR) (Appendix S).

Response to durvalumab (all BICR assessments per RECIST 1.1); PD-L1 ≥1% group (22 March 2018 DCO)

One hundred and ninety-seven (92.9%) of 212 patients in the durvalumab arm and 85 (93.4%) of 91 patients in the placebo arm of the PD-L1 ≥1% group had measurable disease at baseline (according to BICR, per RECIST 1.1). ORR was analysed in this subgroup of patients.

- **Treatment with durvalumab resulted in a significant and clinically meaningful improvement in ORR compared to** placebo. At the time of the 22 March 2018 DCO, 32.5% of patients treated with durvalumab and 16.5% of patients treated with placebo achieved an objective response (Table 15). Two patients (1.0%) in the durvalumab group and no patients in the placebo group achieved a CR, while 62 patients (31.5%) and 14 patients (16.5%) in durvalumab and placebo groups, respectively, had a PR (Table 15). It is worth noting that responses in the placebo group may reflect the residual impact of prior-CRT.

Table 15: Response to treatment (BICR assessment per RECIST 1.1); patients with measurable disease at baseline (PACIFIC PD-L1 ≥1% group, 22 March 2018 DCO)

	Durvalumab (N=197)[a]	Placebo (N=85)[a]
Objective response		
Patients with objective response, n (%)[a]	64 (32.5)	14 (16.5)
95% CI (%) for objective response rate[b]	26.0, 39.5	9.3, 26.1
Odds ratio[c] (95% CI); two-sided *P*-value*	2.46 (1.32, 4.85), *P*<0.0042	
Rate ratio[c] (95% CI); two-sided *P*-value*	2.00 (1.23, 3.53), *P*<0.0037	
Rate difference[c], % (95% CI); two-sided *P*-value)*	16.25 (5.26, 26.24); *P*<0.0045	
Median duration of response[d, e], months (95% CI)	NR (23.6, NR)	24.5 (12.9, NR)
Percentage remaining in response at[e]		
6 months	86.6	100.0
12 months	80.8	91.7
18 months	73.6	82.5
Response, n (%)	**64 (32.5)**	**14 (16.5)**
Complete response[f]	2 (1.0)	0
Partial response[f]	62 (31.5)	14 (16.5)
Non-response	**133 (67.5)**	**71 (83.5)**
Stable disease (≥8 weeks)	104 (52.8)	47 (55.3)
Progressive disease	25 (12.7)	23 (27.1)
RECIST 1.1 progression	23 (11.7)	21 (24.7)
Death	2 (1.0)	2 (2.4)
Not evaluable	4 (2.0)	1 (1.2)
Stable disease <8 weeks	0	0
Incomplete post-baseline assessments	4 (2.0)	1 (1.2)

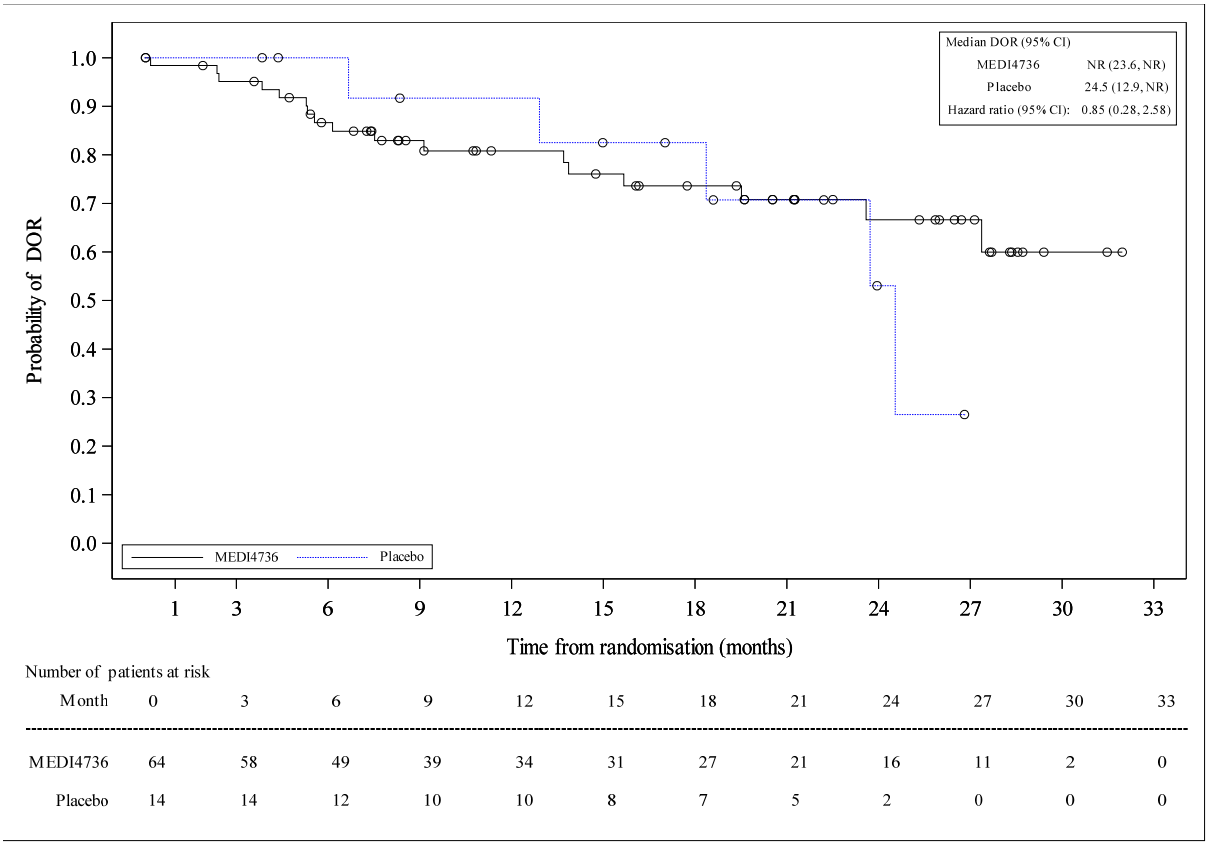
Key: BICR, blinded independent central review; CI, confidence interval; CR, complete response; CSR, clinical study report; DCO, data cut-off; NR, not reached; ORR, objective response rate; PD-L1, programmed cell death ligand 1; PR, partial response; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1.

Notes: [a], The analysis was performed with data from patients with measurable disease at baseline as determined by a blinded independent central reviewer; [b], Responses include unconfirmed responses, using RECIST version 1.1. 95% confidence intervals are calculated using the Clopper Pearson method. [c], The Odds ratio, Rate ratio, and Rate difference analyses were performed using logistic regression, log-binomial, and binomial models (respectively) with treatment, age at randomisation (<65 versus ≥65), sex (male versus female), and smoking history (smoker versus non-smoker) as factors. P-values are two-sided. Likelihood ratio confidence limits and test are based on profile likelihood. An odds ratio and rate ratio > 1 favours durvalumab; a rate difference > 0 favours durvalumab.[d], Duration of response is the time from the first documentation of CR / PR until the date of progression, death, or the last non-missing RECIST assessment for patients that do not progress or for patients who progress or die after two or more missed visits.[e], calculated using the Kaplan–Meier technique. [f], Response does not require confirmation. *, Note that this methodology is not consistent with what was used in ITT (Fisher's exact).

Source: PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO CSR[92]

- **Treatment with durvalumab resulted in a longer DoR compared to placebo.** Median DoR was not reached at the time of the 22 March 2018 DCO (Figure 18). KM estimates of DoR showed that 80.8% and 73.6% of responses to durvalumab were on-going at both 12 and 18 months. These data indicate that not only do more patients respond to durvalumab, but that these responses are sustained for a longer period. The KM-curve for DoR in the placebo arm was based on just 14 responses and should be interpreted with caution; nonetheless, clear separation in favour of durvalumab is evident at ~24 months (Figure 18).

Figure 18: KM plot of DoR (BICR assessment per RECIST 1.1); PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)



Key: BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; DoR, duration of response; KM, Kaplan–Meier; PD-L1, programmed cell death ligand 1; MEDI4736, durvalumab; NR, not reached; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Note: Each circle indicates a censored observation.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

TTDM (BICR assessment per RECIST 1.1); PD-L1 ≥1% TC subgroup (22 March 2018 DCO)

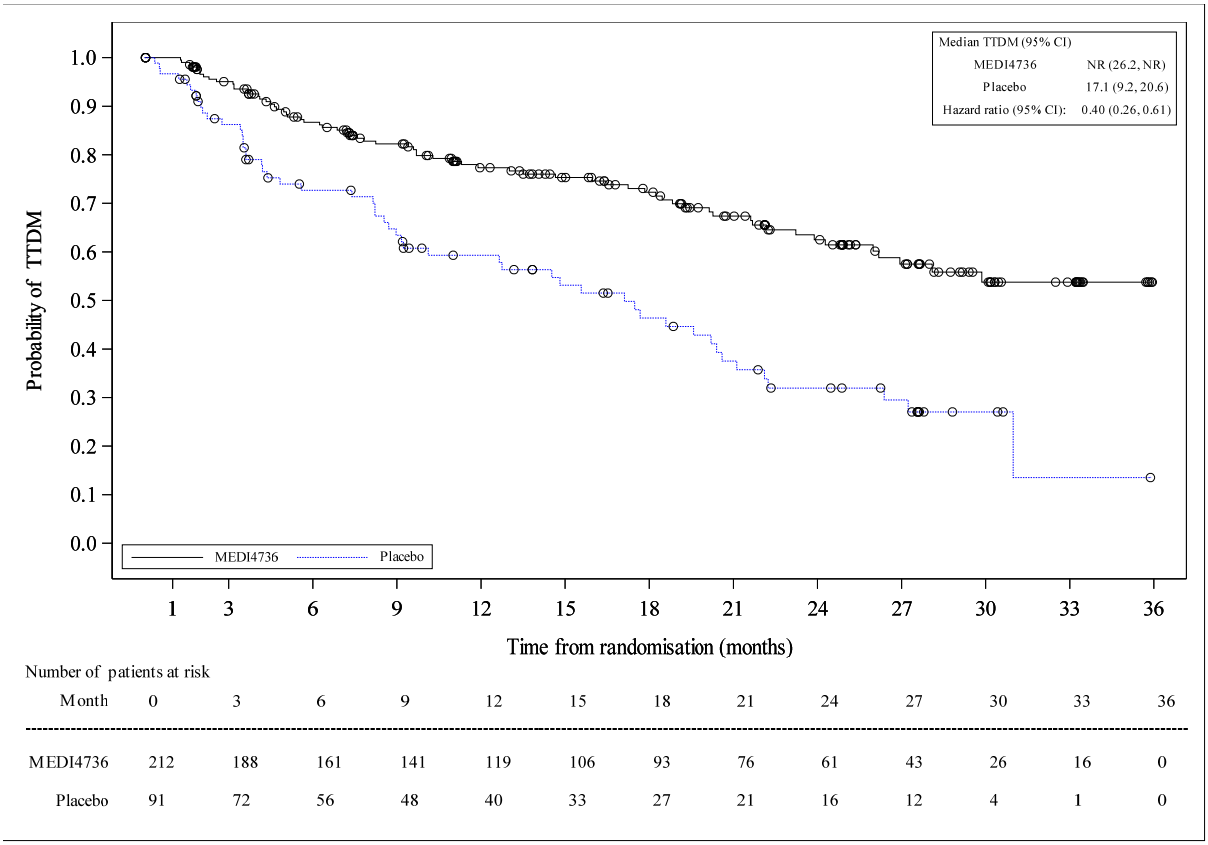
Treatment with durvalumab led to fewer events and significantly-prolonged TTDM compared to placebo in both the ITT population (Table 16; see CSR Addendum for details) and the PD-L1 ≥1% group (HR, 0.40; 95% CI 0.26, 0.61; *P*<0.0001).[74, 75] Median TTDM was not reached in the durvalumab group (95% CI: 26.2, NR) versus 17.1 months in the placebo group (95% CI: 9.2, 20.6; Table 16). Durvalumab treatment produced a sustained benefit, evident from the early and consistent separation of KM-curves in favour of durvalumab (shown in Figure 19).

Table 16: Summary of TTDM analyses (BICR assessment per RECIST 1.1); PD-L1 ≥1% group (22 March 2018 DCO)

	Durvalumab (N=212)	Placebo (N=91)
Total events, n (%)[a]	**66 (31.1)**	**52 (57.1)**
Distant metastasis[b]	27 (12.7)	26 (28.6)
Death in the absence of distant metastasis	39 (18.4)	26 (28.6)
Censored patients, n (%)	**146 (68.9)**	**39 (42.9)**
Censored distant metastasis[c]	1 (0.5)	0
Censored death[d]	13 (6.1)	3 (3.3)
Distant metastasis free at time of analysis	121 (57.1)	33 (36.3)
Lost to follow-up	0	0
Withdrawn consent	11 (5.2)	3 (3.3)
Discontinued study	0	0
Median TTDM, months[e] (95% CI)	**NR (26.2, NR)**	**17.1 (9.2, 20.6)**
Hazard ratio[f] (95% CI); two-sided *P*-value	**0.40 (0.26, 0.61); *P*<0.0001**	

Key: BICR, Blinded Independent Central Review; CI, Confidence interval; DCO, data cut-off; NR, not reached; PD-L1, programmed cell death ligand 1; RECIST 1.1 Response Evaluation Criteria In Solid Tumors version 1.1; TTDM, time to death or distant metastasis.
Notes: [a], Patients who had not died or developed distant metastasis, or who died or developed distant metastasis after ≥2 missed visits, were censored at the latest non-missing RECIST 1.1 assessment, or on Day 1 if there were no non-missing visits or baseline data, unless they died within 2 visits of baseline;
[b], Distant metastasis was defined as any new lesion outside of the radiation field (per RECIST 1.1), or proven by biopsy;
[c], Distant metastasis event either occurred after ≥2 missed visits, or the patient had no non-missing visits or a baseline assessment;
[d], Death that occurred after ≥2 missed visits in the absence of distant metastasis;
[e], Calculated using the Kaplan–Meier technique;
[f], Analysis 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.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO[92]

Figure 19: KM plot of TTDM (BICR assessment per RECIST 1.1); PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)



Key: BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; ITT, intention to treat; KM, Kaplan–Meier; MEDI4736, durvalumab; NR, not reached; PD-L1, programmed-death ligand-1; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1; TTDM, time to death or distant metastasis.
Notes: Each circle indicates a censored observation. The ITT population included all patients who underwent randomisation.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO[92]

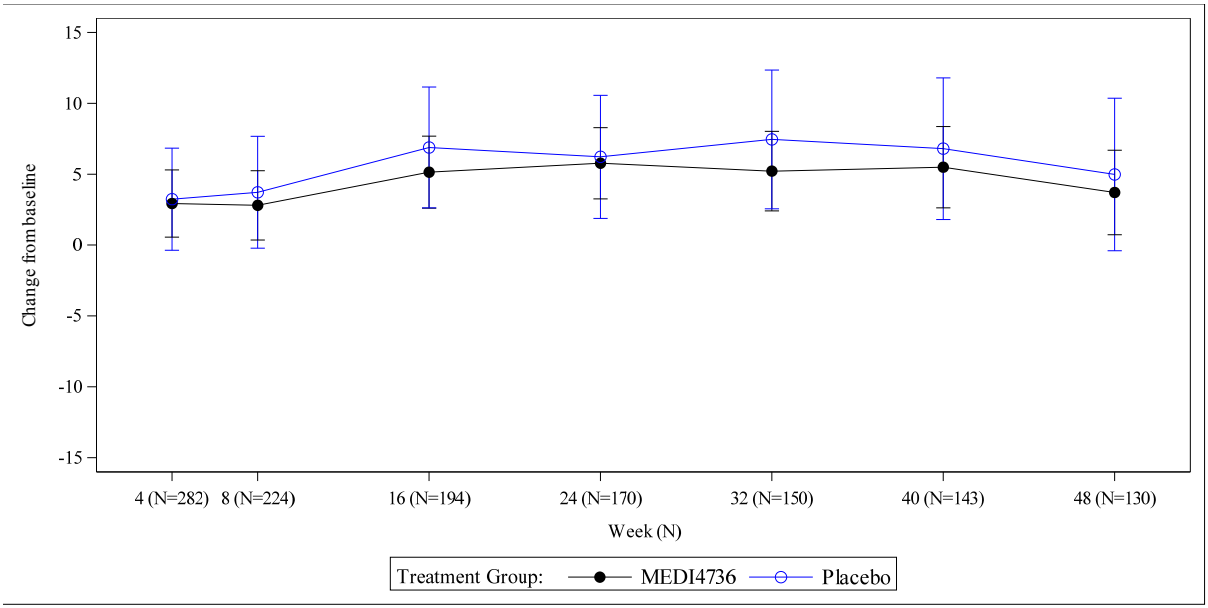
Distant metastases are associated increased disease burden and deterioration in HRQL and wellbeing of patients (as described in Section B.1.3, page 20). **Durvalumab treatment therefore provides additional meaningful patient benefit through controlling systemic disease spread, and reducing the frequency and time to development of distant metastases.**

Patient-reported health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-LC13

At the time of the 22 March 2018 DCO, there were no clinically meaningful differences in the global health status of patients in durvalumab and placebo arms of the PD-L1 ≥1% group (as analysed by MMRM, Figure 20).

Figure 20: Change from baseline in global health status, MMRM; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

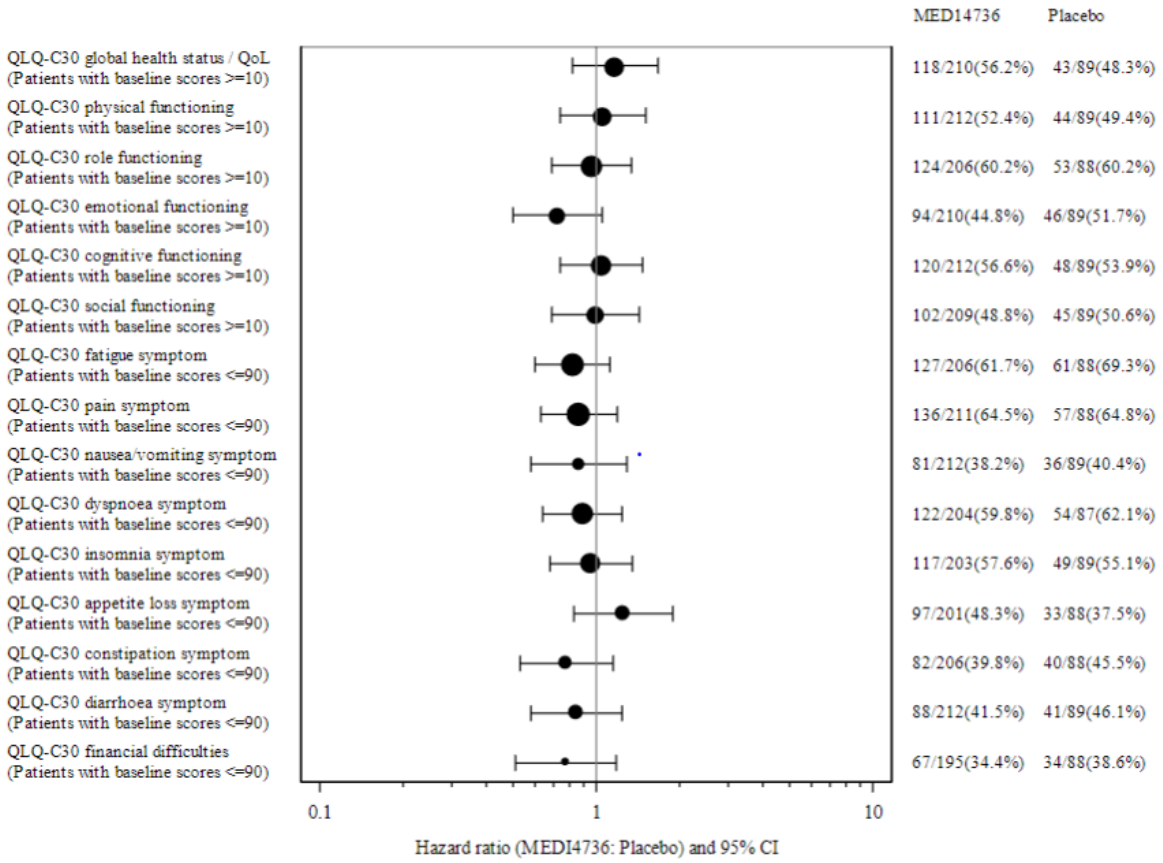


Key: DCO, data cut-off; LS, least squares; MMRM, Mixed Model Repeated Measures; MEDI4736, durvalumab; PD-L1, programmed cell death ligand 1; PRO, patient-reported outcome;
Notes: A negative change from baseline denotes an improvement in PRO symptoms, whilst a positive change from baseline denotes worsening PRO symptoms. N is the number of patients which contribute to the change from baseline measurement at each visit, or any visit for the overall change from baseline estimates. The LS mean estimates were determined using an MMRM model, which include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, age at randomisation (<65 versus ≥65 years of age), sex (male versus female), smoking history (smoker versus non-smoker), as well as the continuous fixed covariate of baseline score and the baseline score-by-visit interaction.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

Furthermore, no clinically meaningful differences in time to deterioration were reported between durvalumab and placebo arms of the PD-L1 ≥1% group across the different subscales evaluated (Figure 21 and Figure 22), although time to deterioration of '*other pain*' was notably longer with durvalumab than placebo (Figure 22). The results in the PD-L1 ≥1% group were consistent with those from the ITT population (13 February

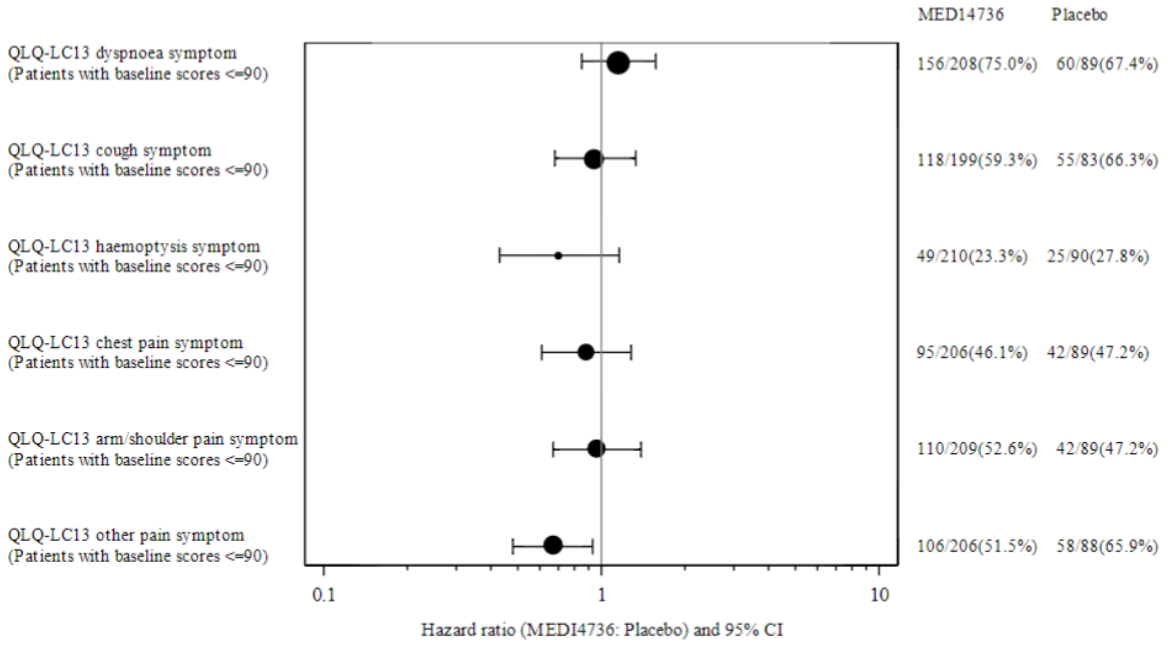
2017 and 22 March 2018 DCOs; see Section 7.1.2.5, PACIFIC Interim CSR,[75] and Figure 11.2.2.2.OS and Figure 11.2.2.4.OS, CSR Addendum,[77] respectively).

Figure 21: Forest plot of time to deterioration of EORTC QLQ-C30 subscales and items; PD-L1 ≥1% group (22 March 2018 DCO)



Key: CI, confidence interval; DCO, data cut-off; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; MEDI4736, durvalumab; PD-L1, programmed cell death ligand 1; QoL, quality of life.
Notes: A hazard ratio <1 implies a lower risk of deterioration on MEDI4736 study treatment. Size of circle is proportional to the number of events.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

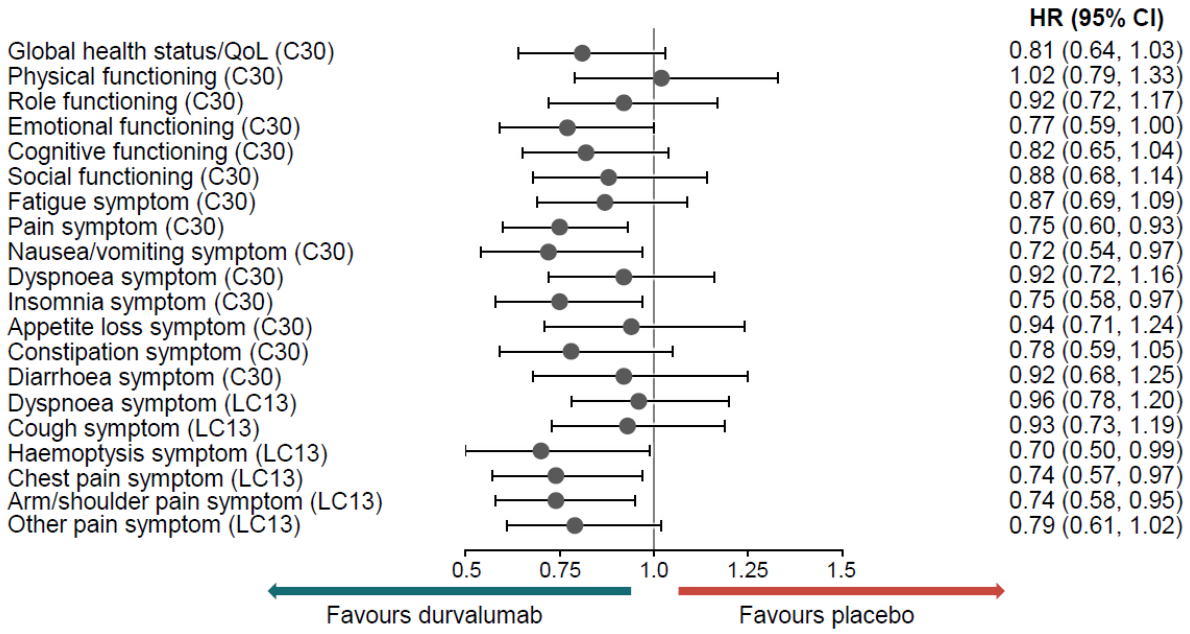
Figure 22: Forest plot of time to deterioration of EORTC QLQ-LC13 subscales and items; PD-L1 ≥1% group (22 March 2018 DCO)



Key: CI, confidence interval; DCO, data cut-off; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer quality of life questionnaire and lung cancer module; MEDI4736, durvalumab; PD-L1, programmed cell death ligand 1.
Notes: A hazard ratio <1 implies a lower risk of deterioration on MEDI4736 study treatment. Size of circle is proportional to the number of events.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

Transient changes (e.g. temporary symptoms due to treatment side effects or comorbidities) can introduce bias and confound analysis of symptom change associated with disease progression. Therefore, exploratory *post-hoc* analyses were conducted in the ITT population (13 February 2017 DCO) in which clinically relevant deterioration had to be confirmed at the next consecutive time point after the first observation, to minimise bias and better understand the impact of durvalumab treatment on disease symptoms. These analyses showed that time to deterioration was notably longer with durvalumab than placebo for emotional functioning, overall pain, nausea / vomiting, insomnia, haemoptysis, chest pain, and arm / shoulder pain (Figure 23).

Figure 23: Forest plot of post-hoc analysis of time to deterioration of EORTC QLQ-C30 and QLQ-LC13 subscales and items; ITT population (13 February 2017 DCO)



Key: CI, confidence interval; DCO, data cut-off; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer quality of life questionnaire and lung cancer module; HR, hazard ratio; ITT, intention to treat; QoL, quality of life.
Notes: Other pain refers to anything other than chest pain and arm/shoulder pain.
Source: Hui et al., 2018.[99]

Collectively, these analyses confirm that durvalumab treatment had no detrimental impact on patient symptoms, functioning, and HRQL compared with placebo, despite a longer treatment duration and observation period. Furthermore, data from the *post-hoc* analyses conducted in the ITT population (13 February 2017 DCO) indicate a positive impact of durvalumab treatment on distressing and burdensome symptoms such as pain, nausea / vomiting, insomnia, and haemoptysis. Alongside the positive efficacy and safety data from the PACIFIC study, these findings further support the clinical and patient benefit of durvalumab in the locally-advanced, unresectable, Stage III NSCLC setting.

EQ-5D-5L

The EQ-5D-5L analyses were used in the cost-effectiveness model and are described in further detail in Section B.3.4 (and Appendix P). Briefly, these analyses confirmed

the impact of disease progression on patients' HRQL, evidenced by post-progression utility scores of 0.776, versus 0.810 in the pre-progression state (Appendix P).

B.2.7. Subgroup analysis

A summary of PFS and OS data in pre-specified subgroups, based on demographics, regions, prior CRT regimens / response to treatment, and disease characteristics, is provided in Appendix E. A survival benefit, in favour of durvalumab, was observed across stratification factors and all pre-specified subgroups, including by PD-L1 <25%, ≥25%, and "unknown" TC expression (Appendix E; Figures 7–8). As described previously, the 25% TC cut-off was selected based on data from Study1108 that became available during the course of the PACIFIC study[r].[82-84] Further exploratory *post-hoc* analyses were conducted by additional PD-L1 expression cut-offs at the request of the CHMP (Appendix E; Figure 9). A PFS benefit with durvalumab treatment was observed in PD-L1 <1%, PD-L1 ≥1%, PD-L1 1–24% groups. Taken together, these data argue that all patients derive some PFS benefit from durvalumab, regardless of pre-CRT PD-L1 expression on TCs. The fact that the PD-L1 "unknown" population obtained a PFS benefit is important, as PD-L1 testing may not be feasible in all patients with Stage III NSCLC.

OS benefit, in favour of durvalumab, was also observed in PD-L1 ≥1% and PD-L1 1–24% patients, in addition to the pre-specified PD-L1 <25%, PD-L1 ≥25%, and PD-L1 status "unknown" subgroups (Appendix E; Figure 9). The observed HR for OS in the PD-L1 <1% TC subgroup was more than 1.0, with a wide 95% CI that included 1. Although inconclusive and based on a small number of patients (148 of 713), these

[r] The first 20 patients in Study 1108 were enrolled regardless of PD-L1 expression; however, preliminary data suggested that PD-L1 may be expressed more commonly on immune cells than on TCs. Therefore, to ensure assessment of the contribution of PD-L1–expressing TCs to response with durvalumab, subsequently enrolled patients were required to have PD-L1 expression of at least 5% on TCs. An interim analysis, however, showed that ORRs in patients with less than 5% PD-L1 expression were similar to ORRs in all patients. Therefore, a protocol amendment removed this requirement. For purposes of biomarker analyses, a 25% cut-off for defining TC-dependent expression status was chosen, because this cut-off seemed to enrich for response, based on review of PD-L1 expression in the first 20 enrolled patients who were followed for a minimum of 12 weeks.

data formed the basis of the CHMP recommendation to restrict marketing authorisation to those patients who express PD-L1 on ≥1% of TCs.[3]

B.2.8. Meta-analysis

The PACIFIC clinical trial is the only study of durvalumab versus placebo in this treatment setting; therefore, a meta-analysis of available evidence was not applicable to this appraisal.

B.2.9. Indirect and mixed treatment comparisons

As stated previously (Section B.2.1 and Appendix D), the PACIFIC study directly compared durvalumab versus placebo (active follow-up), the intervention and comparator of interest for this appraisal. Therefore, indirect and mixed treatment comparisons were not deemed necessary or appropriate to support the clinical effectiveness of durvalumab versus active follow-up in this treatment setting.

Uncertainties in the indirect and mixed treatment comparisons

Not applicable.

B.2.10. Adverse reactions

The safety analyses were conducted based on the safety analysis set, which included 475 patients in the durvalumab group and 234 patients in the placebo group. Two patients randomised to the placebo group inadvertently received a single infusion of durvalumab therapy (one patient at Week 8 and another at Week 28) and were therefore included in the safety analysis set for durvalumab. This deviation was discovered post-unblinding; therefore, the integrity of the blind remained intact.

Patients in the durvalumab group received 10 mg/kg Q2W for up to 12 months, which is consistent with the CHMP opinion for durvalumab monotherapy in locally-advanced, unresectable NSCLC.[1, 3] Safety data were updated at the time of the primary OS analysis (22 March 2018 data cut-off). The results of these analyses were consistent with those conducted at the time of the primary PFS analysis (13 February 2017 data cut-off), and no new safety signals were identified. In light of the positive CHMP opinion recommending 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 and whose disease has not progressed following platinum-based CRT, safety data were re-analysed in the PD-L1 ≥1% group to confirm a favourable risk-benefit profile in these patients.

These analyses are briefly described below; full details of safety summaries from both DCOs are available in the 13 February 2017 CSR[75] and the 22 March 2018 addendum.[77] Key data from the full safety analysis set are shown alongside PD-L1 ≥1% group data[92] for information, and to demonstrate the consistency of safety profiles in the PD-L1 ≥1% group of patients.

One patient in the PD-L1 ≥1% group accidentally received a single dose of durvalumab, despite being randomised to placebo. This patient and was therefore included in the safety analysis set for durvalumab.

Treatment exposure in the PACIFIC safety analysis set and PD-L1 ≥1% group (22 March 2018 DCO)

At the time of the primary OS analysis, 109 (51.4%) patients in the durvalumab group and 34 (37.4%) patients in the placebo group had completed the protocol-defined 12 months of treatment. 103 (48.6%) and 57 (62.6%) patients in durvalumab and placebo groups, respectively, had discontinued treatment prior to 12 months.

The median time to treatment discontinuation (TTD; = treatment end date – treatment start date + 1) was [redacted] (95% CI: 8.4, 11.5) in the durvalumab group and [redacted] (95% CI: 4.2, 10.2) in the placebo group. KM-curves for durvalumab and placebo groups start to separate at ~1.5 months and remain separated for the duration of treatment, supporting the longer TTD in the durvalumab group (

Figure 24).

Figure 24: Time to treatment discontinuation; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Key: CSR, clinical study report; DCO, data cut-off; iv, intravenous; ITT, intent to treat; kg, kilogram; mg, milligram; MEDI4736, durvalumab; PD-L1, programmed cell death ligand 1; Q2W, every 2 weeks.

Source: PACIFIC 22 March 2018 DCO CSR.[77]

A summary of treatment exposure at the 22 March 2018 DCO is shown in Table 17. Data for the full safety analysis set are also shown for information, and support the PD-L1 ≥1% group being broadly representative of the full safety population.

Table 17: Summary of treatment exposure; PACIFIC safety analysis set and PD-L1 ≥1% group (22 March 2018 DCO)

	Safety analysis set		PD-L1 ≥1% group	
	Durvalumab (n=475)	Placebo (n=234)	Durvalumab (N=213)	Placebo (N=90)
Total treatment duration, weeks[a]				
Median (range)	48.0 (1–55)	31.7 (1–54)	50.3 (2–55)	33 (2–53)
Mean (SD)	35.5 (18.9)	31.2 (18.5)	35.8 (19.07)	31.4 (19.1)
Actual treatment duration, weeks[b]				
Median (range)	40.1 (1–54)	28.0 (1–53)	41.7 (2–53)	29.0 (2–52)
Mean (SD)	33.3 (18.3)	29.8 (17.9)	33.3 (18.4)	29.8 (18.2)
Number of infusions				
Median (range)	20.0 (1–27)	14.0 (1–26)	21.0 (1–26)	14.5 (1–26)
Mean (SD)	16.7 (9.1)	14.9 (8.9)	16.7 (9.22)	14.9 (9.1)

	Safety analysis set		PD-L1 ≥1% group	
	Durvalumab (n=475)	Placebo (n=234)	Durvalumab (N=213)	Placebo (N=90)

Key: DCO, data cut-off; PD-L1, programmed cell death ligand 1; SD, standard deviation.
Notes: [a], Total treatment duration is defined as (last dose date + 13 days or death date or data cut-off, whichever occurs earlier - first dose date + 1) / 7; [b], Actual treatment duration = total treatment duration, excluding total duration of dose delays;
Source: PACIFIC 22 March 2018 DCO CSR[77] and PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO[92]

Dose interruptions and delays; PACIFIC PD-L1 ≥1% group (safety analysis set; 22 March 2018 data cut-off)

Dose delays and interruptions during the infusion were permitted, as required, in the study protocol. As stated previously, randomisation could be delayed by up to 42 days from the end of the CRT for patients recovering from toxicities associated with prior treatment. For patients who had a toxicity event whilst receiving study treatment, dosing could be temporarily delayed until resolution of the event, and then resumed. Dose reductions were not permitted.

At the time of the primary OS analysis (22 March 2018 DCO), dose delays were reported in 116 (54.5%) patients in the durvalumab group and 30 (33.3%) patients in the placebo group. The majority of patients (62 of 116 in durvalumab group, and 17 of 30 in placebo group) had just one delay. The most common reason for dose delays was AEs (89 of 116 in durvalumab group, and 23 of 30 in placebo group). AEs leading to dose interruptions or dose delays are described further below.

13 (6.1%) patients and four (4.4%) patients in durvalumab and placebo groups, respectively, required infusion interruptions. Most patients (10 of 13 for durvalumab, and 3 of 4 for placebo) required just one interruption. The most common reason for infusion interruptions in the durvalumab group was technical issues (8 of 13), followed by AEs (2 of 13).

Adverse event summaries in the PACIFIC safety analysis set and PD-L1 ≥1% group (22 March 2018 DCO)

Safety summaries were based on those AEs that started after the first dose of study treatment (or for pre-existing AEs, those that worsened in severity after the first dose),

up to 90 days after the last dose or the start of any subsequent systemic anticancer therapy, whichever occurred first.

Overall, durvalumab was well-tolerated and had a manageable safety profile relative to placebo. At the time of the latest DCO (22 March 2018), most patients in the safety analysis set had experienced at least one AE (96.8% and 94.9% in durvalumab and placebo groups, respectively; full safety analysis set). The incidence and severity of AEs were comparable in the two groups, despite the longer duration of durvalumab treatment. The spectrum of AEs was as expected, given the mechanism of action of durvalumab and patients having received prior CRT. Most events were resolved during the study and generally did not affect the ability of patients to remain on durvalumab. Safety data from this analysis were consistent with the profile previously observed and reported for the 13 February 2017 DCO, with no clinically meaningful differences.[74, 75, 77] Safety profiles in the PD-L1 ≥1% group were broadly consistent with the full safety analysis set (shown in Table 18).

Table 18: Summary of key safety events; PACIFIC safety analysis set and PD-L1 ≥1% group (22 March 2018 DCO)

AE category, n (%)[a, b]	Safety analysis set		PD-L1 ≥1% group	
	Durvalumab (n=475)	Placebo (n=234)	Durvalumab (n=213)	Placebo (N=90)
Any AE	**460 (96.8)**	**222 (94.9)**	**205 (96.2)**	**83 (92.2)**
Any AE causally related to treatment[c]	322 (67.8)	125 (53.4)	144 (67.6)	48 (53.3)
Any AE of CTCAE Grade 3 or 4	**155 (32.6)**	**66 (28.2)**	**72 (33.8)**	**21 (23.3)**
Any AE of CTCAE Grade 3 or 4, causally related to treatment[c]	59 (12.4)	11 (4.7)	26 (12.2)	4 (4.4)
Any SAE (including events with outcome of death)	**138 (29.1)**	**54 (23.1)**	**64 (30.0)**	**18 (20.0)**
Any SAE (including events with outcome of death), causally related to treatment[c]	41 (8.6)	9 (3.8)	16 (7.5)	1 (1.1)
Any AE leading to discontinuation of study treatment	**73 (15.4)**	**23 (9.8)**	**36 (16.9)**	**5 (5.6)**
Any AE leading to discontinuation of study treatment, causally related to treatment[c]	47 (9.9)	8 (3.4)	24 (11.3)	2 (2.2)

AE category, n (%)[a, b]	Safety analysis set		PD-L1 ≥1% group	
	Durvalumab (n=475)	Placebo (n=234)	Durvalumab (n=213)	Placebo (N=90)
Any AE with outcome of death	**21 (4.4)**	**15 (6.4)**	**8 (3.8)**	**4 (4.4)**
Any AE with outcome of death, causally related to treatment[b]	7 (1.5)	4 (1.7)	2 (0.9)	0
Any AE leading to dose delay[d]	203 (42.2)	72 (30.8)	96 (45.1)	27 (30.0)
Any other significant AEs[e]	0	0	0	0
Immune mediated AEs[c]	166 (34.9)	39 (16.7)	73 (34.3)	16 (17.8)
Infusion reaction AEs[c]	15 (3.2)	7 (3.0)	3 (1.4)	3 (3.3)

Key: AE, adverse event; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; PD-L1, programmed cell death ligand 1; SAE, serious adverse event.
Notes: The PD-L1 subgroup has been defined using the re-scored PD-L1 data.
[a], Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories; [b], Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first); [c], As assessed by the Investigator. Missing responses are counted as related; [d], AEs on the AE case report form with Action taken = Drug interrupted, excluding those AEs on the dosing CRF forms only leading to infusion interruptions; [e], Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as other significant AEs.
Source: PACIFIC 22 March 2018 DCO CSR[77] and PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO[92]

In the following paragraphs, an overview of common AEs, CTCAE Grade 3 or 4 AEs, SAEs, and AEs leading to discontinuation of treatment or death are provided for the **PD-L1 ≥1%** group, in line with the anticipated Marketing Authorisation for durvalumab in Europe. The incidence of pneumonitis and radiation pneumonitis were noticeably increased in both treatment groups across multiple AE categories (see Table 19, Table 20, Table 21, and Table 24). However, this was expected since all patients in the PACIFIC study had received definitive radiotherapy prior to randomisation, with the last radiation dose being within 42 days of randomisation. Furthermore, most adverse events of special interest (AESIs) of pneumonitis or radiation pneumonitis were of low CTCAE grade. The incidence of clinically important Grade 3 or 4 pneumonitis events was well balanced between durvalumab and placebo groups (Table 20).

No other studies reported additional AEs.

Common adverse events; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Two hundred and five (96.2%) patients in the durvalumab group and 83 (92.2%) patients in the placebo group had experienced ≥1 AE by the time of the 22 March 2018 DCO. 144 (67.6%) and 48 (53.3%) patients in durvalumab and placebo groups, respectively, experienced AEs that were deemed by the Investigator as being causally related to the study treatment. The most commonly-occurring AEs (>5% in any treatment group) are summarised by preferred term in Table 19. This spectrum of common AEs was as expected given the mechanism of action of durvalumab and patients receiving prior CRT. These data were also consistent with common AE-profiles for the full safety analysis set (13 February 2017 and 22 March 2018 DCOs; available in the CSR [pages 116−119] and CSR Addendum [pages 41–44]).

Table 19: Most common AEs (>5% in any treatment group) by preferred term; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Preferred term[a]	Number of patients, n (%)[b, c]	
	Durvalumab (N=213)	Placebo (N=90)
Patients with any AE	**205 (96.2)**	**83 (92.2)**
Cough	71 (33.3)	24 (26.7)
Fatigue	60 (28.2)	19 (21.1)
Radiation pneumonitis[d]	47 (22.1)	10 (11.1)
Dyspnoea	46 (21.6)	23 (25.6)
Diarrhoea	43 (20.2)	14 (15.6)
Pruritus	36 (16.9)	4 (4.4)
Pneumonia	30 (14.1)	7 (7.8)
Pyrexia	29 (13.6)	6 (6.7)
Decreased appetite	28 (13.1)	9 (10.0)
Upper respiratory tract infection	28 (13.1)	8 (8.9)
Rash	27 (12.7)	7 (7.8)
Constipation	27 (12.7)	5 (5.6)
Arthralgia	27 (12.7)	14 (15.6)
Pneumonitis[d]	26 (12.2)	6 (6.7)
Hypothyroidism	26 (12.2)	1 (1.1)
Nausea	24 (11.3)	14 (15.6)
Headache	24 (11.3)	10 (11.1)
Asthenia	23 (10.8)	8 (8.9)
Back pain	22 (10.3)	10 (11.1)

Preferred term[a]	Number of patients, n (%)[b, c]	
	Durvalumab (N=213)	Placebo (N=90)
Nasopharyngitis	22 (10.3)	5 (5.6)
Productive cough	20 (9.4)	6 (6.7)
Vomiting	19 (8.9)	10 (11.1)
Hyperthyroidism	18 (8.5)	1 (1.1)
Anaemia	18 (8.5)	8 (8.9)
Dry skin	18 (8.5)	5 (5.6)
Oedema peripheral	17 (8.0)	5 (5.6)
Non-cardiac chest pain	16 (7.5)	12 (13.3)
Insomnia	15 (7.0)	4 (4.4)
Pain in extremity	15 (7.0)	4 (4.4)
Myalgia	14 (6.6)	5 (5.6)
Bronchitis	14 (6.6)	8 (8.9)
Musculoskeletal pain	14 (6.6)	5 (5.6)
Hypokalaemia	14 (6.6)	6 (6.7)
Dizziness	13 (6.1)	12 (13.3)
Musculoskeletal chest pain	13 (6.1)	7 (7.8)
Hypertension	11 (5.2)	4 (4.4)
Paraesthesia	11 (5.2)	5 (5.6)

Key: AE, adverse event; DCO, data cut-off; MedDRA, Medical Dictionary for Regulatory Activities; PD-L1, programmed cell death ligand 1.
Notes: The PD-L1 subgroup has been defined using the re-scored PD-L1 data.
a, MedDRA version 19.1.
b, Includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication.
c, Patients with multiple AEs are counted once for each preferred term. Included are events that were reported in at least 5% of the patients in either group; patients with multiple events only counted once in each row; includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
d, Pneumonitis or radiation pneumonitis was assessed by investigators with subsequent review and adjudication by the study sponsor. In addition, pneumonitis is a grouped term that includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

CTCAE Grade 3 or higher adverse events; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Seventy-two (33.8%) patients in the durvalumab group and 21 (23.3%) patients in the placebo group had experienced an AE of CTCAE Grade 3 or 4 at the time of the 22

March 2018 DCO. 26 (12.2%) and 4 (4.4%) patients in durvalumab and placebo groups, respectively, experienced a CTCAE Grade 3 or 4 AE that was causally-related to the study treatment. The incidence of CTCAE Grade 3 or 4 AEs were very similar (or, in some cases, slightly lower) in the durvalumab group relative to placebo, despite greater treatment exposure to durvalumab (183.6 patient-years, versus 66.2 patient-years for placebo). The most commonly occurring CTCAE Grade 3 or 4 AEs (≥2% in any treatment group) are presented in Table 20.

Table 20: Most common CTCAE Grade 3 or higher AEs (≥2% of patients in any treatment group) by preferred term; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Preferred term	Number of patients, n (%)[a]	
	Durvalumab (N=213)	Placebo (N=90)
Pneumonia	10 (4.7)	5 (5.6)
Anaemia	6 (2.8)	3 (3.3)
Pneumonitis	6 (2.8)	1 (1.1)
Radiation pneumonitis	5 (2.3)	2 (2.2)
Hypokalaemia	3 (1.4)	3 (3.3)
Haemoptysis	0 (N/A)	2 (2.2)

Key: AE, adverse event; DCO, data cut-off; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; N/A, not applicable; PD-L1, programmed cell death ligand 1.
Notes: [a], Patients with multiple events only counted once in each row. Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

Serious adverse events; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

As of the 22 March 2018 DCO, 64 (30.0%) patients in the durvalumab group and 18 (20.0%) patients in the placebo group had experienced at least one SAE. 16 (7.5%) SAEs in the durvalumab group and 1 (1.1%) SAEs in the placebo group were deemed by the Investigator as being causally related to the study treatment.

The most frequently reported SAEs regardless of causality (with an incidence of ≥2% in either group) are presented in Table 21, and included pneumonia, pneumonitis, and radiation pneumonitis. Occurrence of these events was expected given patients had

received definitive radiotherapy within 42 days of randomisation, and was balanced across durvalumab and placebo groups (with a ≤2% difference for any of the three most-common SAEs), despite the longer treatment exposure to durvalumab versus placebo (183.6 patient-years for durvalumab, versus 66.2 patient-years for placebo).

Table 21: Most common SAEs (≥2% of patients in any treatment group) by preferred term; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Preferred term	Number of patients, n (%)	
	Durvalumab (N=213)	Placebo (N=90)
Patients with any SAE[a]	**64 (30.0)**	**18 (20.0)**
Pneumonia	12 (5.6)	5 (5.6)
Pneumonitis	6 (2.8)	1 (1.1)
Radiation pneumonitis	9 (4.2)	2 (2.2)

Key: AE, adverse event; DCO, data cut-off; MedDRA, Medical Dictionary for Regulatory Activities; PD-L1, programmed cell death ligand 1; SAE, serious adverse event.
Notes: The PD-L1 subgroup has been defined using the re-scored PD-L1 data.
a, Number (%) of patients with an SAE occurring in ≥2% of patients in any treatment group by preferred term. Patients with multiple SAEs are counted once for each system organ class / preferred term. Includes SAEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA version 19.1.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO[92]

Full details of SAEs, by system organ class and preferred term, for the full safety analysis set and the PD-L1 ≥1% group is available in the CSR Addendums (Table 11.3.4.1.1.OS[77] and Table 11.3.4.1.1.1.A[92]).

Adverse events leading to discontinuation of study treatment (PD-L1 ≥1% group; 22 March 2018 DCO)

For patients with AEs, the decision to discontinue study medication was made at the Investigator's discretion. At the time of the 22 March 2018 DCO, 36 (16.9%) patients in the durvalumab group and 5 (5.6%) patients in the placebo group experienced AEs leading to discontinuation of study treatment. 24 (11.3%) patients in the durvalumab group and 2 (2.2%) patients in the placebo group discontinued due to AEs that were deemed by the Investigator as being causally related to study treatment. The most-frequently reported AE leading to discontinuation of study medication was pneumonitis, reported in 10 patients (4.7%) in the durvalumab group and one patient

(1.1%) in the placebo group. Full details of AEs leading to discontinuation of study treatment, by system organ class and preferred term, for the full safety analysis set and the PD-L1 ≥1% group is available in the CSR Addendums.[77, 92]

Adverse events leading to death; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

As of the 22 March 2018 DCO, 15 (7.1%) patients randomised to durvalumab arm and 10 (11.0%) patients randomised to placebo arm had died during treatment or within 90 days after last dose. 8 (3.8%) and 5 (5.5%) patients' deaths in durvalumab and placebo groups, respectively, were classified by the Investigator as being related to the disease under investigation only. Of the patients receiving durvalumab, four (1.9%) had an AE with the outcome of death (Table 22). Of the patients receiving placebo, one (1.1%) had an AE with the outcome of death.

Table 22: Adverse events with outcome of death, by system organ class and preferred term; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

System organ class Preferred term	Number of patients, n (%)[a]	
	Durvalumab (N=213)	Placebo (N=90)
Patients with any AE with outcome of death	**8 (3.8)**	**4 (4.4)**
Infections and infestations	**1 (0.5)**	**1 (1.1)**
Pneumonia	0	1 (1.1)
Septic shock	1 (0.5)	0
Cardiac disorders	**4 (1.9)**	**0**
Cardiac arrest	2 (0.9)	0
Cardiomyopathy	1 (0.5)	0
Myocardial infarction	1 (0.5)	0
Vascular disorders	**1 (0.5)**	**0**
Aortic dissection	1 (0.5)	0
Respiratory, thoracic and mediastinal disorders	**1 (0.5)**	**1 (1.1)**
Dyspnoea	1 (0.5)	0
Haemoptysis	0	1 (1.1)
Gastrointestinal disorders	**0**	**1 (1.1)**
Intestinal obstruction	0	1 (1.1)
Injury, poisoning, and procedural complications	**1 (0.5)**	**1 (1.1)**
Radiation pneumonitis	1 (0.5)	1 (1.1)

Key: AE, adverse event; CSR, clinical study report; DCO, data cut-off; PD-L1, programmed cell death ligand 1. **Notes:** [a], Number (%) of patients with AE with outcome of death, sorted by international order for system organ class and alphabetically for preferred term. Patients with multiple AEs with outcome of death are counted once for each system organ class / preferred term. Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Source: PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO[92]

AESIs and immune-mediated adverse events (imAEs); PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

AESIs included, but were not limited to, events with a potential inflammatory or immune-mediated mechanism that may require more frequent monitoring and / or interventions, such as corticosteroids, immunosuppressants and / or endocrine therapy. A suspected imAE [(s)imAE] was identified and defined as an AESI that required the use of systemic steroids or other immunosuppressants, and / or (for specific endocrine events) endocrine therapy. A confirmed imAE was defined as a suspected imAE that after medical review was consistent with an immune-mediated mechanism of action, and where there was no clear alternate aetiology.

The AESI categories of interest in the PACIFIC study were identified as: pneumonitis, select hepatic events, diarrhoea / colitis, endocrinopathies (adrenal insufficiency, type 1 diabetes mellitus, hypophysitis, hypothyroidism, hyperthyroidism), select renal events, rash / dermatitis, select pancreatic events, other rare / miscellaneous events of an immune-mediated nature and infusion-related / hypersensitivity / anaphylactic reactions. Preferred terms within each category are shown in Table 11.3.5.1.1. of the CSR. The categories of AESIs and preferred terms within each category of AESI were selected based on ongoing surveillance of safety signals, plus instances where events had the potential to be immune-mediated in nature.

As of the 22 March 2018 data cut-off, 317 (66.7%) patients in the durvalumab group and 115 (49.1%) patients in the placebo group had experienced an AESI (full safety analysis set; Table 11.3.5.1.4.1). Incidence was similar in the PD-L1 ≥1% group, with 146 (68.5%) patients in the durvalumab arm and 39 (43.3%) patients in the placebo arm experiencing an AESI. Majority of AESI in both groups were CTCAE Grade 1 or 2 events (121 of 146 in the durvalumab group, and 37 of 39 in the placebo group). 25 (11.7%) patients in the durvalumab group and 2 (2.2%) patients in the placebo group experienced CTCAE Grade 3 or higher AESIs (no Grade 5 events were reported in either group). Guidelines for management of imAEs are described in Table 1 of the SmPC (see Appendix C). A summary of any AESIs / imAEs by CTCAE grade, interventions received, and event outcomes are provided in Table 23.

Table 23: Summary of AESIs and imAEs categories; PD-L1 ≥1% group (22 March 2018 DCO)

	Durvalumab (213)		Placebo (N=90)	
AE, n (%)[a]	**AESI**	**imAE[c]**	**AESI**	**imAE[c]**
Any AE	**145 (68.1)**	**58 (27.2)**	**39 (43.3)**	**4 (4.4)**
Any AE causally related to treatment[b]	104 (48.8)	49 (23.0)	20 (22.2)	3 (3.3)
Any AE of CTCAE Grade 3 or 4	**25 (11.7)**	**12 (5.6)**	**2 (2.2)**	**1 (1.1)**
Any AE of CTCAE Grade 3 or 4, causally related to treatment[b]	16 (7.5)	10 (4.7)	1 (1.1)	1 (1.1)
Any SAE (including events with outcome of death)	**12 (5.6)**	**11 (5.2)**	**1 (1.1)**	**1 (1.1)**
Any SAE (including events with outcome of death), causally related to treatment[b]	11 (5.2)	11 (5.2)	1 (1.1)	1 (1.1)
Any AE leading to discontinuation of study treatment	**15 (7.0)**	**28 (5.9)**	**1 (1.1)**	**1 (1.1)**
Any AE with outcome of death	**0**	**0**	**0**	**0**
Any AE with outcome of death, causally related to treatment[b]	0	0	0	0
Treatment for AEs				
Received systemic corticosteroids	34 (16.0)	33 (15.5)	5 (5.6)	3 (3.3)
Received high dose steroids	18 (8.5)	18 (8.5)	4 (4.4)	2 (2.2)
Received endocrine therapy	29 (13.6)	27 (12.7)	0	0
Received other immunosuppressants	0	0	0	0
Event outcome resolution				
Event outcome resolved	82 (38.5)	28 (13.1)	28 (31.1)	2 (2.2)
Event outcome not resolved	63 (29.6)	30 (14.1)	11 (12.2)	2 (2.2)

Key: AE, adverse event; AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; imAE, immune-mediated adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PD-L1, programmed cell death ligand 1; SAE, serious adverse event. **Notes:** [a], Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories; [b], As assessed by the Investigator. Missing responses were counted as related; c, Immune-mediated AEs were adjudicated by the Sponsor; Includes AEs with an onset date on or after the date of first dose and up to and including 90 days following the date of last dose of study medication or date of subsequent therapy, whichever occurs first; AESI terms of 'Infusion related' / 'Hypersensitivity' / 'Anaphylactic reactions', and 'Radiation pneumonitis' were not included in this table. **Source:** PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO.[92]

The most frequently reported AESIs (in ≥5% of PD-L1 ≥1% patients in either treatment group) at the time of the 22 March 2018 DCO are shown in Table 24 below.

Table 24: AESIs reported in ≥5% of patients in any treatment group; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

AESIs by preferred term; n (%)[a, b]	Durvalumab (N=213)	Placebo (N=90)
Diarrhoea	43 (20.2)	14 (15.6)
Pruritus	36 (16.9)	4 (4.4)
Rash	27 (12.7)	7 (7.8)
Hypothyroidism	26 (12.2)	1 (1.1)
Pneumonitis	26 (12.2)	6 (6.7)
Hyperthyroidism	18 (8.5)	1 (1.1)

Key: AE, adverse event; AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Event; DCO, data cut-off; PD-L1, programmed cell death ligand 1.
Notes: The PD-L1 subgroup has been defined using the re-scored PD-L1 data.
a, Each patient has been represented once, sorted in descending order of frequency in the durvalumab group;
b, Adverse events of special interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms. If a patient has multiple events within an AESI, then the maximum CTCAE grade across those events is counted for that preferred term. Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). MedDRA version 19.1.
Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO[92]

B.2.11. Ongoing studies

The PACIFIC study is still ongoing.

Durvalumab is also available to patients through the EAP, which provides ethical access to durvalumab for patients who meet the eligibility criteria, and, who in their treating physicians' opinion, have an unmet clinical need that cannot be treated with approved and commercially available drugs. PACIFIC-R is a planned retrospective real-world study that will include a large group of patients who have been treated with durvalumab in the EAP. This study is aimed to provide the first real-world data for the use of durvalumab in the locally-advanced, unresectable, Stage III NSCLC patient population outside a clinical trial. Primary objectives of the study are to assess the efficacy of treating patients with durvalumab in a real-world setting by evaluating PFS and OS outcomes. The first data read-out from this study is expected in [redacted]

In addition, durvalumab is also being evaluated in unresectable Stage III NSCLC patients in PACIFIC-5 and PACIFIC-6 studies. Like PACIFIC, PACIFIC-5 is a Phase

III, randomised, double-blind, placebo-controlled, multicentre assessing the efficacy and safety of durvalumab compared with placebo in patients with locally advanced, unresectable, Stage III NSCLC who have not progressed following definitive, platinum-based CRT. However, enrolment in the study will be restricted to maintain a balance between the sequential and overlapping CRT protocols, and majority of patients will be recruited in China. Furthermore, patients will receive a fixed dose of durvalumab 1500 mg Q4W via IV infusion (rather than a weight-based dosing regimen). PACIFIC-6 is Phase II, open-label, multi-centre, international safety study of durvalumab 1500 mg Q4W following sequential CRT in patients with unresectable Stage III NSCLC. Both studies will commence later this year (2018), and will provide an indication of any new safety signals in the sequential CRT population.

Table 25: Ongoing durvalumab studies due to provide additional evidence within the next 12-months

Study	Study design	Population	Intervention(s)	Status
PACIFIC	Phase III, randomised, double-blind, placebo-controlled, multicentre, international study	Patients with unresectable Stage III NSCLC whose disease has not progressed following ≥2 overlapping cycles of definitive, platinum-based CRT	Durvalumab 10mg/kg Q2W	Ongoing
PACIFIC-R	Retrospective, observational review	Patients diagnosed with unresectable, Stage III NSCLC, who have not progressed after CRT and who have received at least one dose of durvalumab following CRT within the EAP	Durvalumab as administered via the EAP	Ongoing
PACIFIC-5	Phase III, randomised, double-blind, placebo-controlled, multicentre study	Patients with locally advanced, unresectable, Stage III NSCLC, who have not progressed following definitive, platinum-based, CRT	Durvalumab 1500mg IV Q4W	To commence in Q4 2018*
PACIFIC-6	Phase II, open-label, multicentre, international, safety study	Patients with stage III, unresectable NSCLC following sequential CRT	Durvalumab 1500mg IV Q4W	
Key: CRT, chemoradiation therapy; EAP, Early Access Programme; IV, intravenous; kg, kilogram; mg, milligram; NSCLC, non-small cell lung cancer; Q2W, every 2 weeks; Q4W, every 4 weeks. **Note: *,** Exact timings are subject to change.				

B.2.12. Innovation

Stage III NSCLC is a serious disease, with one-year survival rates of just 42.5% in England and Wales.[8] The current SoC for patients with locally-advanced, unresectable, Stage III NSCLC is concurrent (i.e. overlapping) CRT administered with a curative intent.[47, 100] Advances in radiotherapy techniques have improved survival through optimising locoregional control.[101] Nonetheless, significant proportions of patients eventually experience disease progression.[51] The majority of patients develop distant metastases,[102] and up to 40% can experience local recurrence.[59] Upon relapse, patients can no longer be treated with curative intent. Furthermore, they tend to experience an increased frequency / severity of disease related symptoms, deterioration in HRQL, and worsening prognosis (Section B.1.3). There are no approved treatment options after CRT, and patients face on-going psychological stress and anxiety while they remain on active follow-up, without further anticancer treatment.[64]

Several randomised studies have confirmed that additional consolidation chemotherapy after CRT does not improve clinical outcomes in the locally-advanced, unresectable, Stage III setting. Molecular targeted therapies (such as gefitinib, cetuximab, and bevacizumab) have also failed to demonstrate a significant treatment benefit.[59, 103-105] As a result, **the SoC for patients with locally-advanced, unresectable, Stage III NSCLC has remained unchanged for the past two decades**, and there is significant unmet clinical and patient need for new therapies that will prevent or delay disease recurrence, and improve the outcomes currently achieved with CRT.

Durvalumab is the first and only immunotherapy option that is available in the locally-advanced Stage III setting, for treatment with curative intent[s]. The addition of durvalumab following CRT (i.e. the "PACIFIC regimen") represents a vital

[s] Nivolumab is the only other immunotherapy that is currently being evaluated in a registrational Phase III study in this setting (i.e. stage III NSCLC patients who have received concurrent cisplatin-etoposide and radiotherapy treatment); however, data from this clinical trial are not expected until 2022.[106]

opportunity to prevent / significantly-delay systemic disease spread, harnessing the immune-priming effects of CRT at a time when tumour burden is at its lowest. In the most recent data-cut of the pivotal Phase III PACIFIC RCT, treatment with durvalumab **treatment with durvalumab resulted in a median PFS of nearly 24 months** (versus 5.6 months in placebo) in patients who express PD-L1 on ≥1% of TCs. This is a remarkable result in a setting where the majority of patients experience disease progression within a year of ***starting*** CRT, and is a far greater PFS benefit relative to what has been achieved with immunotherapies in the metastatic NSCLC setting to date.

Durvalumab is the first and only treatment to show a statistically significant improvement in OS post-CRT in the locally-advanced, unresectable, Stage III NSCLC setting. Treatment with durvalumab reduced the overall risk of death by 46% (HR 0.54; 95% CI 0.35, 0.81; *P*=0.003). The OS benefit achieved with durvalumab was also evident in a scenario analysis (HR 0.66; 95% CI 0.44, 1.00), where all patients in the placebo arm who received a subsequent anticancer treatment upon disease progression were assumed to have received an immunotherapy at the initiation of their first subsequent treatment and no patients in the durvalumab arm received any subsequent immunotherapy. There is thus a clear benefit of treating patients early with immunotherapy (i.e. immediately after CRT in a curative-intent setting), rather than later in the treatment pathway upon disease progression to advanced metastatic NSCLC.

Importantly, the meaningful survival benefits with durvalumab were achieved **without any detrimental impact to patients' HRQL**, and an acceptable safety profile.

Finally, the modelled life years gained with durvalumab over a patient's lifetime was 3.61, which translated into a **QALY gain of 2.94** (see Section B.3.4 for further detail). This level of QALY gain is rarely seen in economic evaluations, and is **greater than that required for a "transformative medicine" designation** in the Accelerated Access Collaborative[107], which specifies "substantial incremental QALY gains at a population level or individual incremental QALY gains perhaps greater than for example 2 QALYs." (Communication from ABPI, AAC, 28 February 2018).

Collectively, these data support the notion that durvalumab represents a significant "step-change" in the management of locally-advanced, unresectable, Stage III NSCLC patients, addressing key clinical and patient unmet needs in this population.

The innovative nature of durvalumab was recognised by the US Food and Drug Administration (FDA), which granted it Breakthrough Therapy Designation for the treatment of patients with locally-advanced, unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.[108] The FDA approved the use of durvalumab in this patient population in February 2018.[78] Durvalumab has also been approved for marketing by Health Canada (04 May 2018),[79] Swiss Medic (11 June 2018)[80] and the Pharmaceutical and Medical Devices Agency (PMDA, Japan; 02 July 2018),[81] and discussions with several other Health Authorities worldwide are currently ongoing. On 27 July 2018, the CHMP adopted a positive opinion, recommending marketing authorisation of durvalumab for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of TCs and whose disease has not progressed following platinum-based CRT.[3]

Durvalumab is currently available in the UK through an EAP that provides ethical access to durvalumab for patients who meet the eligibility criteria, and, who in their treating physicians' opinion, have an unmet clinical need which cannot be treated with approved and commercially available drugs. Since the programme was introduced in the UK in September 2017, [redacted] **patients have received durvalumab treatment across** [redacted] **centres** (as of 21 August 2018)**.[5]** [redacted] **UK centres are currently registered on the EAP portal**. The level of uptake in the EAP highlights the unmet need in this treatment setting and validates AstraZeneca's position that durvalumab should innovative in its potential to produce significant clinical benefit in this patient population.

B.2.13. Interpretation of clinical effectiveness and safety evidence

As described previously, no active treatment options are currently available for locally-advanced, unresectable, Stage III NSCLC patients who have completed CRT; the SoC is active follow-up only. Durvalumab is the first and only immunotherapy to be

approved for Stage III NSCLC and represents a “step change” in the management of these patients.

This appraisal requests a recommendation for durvalumab monotherapy for the treatment of adults with Stage III, unresectable NSCLC whose tumours express PD-L1 on ≥1% of TCs and whose disease has not progressed following definitive platinum-based CRT. The clinical effectiveness evidence for durvalumab in this indication is based on the pivotal Phase III, double-blind, international, PACIFIC RCT. The PACIFIC study demonstrated that durvalumab treatment provides superior efficacy to placebo (active follow-up) in this population, with a manageable safety profile and no detrimental impact on patients’ HRQL. Key clinical efficacy and safety evidence from the PACIFIC study, including strengths / weaknesses of the evidence-base, and generalisability to the UK patient population are briefly discussed below.

Summary and discussion of the available evidence to support durvalumab

Clinical efficacy and HRQL

At the time of the primary analysis of PFS (13 February 2017 DCO), durvalumab treatment demonstrated a statistically significant PFS benefit compared with placebo (HR=0.44; *P-value* <0.0001) in the PD-L1 ≥1% group, (i.e. the intended population, per the recent CHMP opinion). In the most-recent and mature analysis of PFS (22 March 2018 DCO), durvalumab treatment resulted in median PFS of 23.9 months in the PD-L1 ≥1% group, relative to a median PFS of 5.6 months in the placebo group.[t] A PFS improvement of >18 months is unprecedented in this disease setting, where most patients experience disease progression within a year of *starting* SoC CRT (HR 0.44, 95% CI 0.31,0.63; *P*<0.0001). The early separation of KM-curves in favour of durvalumab indicates the potential for an early PFS benefit with durvalumab treatment. **Furthermore, KM estimates of PFS rates at 12 and 18 months indicate that the PFS benefit with durvalumab is sustained over time (PFS12: 61.6% versus 36.4%, PFS18: 55.8% versus 27.8% [durvalumab versus placebo]; 22 March 2018**

[t] Median PFS in the placebo arm is broadly comparable to historical data from START[109, 110] and SOCCAR[111] RCTs. This is discussed further below (Strengths and limitations of the evidence base and generatability to the UK).

DCO). Collectively, these data highlight an important role for durvalumab in improving outcomes on SoC CRT through controlling systemic disease spread, preventing / delaying disease progression to metastatic NSCLC, and thereby increasing the chances of cure.

To our knowledge, this is the first reported study in this disease setting that assessed a PFS endpoint using BICR. The placebo-control, double-blind study design and the objective assessment of PFS make the interpretation of these results robust and unbiased. The PFS benefit with durvalumab was also observed the ITT population (HR 0.52; *P*<0.001), as well as in all the pre-specified sensitivity analyses, and across all pre-specified subgroups (including PD-L1 <25%, ≥25%, and "unknown"), confirming the robustness of the PFS data.

Treatment with durvalumab also resulted in a **statistically significant and clinically meaningful improvement in OS** compared with placebo (HR: 0.54; *P*=0.003) in the PD-L1 ≥1% group (22 March 2018 DCO). The separation of durvalumab and placebo KM curves occurred early, indicating rapid onset of benefit, and was sustained (in favour of durvalumab) over the treatment period. A sustained benefit of durvalumab treatment is supported by estimates of the 12-month and 24-month OS rates, **with the durvalumab group demonstrating numerically higher OS rates than placebo at both the OS12 (86.5% [95% CI 81.1, 90.5] versus 74.7% [95% CI 64.2, 82.6]) and OS24 (72.8% [95% CI 66.2, 78.4] versus 53.6% [95% CI 42.5, 63.4]) landmark assessments.**

It is important to reiterate that durvalumab met its second primary endpoint of OS in the full PACIFIC ITT population (22 March 2018 DCO), demonstrating a statistically significant and clinically meaningful improvement in OS compared with placebo (HR: 0.68; *P*=0.003). The OS benefit with durvalumab treatment was observed across stratification factors (i.e., age, sex, and smoking history), and all pre-specified subgroups (including PD-L1 <25%, ≥25%, and "unknown"), confirming the robustness of OS data from the PACIFIC trial.

Consistent with PFS and OS results, **durvalumab treatment was associated with statistically-significant and clinically meaningful improvements across**

secondary efficacy endpoints of TFST, PFS2 and TSST (*P*>0.0005; PD-L1 ≥1% group).

Intermediate efficacy endpoints of PFS2 and TSST provide information about the long-term benefits of a treatment and reflect real-life treatment decisions and patient experience. In the PACIFIC study, nearly a quarter (24.2%) of all patients in the PD-L1 ≥1% group received subsequent immunotherapy after disease progression on placebo. Use of subsequent immunotherapy was much lower amongst patients who received durvalumab (8.5% of patients; PD-L1 ≥1% group). Meaningful improvements in PFS2 and TSST in favour of durvalumab, despite greater immunotherapy use in the placebo arm, underscore the clinical and patient benefit of using immunotherapy earlier in the treatment pathway. This is further corroborated through the RPSFT analysis, which showed that durvalumab treatment reduced the overall risk of death by 34% versus placebo, even in a scenario where all patients in the placebo arm who received a subsequent therapy had immunotherapy in first line ***and*** no patients in the durvalumab arm received subsequent immunotherapy.

In patients who had measurable disease at baseline, durvalumab treatment demonstrated a statistically-significant improvement in ORR over placebo of 16% in the PD-L1 ≥1% group (*P*<0.0045). Furthermore, 80.8% and 73.6% of responses to durvalumab in the PD-L1 ≥1% group were still ongoing at 12 and 18 months, indicating durable responses in these patients. Consistent with this, durvalumab treatment also prolonged the TTDM compared to placebo. While median TTDM was not reached in the durvalumab arm, early and consistent separation of durvalumab and placebo KM-curves in favour of durvalumab demonstrate a meaningful extension in TTDM in PD-L1 ≥1% group (HR 0.40; *P*<0.0001). Furthermore, at the time of the latest DCO, over 81.6% of patients in the PD-L1 ≥1% group who received durvalumab treatment had no new lesions, relative to 63.7% in the placebo group. Furthermore, the incidence of burdensome and clinically-challenging brain lesions was nearly three times lower in the durvalumab group versus placebo (4.7% and 12.1%, respectively). These data further emphasise the important role for durvalumab in maintaining local control and preventing / delaying systemic spread and disease progression to metastatic NSCLC, which marks loss of curative intent, worsening prognosis, and increasing physical and psychological burden on patients.

Patient reported outcome data showed high level of compliance (80% for both groups for up to 48 weeks). Results across EORTC QLQ-C30 and EORTC QLQ-LC13 sub-scales did not indicate any meaningful difference in symptom deterioration between durvalumab and placebo arms of the PD-L1 ≥1% group, despite a longer duration of study therapy for the durvalumab group. No clinically meaningful differences were observed in the global health status of patients either. Furthermore, exploratory *post-hoc* analyses in the ITT population, where clinically relevant deterioration had to be confirmed at the next consecutive time point after the first observation, showed that time to deterioration was notably longer with durvalumab than placebo for emotional functioning, overall pain, nausea / vomiting, insomnia, haemoptysis, chest pain, and arm / shoulder pain, suggesting important patient benefits of durvalumab treatment versus placebo.

Safety and tolerability

Durvalumab was well-tolerated and had a manageable safety profile relative to placebo. The safety profile of durvalumab in the PACIFIC population was consistent with that of other immunotherapies, with its known safety profile as monotherapy in patients with advanced metastatic Stage IV disease,[112] and with patients receiving prior CRT. Safety data in the PD-L1 ≥1% group was consistent with the ITT population, with no clinically meaningful differences in the different categories of AEs. Most AEs were manageable and treated according to standard treatment guidelines and were resolved during the study without affecting the ability of patients to remain on durvalumab.

The incidence of pneumonitis and radiation pneumonitis was noticeably increased in both treatment groups across multiple AE categories. However, this was expected since all patients in the PACIFIC study had received definitive radiotherapy prior to randomisation, with the last radiation dose being within 42 days of randomisation. Furthermore, most AESIs of pneumonitis or radiation pneumonitis were of low CTCAE grade. The incidence of clinically important Grade 3 or 4 pneumonitis events was well balanced between durvalumab and placebo groups (2.8% and 1.1%, respectively), and lower than that what has been observed in other studies in the same disease context.[113, 114] Collectively, these data suggest that the addition of durvalumab after CRT is associated with manageable side-effects. This is further corroborated by PRO

data, which shows that durvalumab treatment has no detrimental impact on patient symptoms, functioning, and HRQL relative to placebo.

Strengths and limitations of the evidence base, and generalisability to the UK

PACIFIC was a well-designed, multicentre, randomised, double-blind, placebo-controlled, Phase III study that provides comparative evidence of durvalumab versus current SoC (i.e. active surveillance) in adults with locally-advanced, unresectable Stage III NSCLC whose disease has not progressed following definitive, platinum-based CRT. The study protocol and amendments were approved by relevant ethics committees, and it was conducted in line with GCP guidelines and the Declaration of Helsinki.[75] Quality of data was assured through monitoring of investigational sites, appropriate training for study personnel, and use of data management procedures.[90] In addition, an IDMC was created to assess the safety of the study on a regular basis.[75]

The PACIFIC study enrolled patients regardless of their PD-L1 status, and was **not designed** to evaluate the efficacy and safety of durvalumab in the subpopulation of patients whose tumours express PD-L1 on ≥1% of TCs. At the time of study design, there was limited understanding of the predictive value of PD-L1 expression in NSCLC, particularly in Stage III NSCLC, and no biomarker had ever been used to guide therapeutic decisions in this setting. Furthermore, biopsy of tumour tissue that had been treated with CRT was not considered clinically feasible. Therefore, PD-L1 testing was not made mandatory for inclusion in the study. Instead, PD-L1 testing was conducted retrospectively on tumour samples collected at the time of diagnosis (if available), and outcomes analysed by <25% or ≥25% TC PD-L1 expression levels in a subgroup analysis. Exploratory *post-hoc* analyses by additional PD-L1 expression cut-offs were subsequently conducted, at the request of the CHMP. While robust, the PD-L1 data are limited by the fact that they do not capture any potential changes in PD-L1 expression that may have occurred due to CRT, and do not necessarily reflect the PD-L1 status immediately prior to starting durvalumab treatment or placebo.

Although patients were not stratified based on PD-L1 expression, **similar proportions of patients had pre-CRT PD-L1 expression on ≥1% of TCs in durvalumab and placebo groups (44.5% and 38.4%, respectively)**. In addition, baseline characteristics in terms of major prognosis factors (i.e. age, histology, stage, smoking

status, and performance status) were all well-balanced between durvalumab and placebo arms of the PD-L1 ≥1% group, and representative of the intended patient population.

Prior CRT was also well-matched in durvalumab and placebo arms of the PD-L1 ≥1% group, and reflective of UK real-world treatment practice. RCR audit data collected from 45 radiotherapy departments in the UK shows that most patients receive either cisplatin + vinorelbine, cisplatin + etoposide, or carboplatin + vinorelbine as part of CRT protocols.[53, 56] [redacted]; AstraZeneca data on file).[45] All three regimens were well represented in the PACIFIC trial, with cisplatin + etoposide or cisplatin + vinorelbine being two of the most commonly-used regimens. Prior definitive radiotherapy doses in the PACIFIC study (i.e. 54 to 66 Gy) were also aligned with UK clinical practice. In the RCR audit, nearly all patients received either 64−66 Gy/32−33 fractions (48%) or 55 Gy/ 20 fractions (47%) of definitive radiotherapy as part of CRT protocols. [redacted] (AstraZeneca data on file).[45] The proportion of patients who received induction chemotherapy in the PACIFIC trial is also similar to reported usage in the UK (23% and 20% [RCR audit]).[56]

One limitation of the PACIFIC study was that it restricted enrolment in the trial to patients who received two or more overlapping cycles of definitive chemotherapy and radiotherapy. This was appropriate given that overlapping / concurrent CRT is SoC in unresectable Stage III NSCLC patients, and recommended as treatment-of-choice over sequential protocols.[46, 47, 51] Nonetheless, data from the latest NLCA suggests that the majority of UK unresectable Stage III NSCLC patients, who are suitable for treatment with curative intent, receive sequential rather than overlapping CRT (66% and 34%, respectively; personal communication with Dr Susan Harden, data to be presented at the 19th World Conference on Lung Cancer, Toronto, 23rd–26th September 2018). It is likely that a multitude of factors, including clinician / patient preference, patients' health and fitness, presence of comorbidities, and logistical / resource constraints contribute towards this. **While the efficacy and safety of durvalumab was not evaluated after sequential CRT in the PACIFIC trial, this will be investigated in PACIFIC-5 and PACIFIC-6 studies.** Both trials are due to

commence later this year (2018). Furthermore, of the [redacted] UK patients who are currently receiving durvalumab through the EAP, [redacted] had received sequential CRT (as of 21 August 2018).[5] Of the remaining patients, [redacted] had received overlapping CRT; type of CRT protocol (i.e. sequential or overlapping) is not confirmed for [redacted] patients at the time of internal AstraZeneca audit. Outcomes data from the EAP will be collected in a retrospective real-world study (PACIFIC-R). The first data read-out from this study is expected in [redacted] and will provide valuable evidence on the use of durvalumab after sequential CRT. It is also important to emphasise that the CHMP **did not** restrict the use of durvalumab to patients who had been treated with overlapping CRT, instead recommending marketing authorisation for locally-advanced, unresectable, Stage III NSCLC in adults whose tumours express PD-L1 on ≥1% of TCs, and whose disease has not progressed **following platinum-based CRT**. Durvalumab has also received approval for the full CRT population by Health Canada (04 May 2018),[79] Swiss Medic (11 June 2018)[80] and the Pharmaceutical and Medical Devices Agency (PMDA, Japan; 02 July 2018).[81]

The co-primary efficacy endpoints of OS and PFS are clinically relevant and were directly referenced in the final scope for this appraisal and the decision problem. OS is the main endpoint that is routinely used to demonstrate superiority of antineoplastic therapies. Treatment with durvalumab resulted in a statistically-significant and clinically-meaningful benefit versus placebo in the PD-L1 ≥1% group (HR 0.54; *P*=0.0034). **To our knowledge, durvalumab is the first and only immunotherapy to show a statistically-significant OS benefit in this disease setting.** While these data are not fully mature (33.0% maturity in the durvalumab arm, versus 49.5% in the placebo arm), they nonetheless demonstrate a clear, consistent, and early benefit of durvalumab treatment that is sustained throughout the study period (KM curves shown in Figure 16; maximum follow-up = 41 months). Median OS was not reached in the durvalumab, and was 29.1 months in placebo arm. While this is higher than what is expected with SoC (i.e. active follow-up) in the UK (see discussion on life expectancy below), it can at least in part be explained by the lower mean age, generally better "health", and more intensive management of patients in a clinical trial, versus a real-world cohort of patients. Patients in the PACIFIC study are still being followed-up for survival; final analysis of OS is expected in [redacted]

In the primary analysis of PFS, treatment with durvalumab also resulted in a statistically-significant benefit versus placebo in the PD-L1 ≥1% group (HR 0.44, *P*<0.0001; 13 February 2017 DCO). In the latest PFS analysis (22 March 2018 DCO; 46.7% maturity in durvalumab arm, and 72.5% in placebo arm), **treatment with durvalumab resulted in a median PFS benefit of >18 months versus placebo**. A benefit of this magnitude is unprecedented for any IO approved in NSCLC, and supports the use of immunotherapy directly after immune-priming CRT in effectively controlling systemic disease spread and preventing progression to advanced metastatic disease. Median PFS of 5.6 months in the placebo arm is broadly comparable to historical data from the international Phase III START study (8.3 months, ITT population; digitised from patient-level data), and from the UK-specific Phase II SOCCAR clinical trial (median PFS of ~12 months from ***start*** of CRT[u]). [109, 110 111] PFS curves from the PACIFIC trial used in health economic modelling were also validated with UK clinicians and confirmed as being representative of the UK cohort of unresectable Stage III NSCLC patients (AstraZeneca data on file).[115]

Finally, the PFS and OS results are supported by secondary endpoints / supportive summaries of TFST, PFS2, TSST, and TTDM, ***all*** of which show a statistically-significant benefit versus placebo in the PD-L1 ≥1% group. Furthermore, **these remarkable clinical benefits were achieved with no detrimental impact on patients' HRQL and acceptable tolerability.**

Collectively, PACIFIC data provide a robust and relevant body of evidence that clearly demonstrate the remarkable clinical and patient benefit achieved with durvalumab monotherapy in a disease setting of high unmet need, where currently no other active treatments exist.

[u] Assuming treatment duration of 3 months for concurrent (overlapping) CRT, plus 1.5 months recovery time, estimated PFS from a comparable time-frame to start of durvalumab treatment in the PACIFIC trial will be 6.5 months.

Life expectancy of the UK cohort of unresectable Stage III NSCLC patients who have not experienced disease progression after CRT

In the PACIFIC study, median OS in the placebo arm was 28.7 months in the ITT population, and 29.1 months in the PD-L1 ≥1% group of patients. While robust, these data may not reflect **real-world survival outcomes** in the **UK cohort** of locally-advanced, unresectable, Stage III NSCLC patients. Indeed, intensive management of patients and other factors that are unique to a clinical trial setting can improve patient outcomes relative to what is known / expected in real-world settings.

To better understand survival outcomes in the **UK population of eligible patients**, we explored several sources of local (i.e. UK-specific) data (described below). Data from all these sources suggest that **life expectancy for unresectable Stage III NSCLC patients who have completed treatment with SoC overlapping CRT is less than 24 months**. Survival outcomes are poorer still for those patients who, for whatever reason, receive sequential (rather than overlapping) CRT.

National / multicentre audits

In the latest NLCA, 2,248 of 5,284 patients (42.5%) diagnosed with Stage III NSCLC (between 1st January and 31st December 2016) were alive at just one year from diagnosis.[8, 116] While these data illustrate the poor prognosis of this group of patients, it is important to highlight that outcomes are likely to vary by patients' health / performance status, presence of comorbidities, and treatment received (i.e. curative intent treatment versus palliative treatment or BSC, as illustrated in Figure 5). A recent study of 176,225 lung cancer patients diagnosed between 2010−2014 showed that the use of active treatment varied between geographical areas and correlated with survival rates.[117] For Stage III patients, there was a statistically significant trend of higher survival in areas with high use of radical radiotherapy (with 48% of these patients also receiving chemotherapy). **Overall survival nonetheless remained poor, with two-year survival probability of <25% (from time of diagnosis) across all areas categorised by quintiles of radical radiotherapy rates.**

Similar findings were also reported in an international benchmarking study conducted by the Royal College of Radiologists (based on 317 NSCLC patients who began radical radiotherapy treatment between October−December 2013).[53] Median OS was

22 months (N=186), with a two-year survival rate of 44%. **Prognosis remained poor even for Stage III patients treated with SoC concurrent (overlapping) CRT, with two-year OS of 46% (N=22).** UK survival rates were similar to European cohorts.

Bespoke analysis of Public Health England (NHS Digital) data

This analysis was based on a cohort of [redacted] patients in England from the National Cancer Registration and Analysis Service, with linked data sources[v] (Cancer Registry, Systemic Anti-Cancer Therapy [SACT], National Radiotherapy Dataset [RTDS], Office of National Statistics [ONS, mortality], and Hospital Episode Statistics [HES]) who:

- Were diagnosed with Stage III NSCLC between 2013 and 2015
- Did not undergo surgical resection of tumours
- Received overlapping CRT.

KM-estimate of median OS in this cohort of patients (from the date of the last radiotherapy dose) was [redacted] months (95% CI [redacted]) (AstraZeneca data on file).[45]

UK-specific RCT data

The Phase II, randomised, non-blinded, multicentre, SOCCAR clinical trial compared sequential and overlapping (concurrent) CRT protocols in 150 locally-advanced, unresectable, Stage III NSCLC patients in the UK (recruited between December 2005 and March 2010). All patients received three or four cycles of cisplatin + vinorelbine given either sequentially or concurrently with definitive radiotherapy (55 Gy / 20 fractions) delivered over four weeks. **Median OS was 24.3 months and 18.4 months from the *start* of concurrent and sequential CRT, respectively.** Median survival would therefore be <24 months in both groups from the point of completion of CRT (assuming an approximate duration of three months for concurrent CRT and four months for sequential CRT, median survival would be ~21 months and ~14 months, respectively, from completion of CRT).

Insights from UK clinical experts

While data from the sources described above represent (to our knowledge) the most robust survival estimates for Stage III NSCLC patients in the UK, we acknowledge that

[v] Latest available data: Cancer Registry / ONS Mortality, January 2018; SACT, January 2017; RTDS, March 2016; HES, February 2017.

several new treatments have become available in the metastatic NSCLC setting more recently than the time-frames of some of these analyses and are currently being used to treat unresectable Stage III patients upon disease progression after CRT. To understand the current real-world impact of these life-extending therapies on the overall survival of unresectable Stage III patients, we sought the input of UK clinical experts. We focused on patients who are fit and able to receive treatment with SoC concurrent (overlapping) CRT, to understand the best-possible outcomes achievable in current UK clinical practice.

Feedback from 10 UK clinical experts confirmed <24 months OS (mean = 22.3 months)[44] for locally-advanced, unresectable, Stage III NSCLC patients who had completed treatment with overlapping CRT, despite the availability of life-extending anti−PD-1 / PD-L1 agents and targeted therapies in the metastatic setting.

Collectively, the data described above and the statistically-significant OS benefit achieved with durvalumab treatment versus placebo in the PACIFIC ITT population support the applicability of end-of-life criteria for this appraisal.

Table 26: End-of-life criteria

Criterion	Data available	Reference in submission (section; page)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**PACIFIC RCT** (unresectable Stage III patients who have not experienced disease progression after completing CRT)[92] - Median OS = 28.7 months (ITT) and 29.1 months (PD-L1 ≥1% group)	Section B.2.6; Page 66
	UK-specific data • NLCA (2016 audit period)[8] – Average 1-year survival rate from diagnosis (all Stage III) = 42.5% • Møller *et al* audit (patients treated with radical radiotherapy)[117] – 2-year survival probability from diagnosis = <25% • RCR audit[56] – Median OS (radical radiotherapy) = 22 months; 2-year survival rate = 44% – 2-year survival rate (overlapping CRT) = 46% • Public Health England (NHS digital)[45]	Section B.2.13, page 106

Criterion	Data available	Reference in submission (section; page)
	– Median OS (unresected Stage III patients who had received overlapping CRT) = [redacted] months • SOCCAR RCT[111] – Median OS from ***start*** of overlapping CRT = 24.3 months – Median OS from ***start*** of sequential CRT = 18.4 months • UK KEE opinion[44] – Median OS (mean of 10 responses = 22.3 months)	
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	**PACIFIC RCT OS data (durvalumab versus active follow-up)** • ITT[77] – HR (95% CI), *P*-value = 0.68 (0.53, 0.87); 0.003 – Median OS ▪ Durvalumab: NR (95% CI 34.7, NR); lower bound indicates OS benefit of minimally 6 months versus median OS for placebo (below). ▪ Placebo: 28.7 (22.9, NR) • PD-L1 ≥ 1% group[92] – HR (95% CI) = 0.53 (0.36, 0.77) – OS24 ▪ Durvalumab: 72.8% (95% CI 66.2, 78.4) ▪ Placebo: 53.6% (95% CI 42.5, 63.4)	Section B.2.6; Page 66
Key: CI, confidence interval; CRT, chemoradiation therapy; KEE, key external expert; HR, hazard ration; ITT, intention to treat; NHS, National Health Service; NLCA, National Lung Cancer Audit; NR, not reached; PD-L1, programmed cell death ligand 1; OS, overall survival; OS24, proportion of patients alive after 24-months; RCR, Royal College of Radiologists; RCT, randomised controlled trial.		

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

An SLR was conducted to identify studies reporting economic evaluations in adults with locally-advanced, unresectable, Stage III NSCLC or advanced metastatic Stage IV NSCLC, investigating a range of interventions of interest. The SLR was broader in scope than the population of interest for this appraisal. This population was selected as the economic model includes health states reflecting disease progression from Stage III NSCLC, where the disease may have advanced to metastatic Stage IV NSCLC.

The SLR was conducted in two stages. An original search was conducted in October 2016, and captured published economic evaluations of CRT in adults with locally-advanced, unresectable, Stage III NSCLC. An update was conducted in March 2018 to:

1. Identify evidence published since the original review was conducted.

2. Extend the scope of the review to include adults with locally-advanced, unresectable, Stage III NSCLC or advanced metastatic Stage IV NSCLC, with **no** restriction to patients treated with CRT.

Full details of the search methodology and a summary of the included studies are provided in Appendix G. In summary, 21 UK-focused economic evaluations were identified for inclusion in the cost-effectiveness review (one full publication,[118] and 20 HTA submissions covering 11 unique interventions[26-28, 32, 35, 39, 85, 86, 119-130]).

None of the included publications were exactly aligned with the population of interest as detailed in the decision problem (Table 1), i.e. adults with locally-advanced, unresectable, Stage III NSCLC whose tumours express PD-L1 on ≥ 1% of TCs and whose disease has not progressed following platinum-based CRT. However, the publications do report data of interest on model methodology and were therefore considered relevant for the purposes of this submission. A summary of the 21 economic evaluations is provided in Table 27. A more detailed extraction of model structure and results is provided in Appendix G.

Table 27: Summary of UK-focused published cost-effectiveness studies

Study	Year	Summary of model (as reported in publication)	Patient population (mean age, years)	Incremental QALYs (intervention, comparator)	Incremental costs (intervention, comparator)	ICER (per QALY gained)
Le Lay 2007 [118]	2003	Six-state Markov model	Patients with advanced NSCLC treated in the first-line setting. Mean age of population not reported.	NA	Compared with oral vinorelbine, 60 mg/m^2, day 1−day 8, incremental costs varied between £561 (oral vinorelbine, day 1−day 8, 60-80 mg/m^2) and £4,009 (paclitaxel, 200 mg/m^2)	NA
NICE TA124 [127] SMC 342/07 [119]	2007	Three-state Markov model	Patients with advanced NSCLC who had relapsed following prior chemotherapy. (Note: Data for the base case obtained from pooling several Phase III clinical studies). Median age across included studies ranged from 57−63 years.	• Pemetrexed vs. docetaxel, 0.07 • Pemetrexed vs. SoC, 0.21	• Pemetrexed vs. docetaxel, £1,375 • Pemetrexed vs. SOC, £3,379	• Pemetrexed vs. docetaxel, £18,672 [reported as £21,926 in SMC submission] • Pemetrexed vs. SoC, £16,458
NICE TA181 [39] SMC 531/09 [120]	2009	Markov model	Patients with non-squamous NSCLC who are not amenable to surgery, in the first-line setting. Median age (range) in JMDB [131], 61.1 years (29−83).	• Pemetrexed / cisplatin vs. gemcitabine / cisplatin, 0.041 • Pemetrexed / cisplatin vs. gemcitabine / carboplatin, 0.092 • Pemetrexed / cisplatin vs.	• Pemetrexed / cisplatin vs. gemcitabine / cisplatin, £1,346 • Pemetrexed / cisplatin vs. gemcitabine / carboplatin, £1,988 • Pemetrexed / cisplatin vs. docetaxel / cisplatin, £1,380	• Pemetrexed / cisplatin vs. gemcitabine / cisplatin, £33,065 • Pemetrexed / cisplatin vs. gemcitabine / carboplatin, £21,585

Study	Year	Summary of model (as reported in publication)	Patient population (mean age, years)	Incremental QALYs (intervention, comparator)	Incremental costs (intervention, comparator)	ICER (per QALY gained)
				docetaxel / cisplatin, 0.075		• Pemetrexed / cisplatin vs. docetaxel / cisplatin, £18,401
NICE TA190 [128] SMC 642/10 [121]	2010	Simple, trial-based model with an extrapolation component.	Patients with Stage IIIB / Stage IV non-squamous NSCLC who have received four cycles of first-line chemotherapy (based on a platinum doublet including gemcitabine, docetaxel, or paclitaxel only) and whose disease has not progressed. Median age across both treatment arms ranged from 60.4−60.6 years in JMEN [132].	Pemetrexed vs placebo, 0.27	Pemetrexed vs placebo, £9,137 [reported as £12,265 in SMC submission]	Pemetrexed vs placebo, £33,732 [reported as £46,216 in SMC submission]
NICE TA347 [35] SMC 1027/15 [122]	2015	Three-state partitioned survival model	Patients with advanced, metastatic or recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy. Mean age in LUME-Lung 1 trial [133], 58.5 years.	Nintedanib + docetaxel vs. docetaxel, 0.22	Nintedanib + docetaxel vs. docetaxel, £11,051	Nintedanib + docetaxel vs. docetaxel, £50,776 [£33,412 in submission to SMC following agreement of PAS]
NICE TA402 [32]	2016	Three state-transition Markov model†	Patients with locally advanced or metastatic NSCLC, eligible for maintenance treatment, whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin.	Pemetrexed vs. placebo, 0.2554 [Pre-progression, 0.19; post-progression, 0.06]	Pemetrexed vs. placebo, £12,582 [Pre-progression, £13,118; post-progression, -£535]	Pemetrexed vs. placebo, £49,258

Study	Year	Summary of model (as reported in publication)	Patient population (mean age, years)	Incremental QALYs (intervention, comparator)	Incremental costs (intervention, comparator)	ICER (per QALY gained)
			Median age (range) in PARAMOUNT [134, 135], 61 years (32−83).			
NICE TA403 [129]	2016	Three-state partitioned survival model	Patients with locally advanced or metastatic NSCLC whose disease progressed during or after one prior platinum-based chemotherapy, with or without maintenance therapy, for advanced disease. Median age across both treatment arms ranged from 61-62 years in REVEL [136, 137].	Ramucirumab + docetaxel vs. docetaxel, 0.125 [Before progression, 0.079; after progression, 0.046]	Ramucirumab + docetaxel vs. docetaxel, £24,288	Ramucirumab + docetaxel vs. docetaxel, £194,919
NICE TA428 [26] SMC 1204/17 [125]	2017	Three-state partitioned survival model	Patients with advanced, PD-L1 positive NSCLC whose disease has progressed after platinum-containing doublet chemotherapy. Mean age in KEYNOTE-010 [96], 62 years.	Total QALYs-base case 1: • Pembrolizumab, 1.30 • Docetaxel, 0.60 Total QALYs-base case 2 • Pembrolizumab, 1.22 • Docetaxel, 0.60	Total costs-base case 1: • Pembrolizumab, £41,209 • Docetaxel, £11,267 Total costs-base case 2: • Pembrolizumab, £41,283 • Docetaxel, £11,267	£43,351 (base case 1) £49,048 (base case 2)
NICE TA447 [28] SMC 1239/17 [126]	TA447 2017 ID134 92018	Three-state partitioned survival model	Patients with advanced NSCLC whose tumours express PD-L1 on at least 50% of their tumour cells, and who received no prior	**TA447** • Pembrolizumab vs. SoC, 1.21	**TA447** • Pembrolizumab vs. SoC, £54,185 [reported as £49.739 in SMC submission]	**TA447** • Pembrolizumab vs. SoC, £44,896 [£41,213 in submission to SMC following

Study	Year	Summary of model (as reported in publication)	Patient population (mean age, years)	Incremental QALYs (intervention, comparator)	Incremental costs (intervention, comparator)	ICER (per QALY gained)
NICE ID1349 (CDF review of TA447) [85]			systemic chemotherapy treatment. Mean age in KEYNOTE-024 [96], 65 years.	**ID1349** *Base case as per TA447‡* • Pembrolizumab vs. SoC, 1.27 *Updated base case§* • Pembrolizumab vs. SoC, 0.96	**ID1349** *Base case as per TA447‡* • Pembrolizumab vs. SoC, £50,506 *Updated base case§* Pembrolizumab vs. SoC, £28,989	agreement of PAS] **ID1349** *Base case as per TA447‡* • Pembrolizumab vs. SoC, £39,772 *Updated base case§* Pembrolizumab vs. SoC, £30,244
NICE TA483 [27] SMC 1144/16 [123]	2017	Three-state partitioned survival model	Pre-treated adult patients with advanced or metastatic squamous NSCLC. Median age (range) in CheckMate 017 [94, 95], 62 years (39−85).	Nivolumab vs. docetaxel, 0.76	Nivolumab vs. docetaxel, £65,355 [reported as £35,433 in SMC submission]	Nivolumab vs. docetaxel, £85,950 [£46,598 in submission to SMC following agreement of PAS]
NICE TA484 [86] SMC 1180/16 [124]	2017	Three-state partitioned survival model	Adult patients with locally advanced or metastatic non-squamous NSCLC previously treated with platinum-based chemotherapy. Median age (range) in CheckMate 057 [94], 62 years (21−85).	Nivolumab vs. docetaxel, 0.73	Nivolumab vs. docetaxel, £75,452 [reported as £36,830 in SMC submission]	Nivolumab vs. docetaxel, £103,589 [£50,565 in submission to SMC following agreement of PAS]

Study	Year	Summary of model (as reported in publication)	Patient population (mean age, years)	Incremental QALYs (intervention, comparator)	Incremental costs (intervention, comparator)	ICER (per QALY gained)
NICE TA520 [130]	2018	Three-state partitioned survival model	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Median age (range) in OAK RCT [98], 64 years (33−85).	• Atezolizumab vs. docetaxel, 0.75 • Atezolizumab vs. nintedanib + docetaxel, 0.65 • Nintedanib + docetaxel vs. docetaxel, 0.10	• Atezolizumab vs. docetaxel, £53,970 • Atezolizumab vs. nintedanib + docetaxel, £36,209 • Nintedanib + docetaxel vs. docetaxel, £17,761	• Atezolizumab vs. docetaxel, £72,356.07 • Atezolizumab vs. nintedanib + docetaxel, £56,076.16 • Nintedanib + docetaxel vs. docetaxel, extendedly dominated
Le Lay 2007 [118]	2003	Six-state Markov model	Patients with advanced NSCLC treated in the first-line setting. Mean age of population not reported.	NA	Compared with oral vinorelbine, 60 mg/m^2, day 1−day 8, incremental costs varied between £561 (oral vinorelbine, day 1−day 8, 60-80 mg/m^2) and £4,009 (paclitaxel, 200 mg/m^2)	NA

Key: CDF, cancer drugs fund; ICER, incremental cost-effectiveness ratio; IV, intravenous; NA, not applicable; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PAS, patient access scheme; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QALY, quality-adjusted life year; RCT, randomised controlled trial; SMC Scottish Medicines Consortium; SoC, standard of care; TA, technology appraisal; vs, versus.
Notes: †Although the authors describe the analysis as a Markov model, the use of extrapolated OS and PFS as model inputs and area under the curve (AUC) calculations is suggestive of a partitioned survival analysis. ‡This base case reflected the original submission (TA447) where crossover adjustments were accounted for to reflect the base-case analysis presented in the original submission. §In the updated base case, no crossover adjustments were considered, and patients in the standard of care arm who progressed were assumed to receive pembrolizumab based on the proportion of patients who received a PD1 after progression in KEYNOTE-024[96], with the remaining patients assumed to receive docetaxel.

B.3.2. Economic analysis

None of the included publications from the SLR were aligned with the population of interest (adults with locally advanced, unresectable, Stage III NSCLC whose tumours express PD-L1 on ≥ 1% of TCs and whose disease has not progressed following platinum-based CRT). Therefore, a *de novo* economic evaluation was developed to evaluate the cost-effectiveness of durvalumab treatment versus SoC (defined by active follow-up until disease progression, followed by subsequent therapies in metastatic setting). Key characteristics of the *de novo* analysis are shown in Table 28. More detail is provided in subsequent sections.

Table 28: Summary of the *de novo* analysis

Aspect	Details	Justification	Reference to relevant sections
Patient population	Patients with locally-advanced, unresectable Stage III NSCLC whose tumours express PD-L1 on ≥ 1% of TCs and whose disease has not progressed following ≥2 overlapping cycles of CRT	Aligned with CHMP opinion for durvalumab (Section B.1.1)	Section B.3.2, p117
Analytical methods	• Semi-Markov survival model (base case) • Partitioned survival model (sensitivity analysis)	Due to challenges associated with independently extrapolating PFS and OS, a semi-Markov model using PFS and PPS was selected for the base case analysis.	Section B.3.2, p118
Model structure	Three-health state structure (progression-free, progressed disease, death)	A three-health state structure is consistent with previous technology appraisals anti-cancer treatments in NSCLC	
Time horizon	Lifetime (40 years)	Lifetime time horizon is required to capture all differences in treatment arms; in the economic model, <1% of patients still alive on durvalumab at 40 years	Section B.3.2, p118
Cycle length	2-week until 12 months, 4 weeks thereafter	Smaller cycle lengths increase accuracy of the economic model. 2-week cycle length corresponds to durvalumab administration and is applied	Section B.3.2, p118

Aspect	Details	Justification	Reference to relevant sections
		for the time patients can receive durvalumab treatment.	
Discounting options	Costs and health outcomes at 3.5%	Consistent with NICE reference case[138]	-
Perspective	NHS and PSS	Consistent with NICE reference case[138]	Section B.3.4, Section B.3.5
Treatment arms within executable model	Durvalumab Standard of care	In line with final NICE scope	-
Health effects	Quality adjusted life years (QALYs) Life years (LYs)	Consistent with NICE reference case[138]	Section B.3.4
Clinical efficacy and safety	Clinical systematic review and PACIFIC	Based on systematic review of evidence and available data	Section B.3.3
Costs	A systematic review of published studies; clinical expert opinion[139]		Section B.3.5
Utilities	A systematic review of published studies reporting health utility scores in patients with NSCLC EQ-5D data collected in the PACIFIC study		Section B.3.4

Key: CHMP, Committee for Medicinal Products for Human Use; CRT, chemoradiation therapy; EQ-5D, EuroQol 5-dimension; LYs, life years; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PPS, post-progression survival; PSS, Personal Social Services; QALYs, quality-adjusted life years; TC, tumour cell.

Patient population

The *de novo* economic analysis evaluates the incremental cost-effectiveness of durvalumab therapy compared to SoC in the treatment of 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 platinum-based CRT. This population is in line with CHMP opinion and the anticipated license for durvalumab.[3] Data for this group of patients are available from exploratory *post-hoc* analysis of the PACIFIC study (Section B.2.6).

Intervention technology and comparators

The comparator in the economic model is active follow-up (the SoC in this setting), which was assumed to apply up to disease progression (in line with the treatment pathway in this population; Section B.1.3).

The PACIFIC study included a 12-month stopping rule for patients receiving durvalumab (Section B.2.3), hence the economic analysis reflects a 12-month stopping rule for durvalumab in this treatment setting and population. Time to discontinuation in the economic model was informed from the KM-curves for the PD-L1 ≥1% group in the PACIFIC study.

Evaluation period (cycle length)

State occupancy is evaluated at fortnightly intervals (14 days) during the first 12 months, and every 28 days thereafter, over the course of the modelled time horizon (40 years). 14 days is aligned with the treatment administration and dosing of durvalumab. A small cycle length lessens the risk of over- or under-predicting state occupancy due to averaging the time spent in a state over long evaluation periods (e.g. one-month or one-year evaluation periods).

For calculating LYs and QALYs, the model calculated mid-year estimates in each health state by taking the average of patients present at the beginning and at the end of each cycle (half cycle correction).

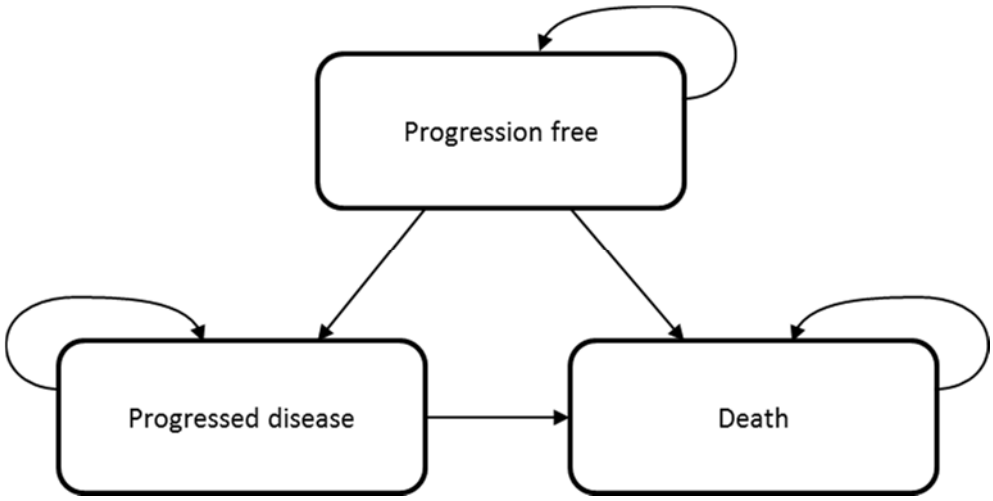
Model structure

Health state structure

A three-health state cohort-based model was developed to evaluate the cost-effectiveness of durvalumab treatment versus SoC 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 platinum-based CRT. A cohort model approach was considered most appropriate as there is limited evidence of heterogenic effect of individual patient characteristics on future survival and disease course.

The model structure (shown in Figure 25) comprises three health states, i.e. progression-free (PF), progressed disease (PD), and death. This model structure is appropriate as the health states considered capture clinically important aspects relating to the treatment of Stage III NSCLC patients; namely the period spent PF and the period spent alive. As highlighted in section B.1.3, disease progression is a clinically important and patient-relevant endpoint. Upon progression to advanced metastatic disease, patients experience deterioration in HRQL, and worsening symptoms. The possibility of cure is lost and patients are treated with palliative intent.

Figure 25: Health-state structure used in the economic model



Although there have not been any previous NICE technology appraisals in this population (i.e. locally-advanced, unresectable, Stage III NSCLC), a three-health state approach has been adopted in other decision models used to estimate the cost-effectiveness of immunotherapies in the advanced metastatic NSCLC setting, and has also been extensively used in other health technology appraisals in NSCLC (Section B.3.1, Table 29).[26-28, 32, 35, 85, 86, 127, 129, 130]

Treatment effect

In the model, the comparative efficacy and tolerability of durvalumab treatment impacted the following aspects of health:

- To increase or decrease the time spent in the PF state.
- To increase or decrease the time spent alive, either in PF or PD states.
- To increase or decrease the incidence of AEs of CTCAE Grade 3 or higher.

Method of evaluation

There are two alternative methods available to estimate the number of patients in each health state over time, in the model structure described above: a partition survival approach, and Markov / semi-Markov techniques. The pros and cons of both methods were recently discussed in the Decision Support Unit (DSU) technical support document (TSD) 19[140], and are summarised below:

- **The partition survival approach** uses PFS and OS data directly to estimate the number of patients in each health state over time. However, because PFS and OS data are used independently, it can be prone to logical inconsistencies where the OS curve falls below the PFS curve.
- **Markov or semi-Markov approaches** use information on the number of patients transitioning between PF, PD, and death to calculate the number of patients in the health states over time. This method ensures that the structural relationship between PFS and OS (i.e. that OS cannot be less than PFS) is maintained.

In the base case analysis, a semi-Markov was applied. PFS and PPS data from the PACIFIC study was used to inform model predictions. This was because:

- All clinically-plausible OS- and PFS-curves, extrapolated using standard techniques, produced logical inconsistencies where the curves crossed, making a partition survival approach complex, and
- Evidence from the PACIFIC study suggests that the benefit of durvalumab is primarily driven by prolonging PFS, and that (conservatively) PPS is similar between durvalumab and placebo (SoC) arms. This data naturally lends itself to a Markov approach, where OS is derived from PFS and PPS data, rather than extrapolated independently (as with the partitioned survival approach).

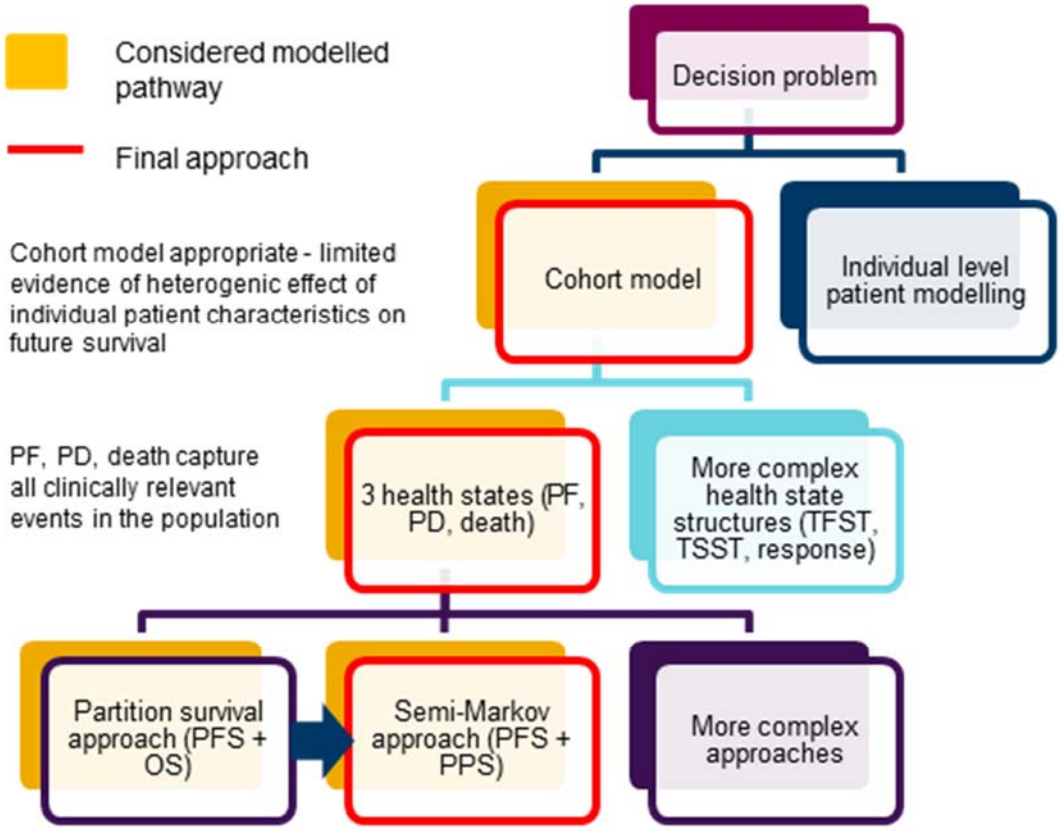
A partitioned survival modelling technique was used in a sensitivity analysis (Section B.3.8). Further details are provided in the following section.

Model conceptualisation and justification for final approach

The approach to selecting the final model approach is shown in Figure 26. At each step of the process, the most parsimonious approach was chosen and considered first,

before moving on to more complex approaches. We initially considered use of a partition survival approach but rejected the technique due to limitations in the analysis.

Figure 26: Model conceptualisation



Key: OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; TFST, time to first subsequent treatment or death; TSST, time to second subsequent treatment or death.

- **Consideration and rejection of partition survival model:** Partition survival modelling has been used extensively for oncology medicines in NICE appraisals, including for other immunotherapies in the advanced metastatic NSCLC setting. In this method, the number of patients occupying each state in the model is estimated using the partitioned survival method. This technique combines the proportion of patients who are alive (derived from the OS curve), and the proportion of patients alive and PF (derived from the PFS curve) to estimate the numbers of patients in each model state.

This is achieved using the following equations:

- **PF = P(PFS)**
- **Death = 1 - P(OS)**
- **PD = P(OS) - P(PFS)**

Where P(PFS) = proportion of patients who are progression-free, P(OS) = proportion of patients alive.

This type of model is well understood, intuitive, easy to communicate and construct, allows replication of the within-trial data with relative ease, and can be constructed using either summary data or individual patient level data for these endpoints. An additional advantage of using this technique for this appraisal is that efficacy inputs for durvalumab and comparator(s) are aligned with primary endpoints of the PACIFIC study (i.e. PFS and OS; Section B.2.3), with limited transformation necessary. For these reasons, a partitioned modelling approach was initially considered for this appraisal.

There are, however, several important limitations with the partition survival modelling approach. The main limitation is that survival curves for PFS and OS are fitted completely independently from each other. This means that no fundamental structural relationship between PFS and OS is imposed within the model itself, although (in reality) OS will always be ≥PFS. This is particularly relevant when the endpoints are of different maturity (as is the case in PACIFIC[w]). Survival extrapolations for a given endpoint reflect observed within-trial trends in that endpoint alone, so if one endpoint is more mature than the other then the more mature endpoint (PFS) can exhibit different trends to the less mature endpoint (OS). This can lead to contradictory results when the curves are combined. The effect is accentuated in disease settings where a long survival tail is expected (i.e. where a small proportion of patients remain PF or alive for a relatively long time), as is the case in Stage III NSCLC (9.4%−11.6% of patients remain alive and progression-free at five years after CRT;[51] Section B.1.3). In line with this, when survival extrapolations for OS and PFS (from the PACIFIC study) were combined, they

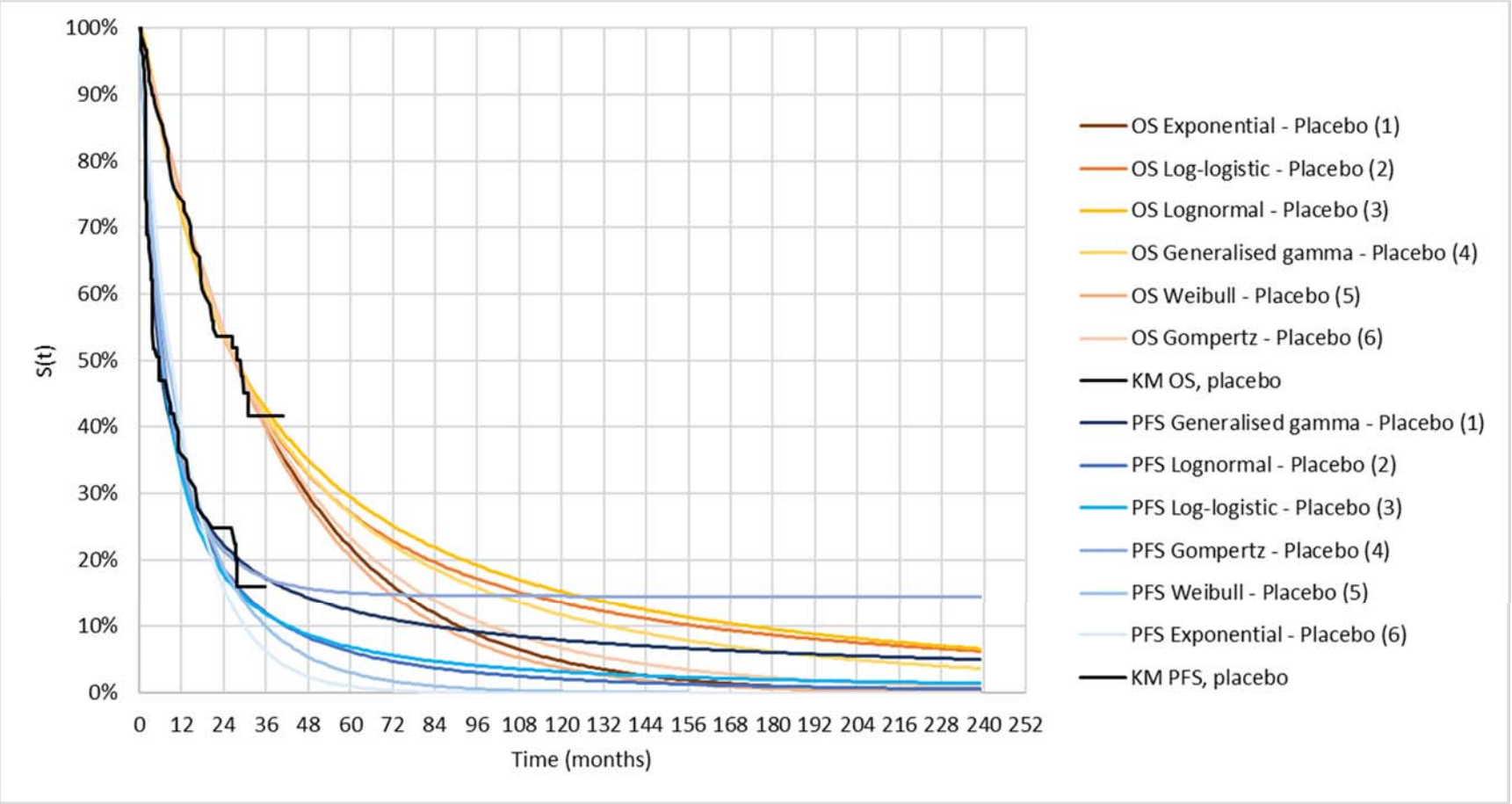
[w] At the 22 March 2018 DCO, PFS data were 73% and 47% mature in the durvalumab and placebo arms of the PD-L1 ≥1% group, respectively. OS data were 50% and 33% mature in the durvalumab and placebo arms of the PD-L1 ≥1% group, respectively.

produced logical inconsistencies which were in direct contradiction with reality and clinical trial data (see Figure 27 and Figure 28).

- In line with DSU guidelines, we fitted a number of parametric distributions to both PFS and OS data from PACIFIC (full details are shown in section B.3.3 and Appendix M).
- Figure 27 and Figure 28 show **all** the fitted survival extrapolations for the durvalumab and SoC arms in the PACIFIC study, respectively. PFS curves are coloured orange, and OS curves are coloured blue; darker colours indicate better statistical fit to the data according to Akaike information criterion (AIC).

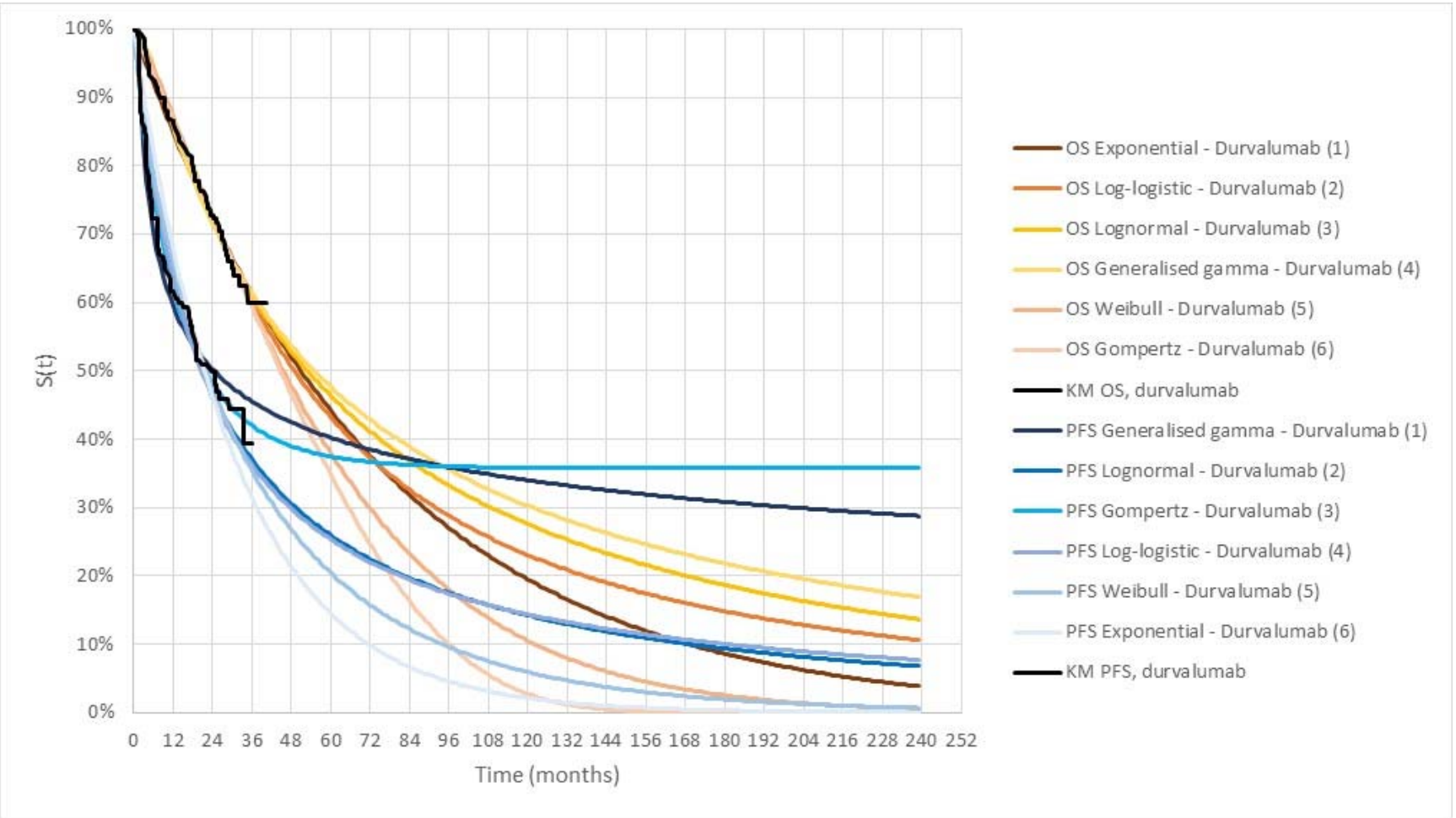
- As can be seen from the figures, there is a clear logical inconsistency between the predicted PFS and OS curves. This is especially prevalent in the durvalumab arm, where the predicted OS curves can drop below the PFS curves (something that is not possible in reality). This issue is present for nearly all combinations of good fitting, clinically-plausible survival curves for both arms. Therefore, this cannot be easily overcome by simply picking different survival curves (see section B.3.3 and Appendix M).

Figure 27: Extrapolated survival curves for SoC arm; PACIFIC PD-L1 ≥1% group (based on 22 March 2018 DCO)



Key: CRT, chemoradiation therapy; DCO, data cut-off; KM, Kaplan–Meier; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; SoC, standard of care.
Notes: Statistical fit order is shown in legend- darker colours indicate better statistical fit according to Akaike information criterion (AIC). **Clinical experts in the UK stated that they expected 15% and 9% of patients to be alive and progression-free at 5- and 10-years following completion of overlapping CRT.[44]**

Figure 28: Extrapolated survival curves for durvalumab arm; PACIFIC PD-L1 ≥ 1% group (based on 22 March 2018 DCO)



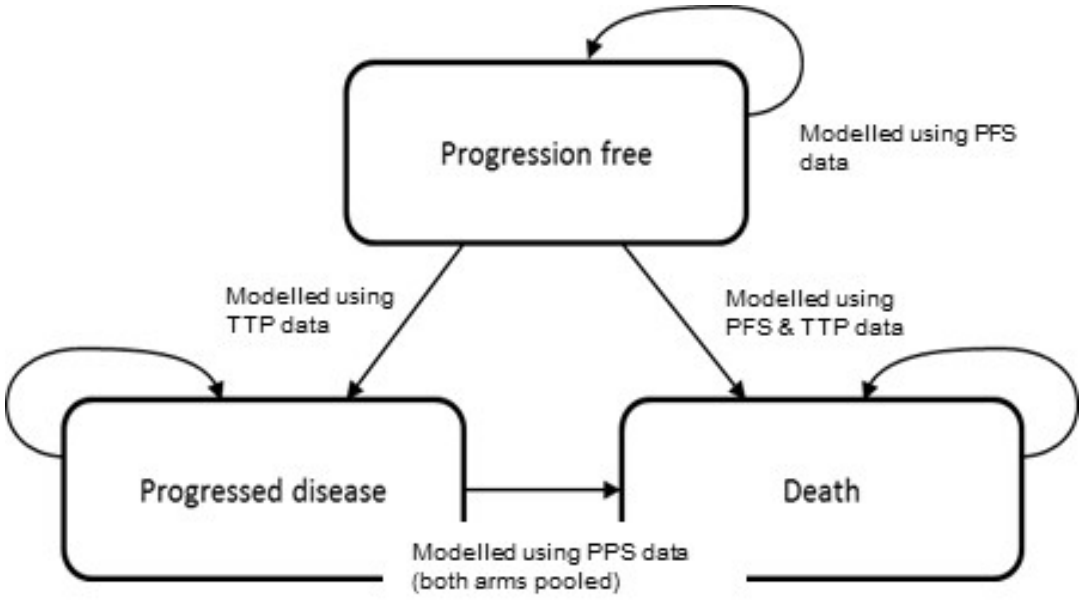
Key: DCO, data cut-off; KM, Kaplan–Meier; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; SoC, standard of care.
Notes: Statistical fit order is shown in legend- darker colours indicate better statistical fit according to Akaike information criterion (AIC).

- **Consideration of semi-Markov approach (base case approach):** Due to the limitations observed with a partition survival modelling approach outlined above, we adopted a semi-Markov approach. The model utilised PFS data from PACIFIC to derive probabilities for PF patients to remain in PF state (i.e., alive and progression free) in each cycle of the model. Time to progression (TTP)[x] data from PACIFIC were used to derive the transition probability from PF state to PD state. Among those who have progressed but are still alive, the model further applied transition probability from PD state to death state. This was estimated based on the PPS data from PACIFIC. PPS was similar between durvalumab and placebo arms of the PD-L1 ≥1% group in PACIFIC for the first 13 months of the study, with a slight separation observed from 13 months onwards in favour of the durvalumab arm. For purposes of the semi-Markov model, PPS data were pooled between the two arms and it was conservatively assumed that there was no difference in PPS between durvalumab and placebo.

  The abovementioned transition probabilities are sufficient to estimate OS at each cycle; therefore, it is not necessary to directly use OS data from the PACIFIC study to extrapolate OS outcomes. Instead, observed OS data from the PACIFIC study were used for internal validation only. Predicted OS using this approach was consistent with that observed in PACIFIC,[74, 75, 77, 92] other relevant clinical studies (Table 34), and estimates from UK clinical experts[44] (Figure 27 and Figure 28).

[x] TTP and PFS were considered by the US FDA in the approval of durvalumab in locally-advanced, unresectable, Stage III NSCLC. TTP is defined as the time from randomisation until objective tumour progression; TTP does not include deaths. PFS is defined as the time from randomisation until objective tumour progression or death.[141]

Figure 29: Health state structure for the economic model



Key: PFS, progression-free survival*, PD, progressed Disease, TTP, time to progression*
Notes: Time horizon was 40 years, reflecting a lifetime approach to capture all costs and outcomes, with a cycle length of two weeks for the first 12 months (aligned with administration of durvalumab), and every four weeks thereafter. *TTP and PFS were considered by the US FDA in the approval of durvalumab in locally-advanced, unresectable, Stage III NSCLC.[141] TTP is defined as the time from randomisation until objective tumour progression; TTP does not include deaths. PFS is defined as the time from randomisation until objective tumour progression or death.

Overview of modelling approach against other relevant appraisals

As stated previously, no publications or previous NICE appraisals in locally-advanced, unresectable, Stage III NSCLC were identified in the SLR. NICE has previously assessed immunotherapies in the advanced, metastatic NSCLC setting (five appraisals relating to three treatments[26-28, 85, 86, 130]). Although these appraisals encountered issues around the long-term plausibility of the survival extrapolations, none involved logically inconsistent PFS and OS curves to the extent seen in Figure 27 and Figure 28. Furthermore, it is important to bear in mind that these appraisals focused on a more advanced disease stage. In contrast to metastatic Stage IV NSCLC, a long survival tail is expected in locally-advanced Stage III disease, where a small proportion of patients achieve very good long-term outcomes on current SoC (15% alive at five years[51]). The presence of a long survival tail can accentuate the issues seen with independently modelling PFS and OS, particularly when the curves have different maturities. A comparison of the chosen modelling approach against these appraisals is shown in Table 29.

Table 29: Features of the economic analysis and comparisons with previous immunotherapy appraisals in the advanced metastatic NSCLC setting

	Previous immunotherapy appraisals in advanced metastatic Stage NSCLC					Current appraisal	
Factor	**TA447 (2017) / TA531 (2018) [CDF review] pembrolizumab**	**TA428 (2017), pembrolizumab**	**TA483 (2017), nivolumab**	**TA484 (2017), nivolumab**	**TA520 (2018), atezolizumab**	**Chosen values**	**Justification**
Setting	1L Stage IV setting: Untreated PD-L1-positive metastatic NSCLC in adults	2L Stage IV setting: Locally-advanced or metastatic PD-L1-positive NSCLC in adults who have had at least one chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour)	2L Stage IV setting: Locally advanced or metastatic squamous NSCLC in adults after chemotherapy	2L Stage IV setting: Locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy	2L Stage IV setting: Locally advanced or metastatic NSCLC in adults who have had chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour)	Stage III: Locally-advanced, unresectable Stage III NSCLC patients whose tumours express PD-L1 on ≥1% TCs and whose disease has not progressed following ≥2 overlapping cycles of CRT	In line with the anticipated EMA Marketing Authorisation
Time horizon	Lifetime (20 years)	Lifetime (20 years)	Lifetime (20 years)	Lifetime (20 years)	Lifetime (25 years)	Lifetime (40 years); in the economic model, <1% of patients on durvalumab are alive at 40 years	Lifetime time horizon is required to capture all differences in treatment arms. Stage III setting is associated with much longer survival than metastatic setting so a longer time horizon is required to capture all differences

	Previous immunotherapy appraisals in advanced metastatic Stage NSCLC					Current appraisal	
Factor	**TA447 (2017) / TA531 (2018) [CDF review] pembrolizumab**	**TA428 (2017), pembrolizumab**	**TA483 (2017), nivolumab**	**TA484 (2017), nivolumab**	**TA520 (2018), atezolizumab**	**Chosen values**	**Justification**
Model structure	Three-state partitioned survival model	Three-state partitioned survival model	Three-state partitioned survival model	Three-state partitioned survival model	Three-state partitioned survival model	Three-state semi-Markov model	Independently fitting PFS and OS curves produces logical inconsistencies
Treatment waning effect	Manufacturer: Treatment effect up to 5 years NICE committee: Accepted company scenarios as plausible	Manufacturer: Lifetime treatment effect (20 years) NICE committee: Unclear	Manufacturer: Lifetime treatment effect (20 years) NICE committee: 3 years treatment effect	Manufacturer: Lifetime treatment effect (20 years) NICE committee: 3 years treatment effect	Manufacturer: Lifetime treatment effect (20 years) NICE committee: Up to 5 years after treatment has been stopped	Up to 10 years	Supported by evidence from PACIFIC study. Aligned with accepted level of benefit of immunotherapies in the metastatic setting, accounting for increased potential for survival in Stage III NSCLC. See section B.3.3.
Treatment duration	Stopped at two years of uninterrupted treatment and no documented disease progression	Stopped at two years of uninterrupted treatment and no documented disease progression	Stopped at two years of uninterrupted treatment and no documented disease progression	Stopped at two years of uninterrupted treatment and no documented disease progression	Stopped at two years of uninterrupted treatment and no documented disease progression	Stop at one year of uninterrupted treatment and no documented disease progression	Aligned with PACIFIC study design

	Previous immunotherapy appraisals in advanced metastatic Stage NSCLC					Current appraisal	
Factor	**TA447 (2017) / TA531 (2018) [CDF review] pembrolizumab**	**TA428 (2017), pembrolizumab**	**TA483 (2017), nivolumab**	**TA484 (2017), nivolumab**	**TA520 (2018), atezolizumab**	**Chosen values**	**Justification**
Source of utilities	EQ-5D data from KEYNOTE-010[73]	EQ-5D 3L data from KEYNOTE-024.[96] The ERG noted that the utility values derived from KEYNOTE-024 were implausibly high*	EQ-5D data from CheckMate 017.[95] Utility decrements were obtained from external sources rather than CheckMate 017	EQ-5D data from CheckMate 057 study.[94] Assumptions and values reported in the NICE appraisal of nintedanib in NSCLC [TA347][35]	EQ-5D data from OAK[§ 98]	EQ-5D-5L mapped to EQ-5D-3L from PACIFIC (PD-L1 ≥1% group)	Most relevant dataset; no other sources of evidence available in population of interest
Source of costs	Drug costs obtained from eMit. Weight distribution in KEYNOTE 010 used to estimate drug cost per patient[±].[73]	Resource use and costs based on KEYNOTE-024 data.[96] NHS reference costs, published data [142], and clinical expert opinion used	Resource use and costs based on CheckMate 017 data.[95] Previous NICE TAs, NHS reference costs, and clinical expert opinion used	Cost and resource use informed by from NICE TAs in this indication (including TA162, TA175, TA347, and TA374), clinical expert opinion, PSS unit costs, and NHS reference costs	Drug acquisition costs from eMit. Costs / resource use also informed by nivolumab [TA483][27] and pembrolizumab [TA428][26] TAs, PSS unit costs, NHS reference costs, and RWD study conducted by manufacturer.[143, 144]	NHS reference costs and other relevant sources	Standard UK data sources

Key: AE, adverse event; ALK, anaplastic lymphoma kinase; CDF, Cancer Drugs Fund; CRT, chemoradiation therapy; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; EQ-5D, EuroQol 5-dimension; EQ-5D-3L, EuroQol 5-dimension, 3-level health state utility index; EQ-5D-5L, EuroQol 5-dimension, 5-level health state utility index; ERG, Evidence Review Group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PSS< Personal Social Services; RWD, real-world data; TA, technology appraisal; TC, tumour cell.
Notes: *The ERG conducted an exploratory analysis limiting the magnitude of the utility values used in the model so that they were no higher than the UK population norm for people of the same age. §Utilities were divided in to categories reflecting the time to death (≤5 weeks before death; 5 and ≤15 weeks before death; 15 and ≤30 weeks before death; >30 weeks before death) and applied these in addition to the on-treatment and off-treatment health states. ±Resource use data per health state obtained from TA347.[35] Costs related to the unit management of AEs were derived from TA374.[35]

B.3.3. Clinical parameters and variables

To estimate PFS and PPS over the 40-year time horizon, parametric survival curves were fitted to patient level data from the PACIFIC PD-L1 ≥1% group and use to extrapolate survival beyond study follow-up. All data were taken from the latest 22 March 2018 DCO. In the PACIFIC study, 24.2% of patients in the placebo arm (PD-L1 ≥1% group) went on to receive subsequent immunotherapy, which is broadly reflective of UK clinical practice (clinical expert opinion suggests that ~30% of Stage III patients would receive subsequent immunotherapy upon progression to advanced metastatic disease [AstraZeneca data on file][44]; Section B.2.6). Therefore, no formal adjustment for treatment switching was included in the economic model for the base case analysis. Alternative settings were tested in sensitivity analyses (section B.3.8).

Approach to parametric survival analysis

The process for fitting parametric survival curves to patient level data was based on methods guidance from the DSU commissioned by NICE.[145] The following parametric distributions were considered in the analysis: exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma.

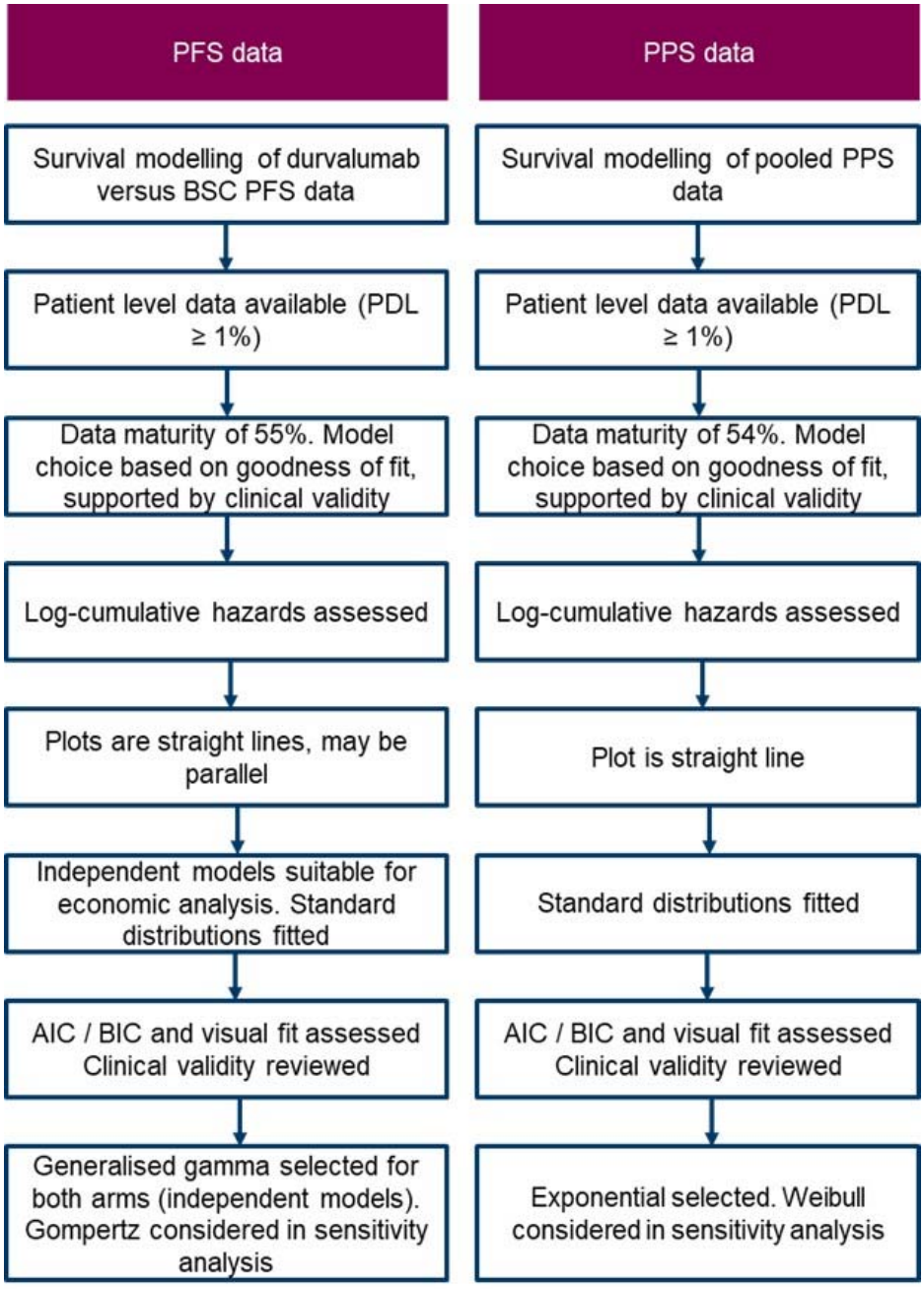
Spline models and more-flexible piecewise modelling approaches were explored, if required, based on the fit of the standard distributions listed above and the shape of the hazard function. None of the models considered here included covariates for patient characteristics as demographics and baseline disease characteristics were well-balanced in the PD-L1 ≥1% group (section B.2.3). Following guidance from the NICE DSU, “best fitting” models were chosen based on assessment of:

- Internal validity
  - Internal goodness of fit of the parametric models using BIC and Akaike Information Criterion (AIC)
  - Visual inspection of the fit of the model to KM-curves
- External validity
  - Assessment of the clinical plausibility of modelled extrapolations
  - Comparison of outcomes against survival data available from PACIFIC, the wider clinical literature, UK real-world evidence, and clinical expert opinion.

Overview of results

Figure 30 shows the 'survival model selection for economic evaluation' process charts for PFS and PPS endpoints. Further detail on model selection is provided in subsequent sections.

Figure 30: Survival model selection for economic evaluation Process Chart



Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; SoC, standard of care; PDL, programmed cell death ligand 1; PFS, progression-free survival; PPS, post-progression survival.

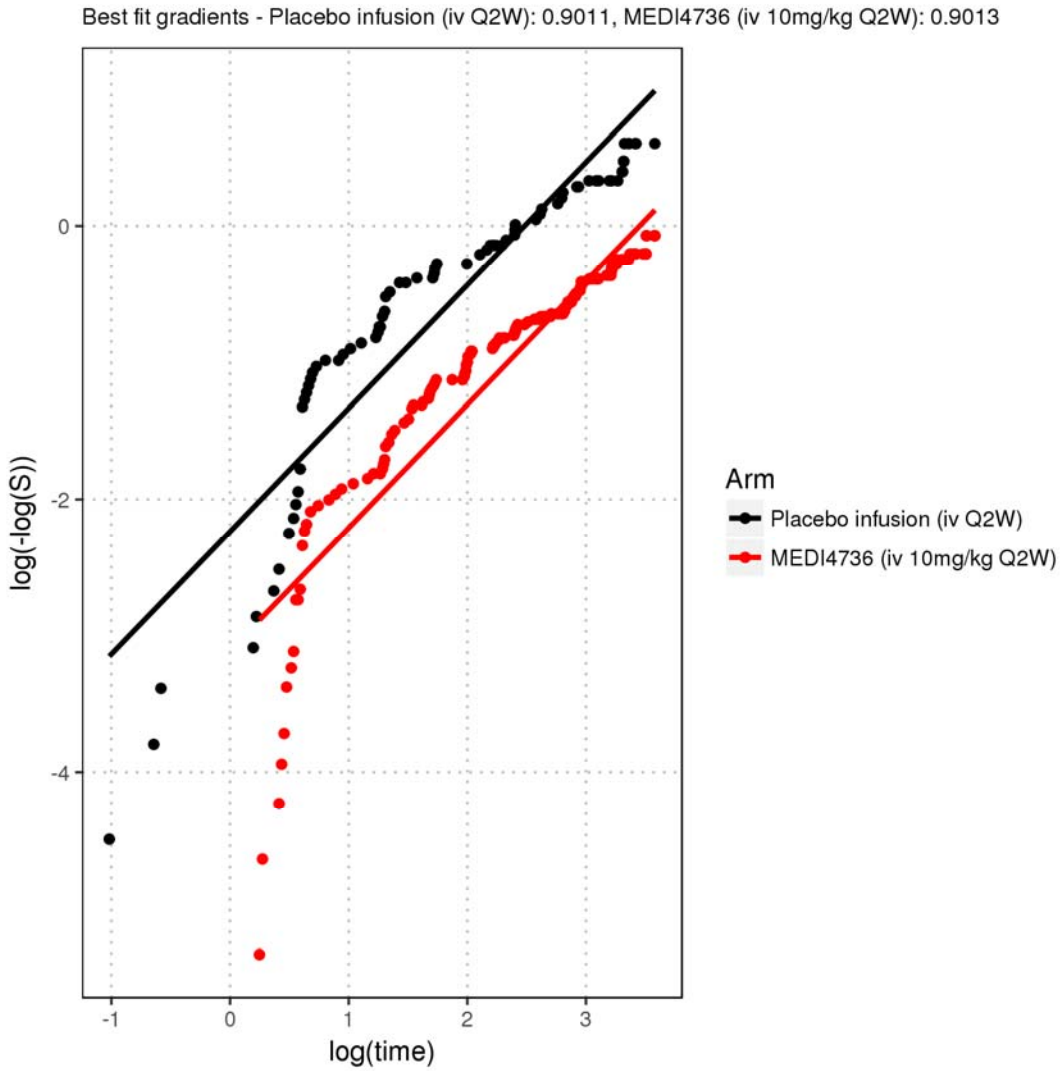
Progression-free survival

The PFS analysis was conducted on the latest data cut (22 March 2018). At this time, 47% and 73% of patients in durvalumab and placebo arms, respectively (PD-L1 ≥1% group), had experienced disease progression or died.

Choice of method

The choice of modelling approach (proportional effects versus independent models) was based on an assessment of the relative proportionality of the cumulative hazard rates for durvalumab and placebo arms of the PACIFIC PD-L1 ≥1% group (Figure 31).

Figure 31: Cumulative hazards plot of PFS; PACIFIC PD-L1 ≥1% group



Key: iv, intravenous; MEDI4736, durvalumab; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; Q2W, every 2 weeks.

As illustrated in Figure 31, the lines on the cumulative hazards plot are parallel for the time where most events occur, suggesting that the proportional hazards assumption may be reasonable. However, the best fitting curve with this assumption showed bad visual fit to the control arm. In addition, 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. The latter (i.e. independent models) was thus explored for the base case analysis.

Within-trial goodness of fit for PFS curves

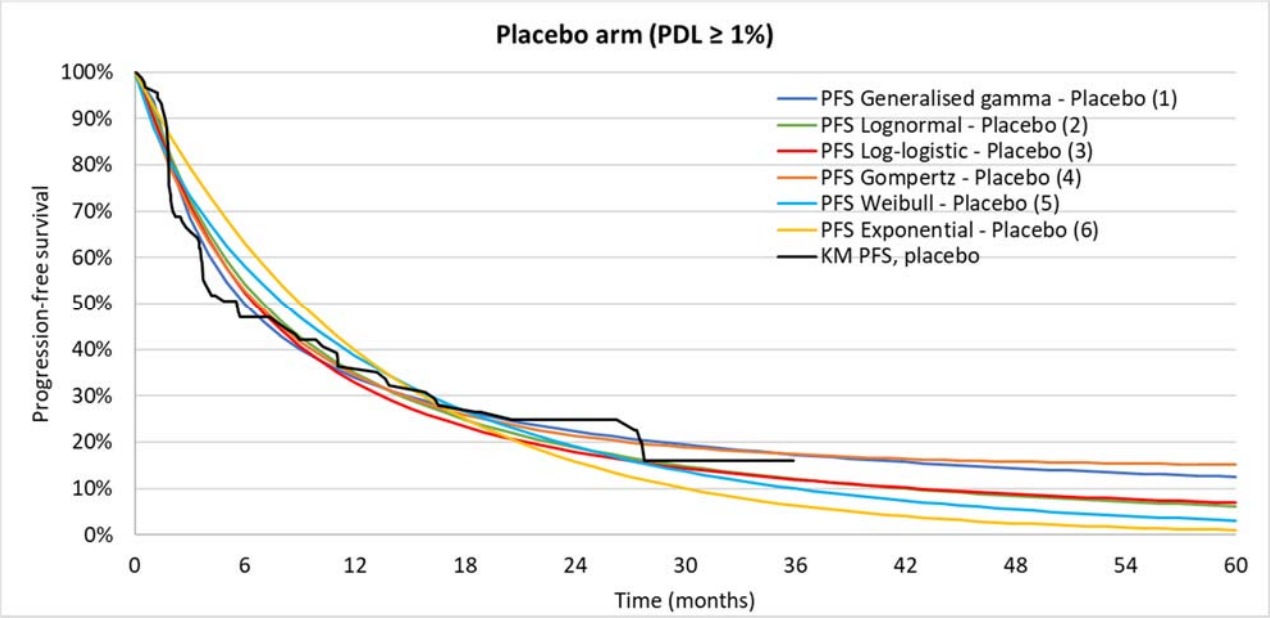
A summary of the AIC and BIC goodness of fit statistics for each distribution explored is provided in Table 30. A plot of the survival functions is shown in Figure 32 and Figure 33 for visual assessment of fit; the predicted survival is shown in Table 31.

Table 30: Summary of goodness of fit data for the parametric survival analysis of PFS data

Distribution	Durvalumab		Placebo	
	AIC	BIC	AIC	BIC
Exponential	880.47	883.83	472.69	475.20
Generalised Gamma	**830.33**	**840.40**	**448.85**	**456.38**
Gompertz	867.34	874.05	460.98	466.00
Log-logistic	869.38	876.10	458.26	463.28
Log-normal	860.46	867.18	454.51	459.53
Weibull	877.55	884.26	469.44	474.47

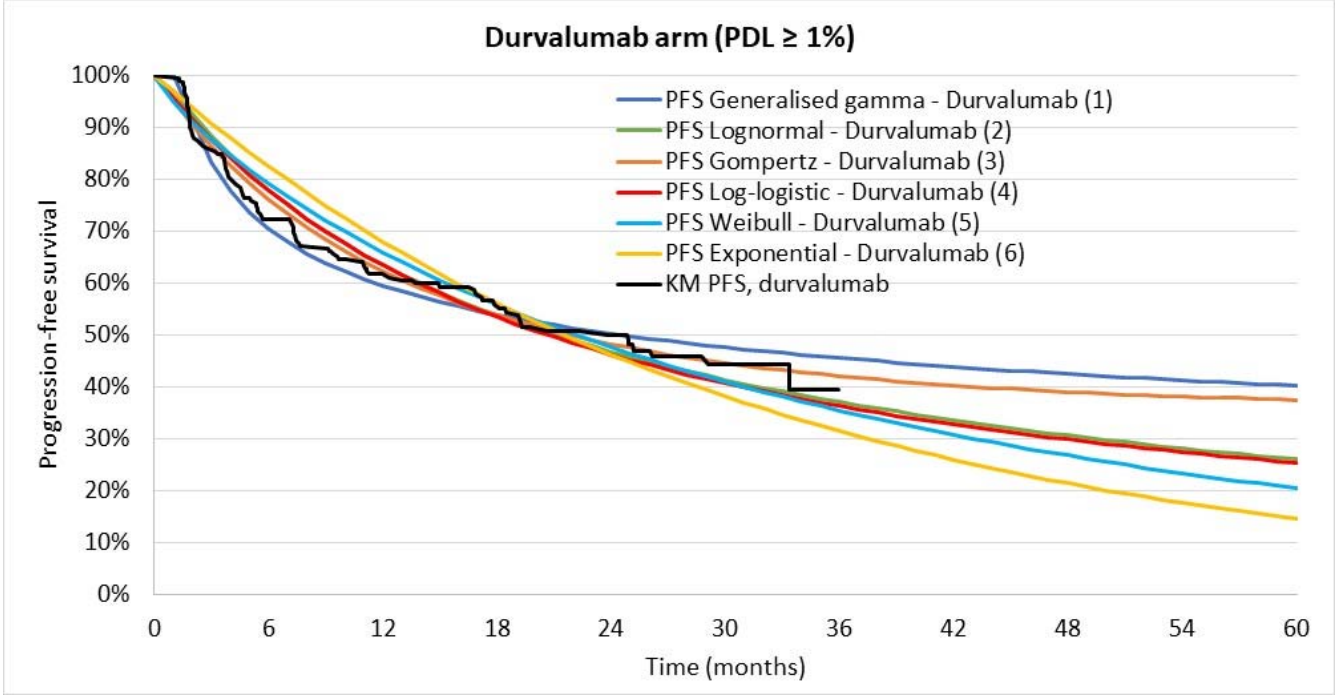
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
Note: Bolded values indicate the best scores.

Figure 32: Visual fit of PFS parametric functions to PACIFIC data; placebo arm, PD-L1 ≥1% group



Key: KM, Kaplan–Meier, PDL, programmed cell death ligand 1; PFS, progression-free survival.
Note: Statistical fit order shown in legend according to Akaike information criterion (AIC).

Figure 33: Visual fit of PFS parametric functions to PACIFIC data; durvalumab arm, PD-L1 ≥1% group



Key: KM, Kaplan–Meier, PDL, programmed cell death ligand 1; PFS, progression-free survival.
Note: Statistical fit order shown in legend according to Akaike information criterion (AIC).

Table 31: Comparison of predicted PFS against data from PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Distribution (fit*)	% PF 1 year		% PF (2 years)		% PF (3 years)	
	Durvalumab	Placebo	Durvalumab	Placebo	Durvalumab	Placebo
PACIFIC study	**61.6% At risk (106)**	**36.4% At risk (27)**	**49.9% At risk (57)**	**24.8% At risk (15)**	**39.4% [1] At risk (1)**	**16.0% [2] At risk (1)**
Generalised Gamma (1)	59.8%	34.4%	50.5%	22.6%	45.7%	17.5%
Log-normal (2)	64.0%	35.5%	47.3%	19.3%	37.4%	12.3%
Gompertz (3)	62.8%	35.0%	48.6%	21.7%	42.2%	17.4%
Log-logistic (4)	63.9%	33.5%	46.8%	18.2%	36.6%	12.1%
Exponential (5)	68.6%	40.6%	47.0%	16.5%	32.0%	6.6%
Weibull (6)	66.4%	39.3%	48.3%	19.6%	35.9%	10.3%

Key: DCO, data cut-off; PD-L1, programmed cell death ligand 1; PF, progression-free; PFS, progression-free survival.
Notes: Numbers in brackets (1−6; column 1) refer to statistical goodness-of-fit. Modelled values are shown at closest model cycle (14 / 28 days) to time point. *By Bayesian information criterion (BIC), [1]at 35.94 months, [2]at 35.88 months.

The generalised gamma, log-normal and Gompertz curves are visually good fits. The generalised gamma function has the best statistical fit, based on AIC and BIC scores. Compared to PACIFIC study data, these curves generally perform well. At three years, the generalised gamma and Gompertz curves may overestimate PFS, although the data from PACIFIC is only based on one patient at this point and so caution should be taken when making comparisons (Table 31).

The corresponding hazard functions for PFS showed similar behaviour for all functions and between arms - an initially high hazard peaking at 2−3 months, which then decreased for the rest of time.

External validity of extrapolated PFS (SoC)

Several parametric survival functions produced a good fit to the PACIFIC data (generalised gamma, log-normal, and Gompertz). To further assess the clinical validity of the extrapolated curves (particularly long-term outcomes), they were compared against other relevant clinical studies, UK real-world data, and estimates of PFS sourced from clinical experts (Table 32).

Clinical experts stated that they would expect to see ~15% of patients PF at five years on SoC, consistent with historical data that shows that a small percentage of patients respond very well to SoC overlapping CRT.[146] Clinical experts also confirmed that the decreasing hazard functions for PFS made sense clinically, adding that they would expect that the majority of progression events to occur within the first two years.[115]

Table 32: Comparison of extrapolated PFS outcomes on SoC against other clinical sources (survival measured from completion of CRT)

PFS	Median (months)	1 year	2 years	3 years	5 years	10 years	15 years	20 years
Modelled								
Exponential	9.2	41%	16%	7%	1%	0%	0%	0%
Generalised Gamma	**6.0**	**34%**	**23%**	**17%**	**13%**	**8%**	**6%**	**5%**
Gompertz	6.4	35%	22%	17%	15%	14%	12%	9%
Log-logistic	6.4	33%	18%	12%	7%	3%	2%	1%
Log-normal	6.9	35%	19%	12%	6%	2%	1%	1%
Weibull	8.3	39%	20%	10%	3%	0%	0%	0%
Observed data from the PACIFIC study								
ITT	5.6	34%	24%	-	-	-	-	-
PD-L1 ≥1% group	5.6	36%	25%	16%*	-	-	-	-
Historical RCT data								
START[a]	8.3	42%	25%	20%	15%	-	-	-
GILT[b]	5.5	28%^	20%^	16%^	10%^	-	-	-
HOG LUN 01-24[c]	10.3	47%^	30%^	20%^	14%^	-	-	-
Carter 2012[d]	10.2	46%	32%	25%	25%	-	-	-
UK clinical expert opinion (AstraZeneca data on file)								
Estimates for PACIFIC ITT population[e,146]	-	-	-	-	15%	9%	-	-

Key: CRT, chemoradiation therapy; ITT, intention to treat; KM, Kaplan–Meier; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RCT, randomised controlled trial; SoC, standard of care; -, not available.
Notes: *At 35.88 months. **At 35.94 months, ^digitised from source. Modelled values are shown at closest model cycle (14/28 days) to time point.
Sources: a, START[109, 110], ITT, KM data digitised, patients randomised upon completion of CRT; b, GILT[147], concurrent (overlapping) cisplatin + vinorelbine (pre-randomisation) followed by SoC, survival measured from randomisation on completion of concurrent cisplatin + vinorelbine therapy. Landmarks digitized from published KM curves, c, HOG[114], concurrent etoposide + cisplatin (pre-randomisation) followed by observation, survival measured from randomisation on completion of concurrent etoposide + cisplatin. Landmarks digitised from published KM curves. d, Carter, 2012[148], induction or concurrent paclitaxel + carboplatin (pre-randomisation) followed by observation, survival measured from randomization on completion of induction or concurrent paclitaxel + carboplatin. Landmarks obtained from publication, e, AstraZeneca data on file[146]

Choice of PFS curve for SoC

Considering both within-trial and external validity, the generalised gamma distribution was chosen for the base case analysis for SoC arm. This curve is considered the most appropriate and plausible survival curve for SoC due to:

- Excellent within-trial goodness of fit with PACIFIC data (best fitting curve).
- Consistency with other clinical data and clinical expert opinion at five years.[146]
- A plausible survival tail from five to 20 years and clear clinical rationale for long-term hazard function observed.

Sensitivity analysis was conducted using other clinically plausible parametric functions (Gompertz). It should be noted that no previous NICE appraisals for immunotherapies have evaluated PFS in locally-advanced, unresectable, Stage III NSCLC patients; therefore, there is no precedence for survival curves used for decision-making for PFS.

Choice of PFS curve - durvalumab

DSU TSD 14 recommends applying the same type of structural model for treatment and placebo, when applying independent models.[145] In addition, the generalised gamma distribution showed excellent with-trial goodness of fit to the durvalumab arm. Therefore, this was chosen for the base case analysis for the durvalumab arm. Sensitivity analysis was conducted using other parametric functions (log-normal and Gompertz).

Long term treatment effect of durvalumab

In line with DSU and NICE guidelines[140], the economic model includes an option to explore different cut-off points for the treatment effect of durvalumab. From this point onwards, the treatment benefit for durvalumab is removed and the PFS hazard is set to equal the SoC arm for the remainder of the model time horizon.

Evidence from PACIFIC supports a durable and sustained treatment benefit of durvalumab treatment, which is observed beyond the discontinuation of treatment and throughout study follow-up. At the time of the primary OS analysis (22 March 2018 DCO), maximum duration of follow-up was 40.5 months and 41.0 months in the durvalumab and placebo arms, respectively (PD-L1 ≥1% group).

In the base case, the treatment benefit cut-off point for durvalumab was set at 10 years (i.e. at this point, the model assumes that the hazard ratio for progression and death become identical between the two arms). This cut-off point gives valid OS estimates for durvalumab (see Table 34 and Table 35 below), which are in line with the survival **benefit** provided in Company submissions for other immunotherapies in the advanced metastatic Stage IV NSCLC setting. For instance, in TA483[26] (second-line advanced metastatic squamous NSCLC), nivolumab treatment produced up to 5-times greater OS benefit relative to docetaxel. At 15 years, nivolumab still tripled the long-term survival benefit versus docetaxel. In TA484[85] (second-line advanced metastatic non-squamous NSCLC), nivolumab ~quadrupled long-term survival benefit at 10 years versus to docetaxel (further details shown in Table 35).

Pre-progression mortality

The PFS curve is used to determine the rate at which patients leave the PF health state. These patients could either have experienced disease progression (i.e. transitioned to PD) or died.

To determine the proportion of patients who transition to PD in each cycle, parametric curves were fitted to TTP data (where deaths were censored) (Appendix M. The transition probability of patients moving from PF to PD was calculated as 1 – probability of remaining progression-free. In the base case analysis, the TTP distribution was set to the same as for PFS (i.e. generalised gamma).

This approach was chosen because at the time of the latest DCO (22 March 2018), only a small number of patients in the PD-L1 ≥1% group in the PACIFIC study died before progression: 13 patients in the durvalumab arm, and 8 patients in the placebo arm among uncensored PFS events[149], making parametric fits to PFS and TTP very similar (Appendix M).

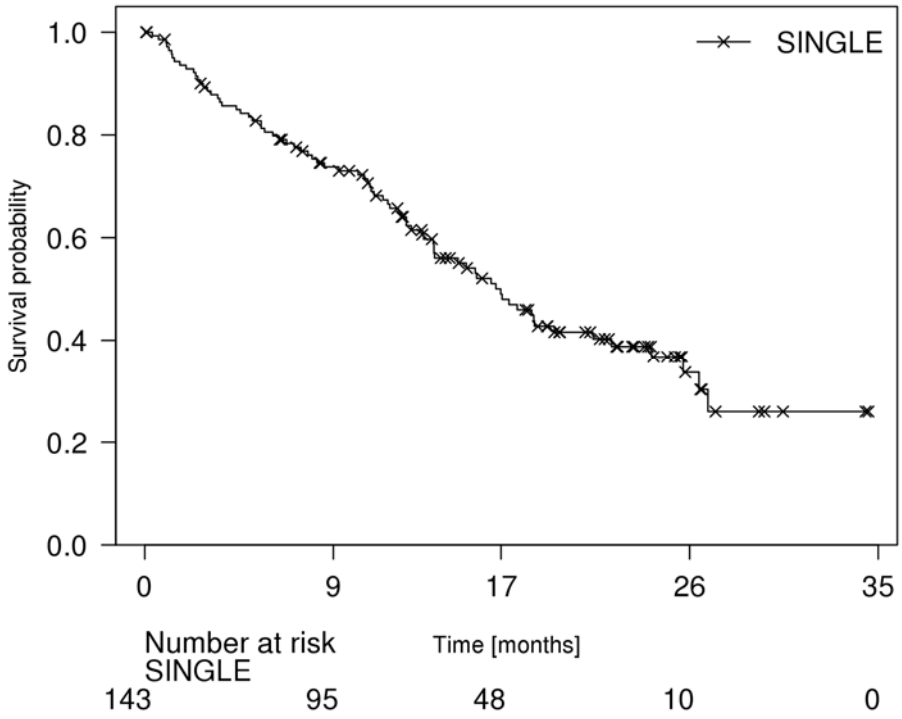
Post-progression survival (PPS)

The PPS analysis was conducted on the latest data cut from PACIFIC (22 March 2018). At this time, this data was 55% mature in the PD-L1 ≥1% group.

For the economic analysis, the PPS data was pooled across both arms (Figure 34). This increases the power, and therefore decreases the uncertainty of the parametric

models fit to these data. The cost-effectiveness model thus assumes that PPS is equal for both treatment arms. This is a conservative assumption given the separation in the KM curves observed in the PPS data from 13 months onwards, in favour of durvalumab (Figure 14).

Figure 34: Pooled post-progression survival (PPS; durvalumab and placebo); PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

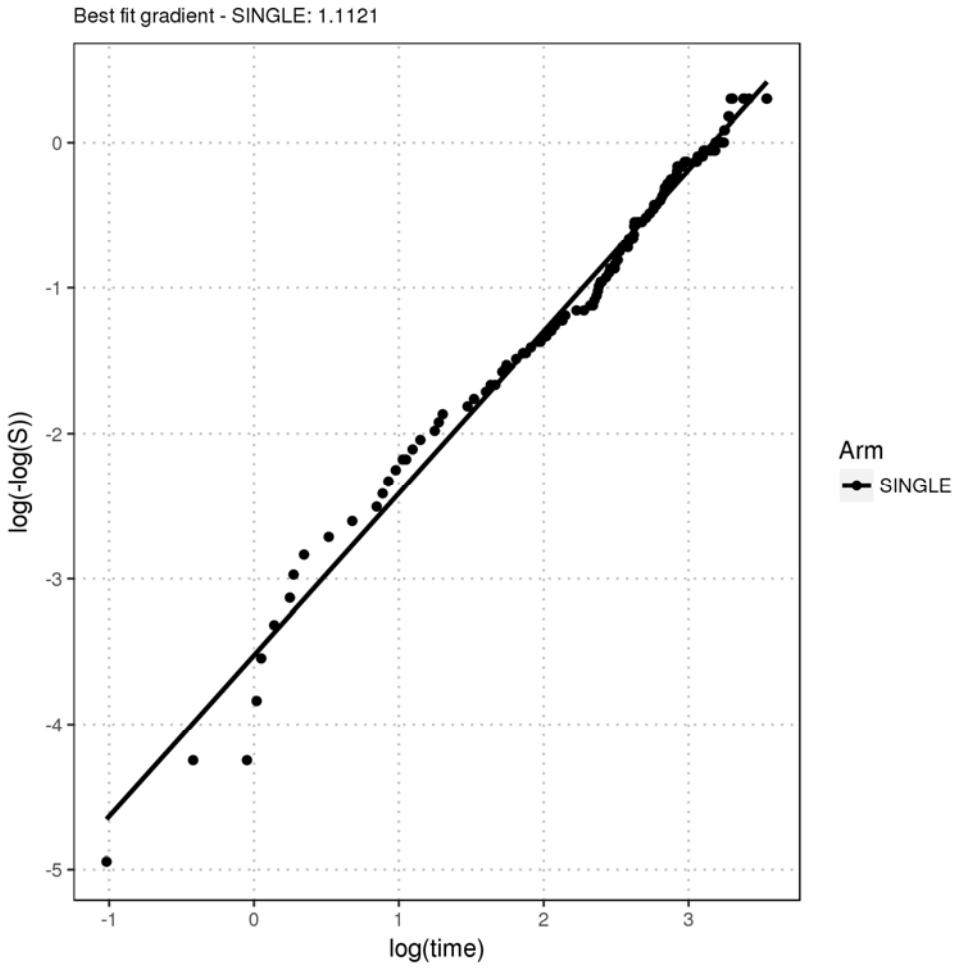


Key: DCO, data cut-off; PD-L1, programmed cell death ligand 1; PPS, post-progression survival.

Choice of method

The log-log plot for pooled PPS is presented in Figure 35.

Figure 35: Log-cumulative hazard plot of post-progression survival (PPS; durvalumab and placebo); PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)



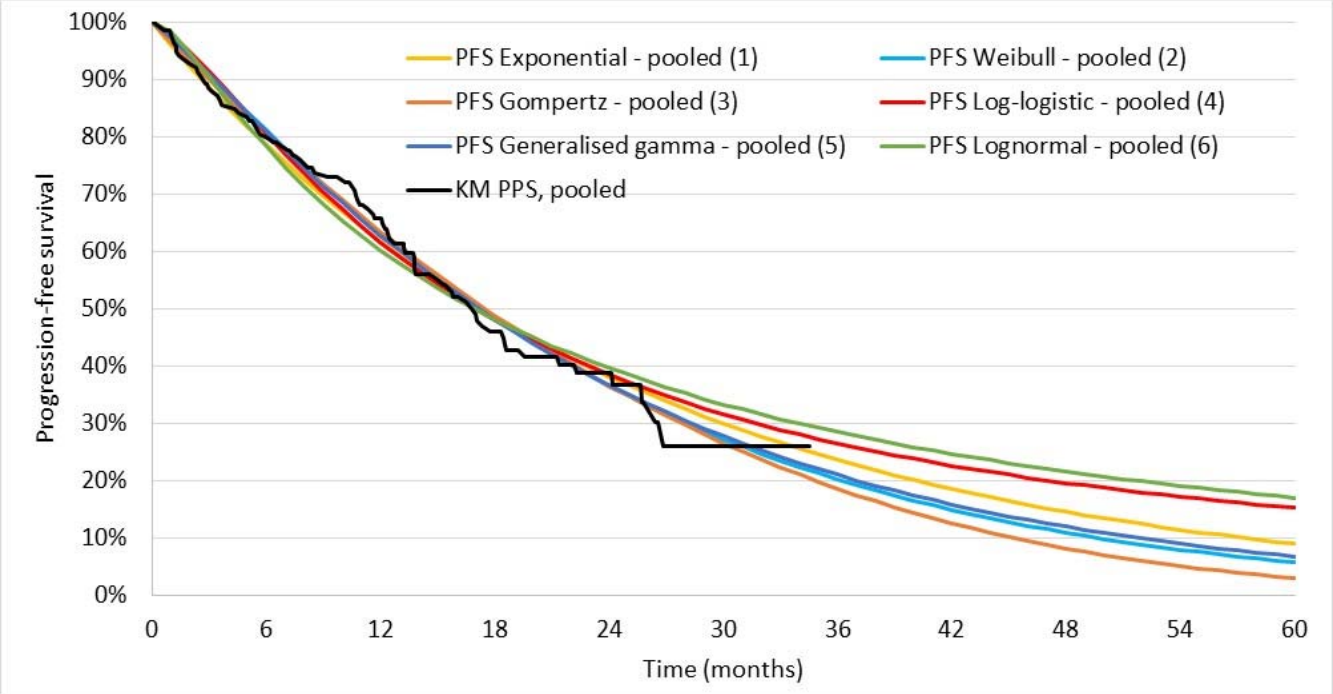
Key: DCO, data cut-off; PD-L1, programmed cell death ligand 1; PPS, post-progression survival.

The straight line indicates that no piecewise or other more-flexible models are required in this case.

Within-trial goodness of fit for the pooled (durvalumab + placebo) PPS curve

All parametric curves had a good visual fit to the data (shown in Figure 36). Based on AIC and BIC, the exponential curve had the best statistical fit to PACIFIC data (Table 33).

Figure 36: PPS KM and stratified extrapolation curves; PACIFIC PD-L1 ≥1% group (durvalumab and placebo pooled)



Key: KM, Kaplan–Meier, PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PPS, post-progression survival.
Note: Statistical fit shown in legend according to Akaike information criterion (AIC).

Table 33: Extrapolation AIC and BIC scores for PPS; PACIFIC PD-L1 ≥1% group (durvalumab and placebo pooled)

Distribution	AIC	BIC
Exponential	**651.39**	**654.35**
Weibull	651.84	657.76
Gompertz	652.33	658.26
Log logistic	653.48	659.41
Generalized Gamma	653.80	662.69
Log normal	655.29	661.22

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PD-L1, programmed cell death ligand 1; PPS, post-progression survival.
Note: Bolded values indicate the best scores.

External validity of PPS curve

The exponential curve was chosen to model PPS for both arms in the base case analysis, as it produced clinically plausible OS estimates (see below). An exponential distribution also aligns with evidence from immunotherapy appraisals in the advanced

metastatic NSCLC setting, where NICE has previously accepted an exponential distribution as the most appropriate curve to model long-term survival. Although not every locally-advanced Stage III NSCLC patient will experience disease progression to advanced metastatic NSCLC, long-term survival could be expected to follow the profile of patients with metastatic disease.

Sensitivity analysis – alternative PPS extrapolation (using START and KEYNOTE-024 data)

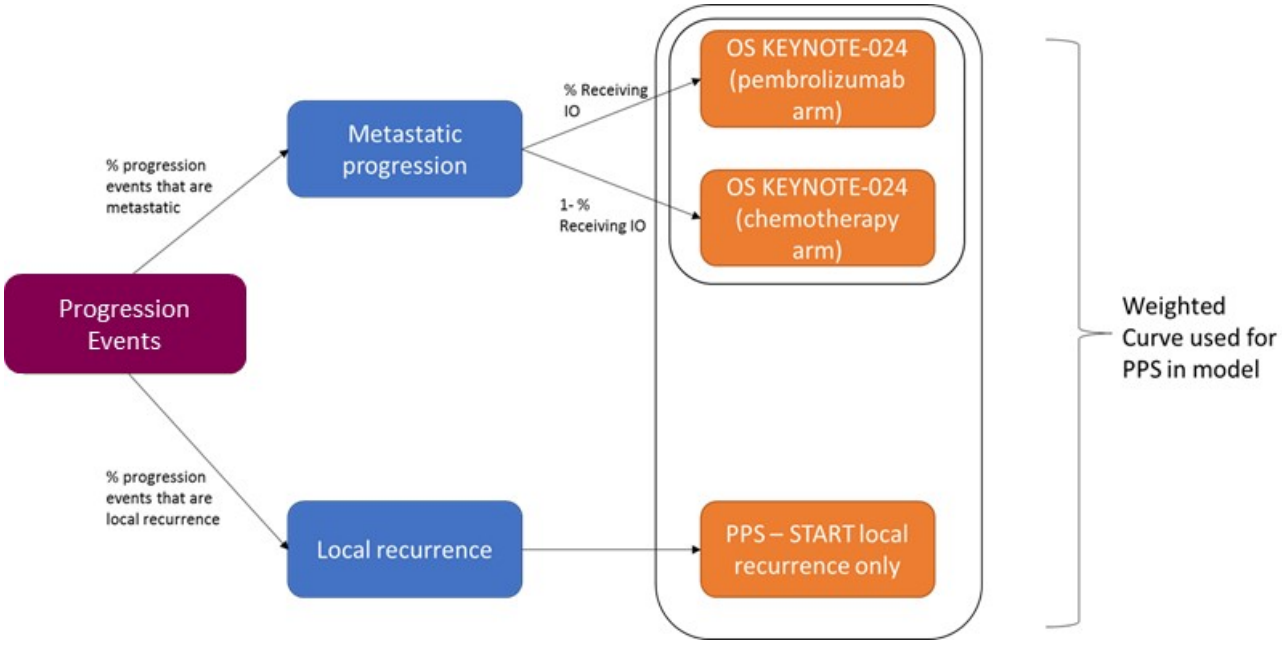
An alternative method for calculating **PPS** was used, based on published data from the KEYNOTE-024 and START studies. **This curve was used to explore the impact of differing levels of subsequent immunotherapy use in sensitivity analyses** (see Section B.3.8). No formal adjustment for treatment switching was included in the base case analysis of the economic model.

- To understand PPS in locally-advanced, unresectable, Stage III NSCLC patients who experience disease progression with **local recurrence**, PPS data from a subset of patients in the START study (who experienced local disease recurrence) were used. START is an international, randomised, double-blind Phase III trial that compared the efficacy and safety of tecemotide therapy versus placebo in locally-advanced Stage III NSCLC patients who had completed CRT (identified in the clinical SLR, see Section B.2.1 and Appendix D). The START and PACIFIC trials are similar in design and conducted in similar patient populations- patient characteristics for the two trials are comparable in terms of age, gender, histology, smoking status, WHO PS, and disease stage. Importantly, the START trial has a longer follow-up time (six years) than PACIFIC (maximum follow-up ~41 months), making it the most robust alternative source of PPS in Stage III NSCLC patients who develop local disease recurrence. One important limitation of START PPS data, however, is that it does not capture the impact of subsequent immunotherapy (since the trial was conducted at a time when these treatments were not available for treating advanced metastatic disease).
- To understand PPS of patients who develop **advanced metastatic** disease, OS data from the KEYNOTE-024 study were used. KEYNOTE-024 is a Phase III trial that evaluated the efficacy of pembrolizumab versus SoC chemotherapy in **previously untreated** advanced metastatic (Stage IV) NSCLC patients whose

tumours express PD-L1 on ≥50% of TCs and who have no sensitising mutation of the *EGFR* gene or translocation of the *ALK* gene.[96] Pembrolizumab is SoC for patients for untreated metastatic NSCLC with PD-L1 expression on ≥50% TCs; chemotherapy is still SoC for *EGFR*- or *ALK*- mutation-negative metastatic NSCLC patients with PD-L1 expression on <50% of TCs.[46] OS data from KEYNOTE-024 is the most up to date alternative data source to estimate PPS in locally-advanced, Stage III NSCLC patients who develop advanced metastatic disease. Since, not all patients are eligible to receive pembrolizumab, an adjusted KEYNOTE-024 curve was derived by weighting the hazards according to the proportion of patients with metastatic progression who are expected to receive pembrolizumab as subsequent therapy (Figure 37). More details can be found in Appendix N.

An **overall weighted PPS curve** was then derived, by weighting both the KEYNOTE-024 curve (for advanced metastatic disease) and the START PPS curve (for local recurrence), by the proportion of progression events in PACIFIC that were metastatic (37%; based on ITT), as illustrated in Figure 37. This PPS curve was used in scenario analyses, as a basis to explore the impact of varying levels of subsequent immunotherapy use in placebo and durvalumab arms, in the economic model (section B.3.8).

Figure 37: Weighting START and KEYNOTE-024 data to estimate the PPS curve based on metastatic progressions and local recurrences



Key: IO, immuno-oncology therapy; OS, overall survival; PPS, post-progression survival.

General population mortality

General population mortality was taken from the English National Life Tables of the Office for National Statistics.[150] A mortality rate is calculated for each model cycle based on the age and sex distribution of the PACIFIC trial cohort.

If the mortality rate predicted from the OS extrapolation falls lower than the age-adjusted general population mortality rate, the model caps mortality rates at the age-adjusted general population level. This ensures clinical validity of all the mortality rates that occur throughout the model.

Validation of overall survival predictions (for durvalumab and SoC)

Table 34 shows the predicted OS for durvalumab and SoC from the economic model, compared against relevant clinical trials, UK real-world data, and clinical expert opinion. The modelled OS for SoC broadly matches survival from all available sources of evidence.

Table 35 shows the predicted OS for durvalumab versus SoC, compared to values accepted by NICE for immunotherapies in the advanced metastatic NSCLC setting. Although these are distinct populations and disease stages, the illustrative comparison shown in Table 35 reiterates that the base case economic model for durvalumab is predicting a treatment effect in line with that seen for other immunotherapies and accepted by NICE, when accounting for the greater potential for long-term survival in locally-advanced, Stage III NSCLC patients who can be treated with curative intent.

Table 34: Comparison of extrapolated OS outcomes against other clinical sources (survival measured from completion of CRT)

	Median (months)	1 year	2 years	3 years	5 years	10 years	15 years	20 years
Standard-of-care								
Modelled	**28.5**	**77%**	**57%**	**42%**	**24%**	**10%**	**7%**	**5%**
PACIFIC (PD-L1 ≥ 1%)	29.1	75%	54%	42%	-	-	-	-
PACIFIC (ITT)	28.7	75%	56%	43%	-	-	-	-
START[1]	22.5	74%	46%	37%	20%	-	-	-
GILT[2]	18.5	67%*	42%*	28%*	18%*	-	-	-
HOG LUN 01-24[3]	26.1	66%*	49%*	26%	23%*	-	-	-
Carter 2012[4]	26.9	77%	58%	38%	-	-	-	-
UK RWE, Public Health England[5]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Clinical expert opinion[6]	-	75%	50%	38%	25%	10%	-	-
Durvalumab								
Modelled	**58.0**	**86%**	**73%**	**63%**	**49%**	**36%**	**27%**	**20%**
PACIFIC (PD-L1 ≥1% group)	NR	87%	73%	60%	-	-	-	-
PACIFIC (ITT)	NR	83%	66%	53%	-	-	-	-

Key: -, not available, CRT, chemoradiation therapy; ITT, intention to treat; KM, Kaplan–Meier; OS, overall survival; PD-L1, programmed cell death ligand 1; RWE, real-world evidence; SoC, standard of care.
Notes: Modelled values were informed by generalised gamma PFS distribution, followed by same PPS, including general mortality cap. Modelled values are shown at closest model cycle (14 / 28 days) to time point. *digitised from source.
Sources: 1, START[109, 110], KM data digitised; 2, GILT[147], concurrent cisplatin + vinorelbine (pre-randomisation) followed by SoC, landmarks digitised from publication; 3, HOG[114], concurrent etoposide + cisplatin (pre-randomisation) followed by observation, landmarks digitised from publication; 4, Carter, 2012[148], induction or concurrent paclitaxel + carboplatin (pre-randomisation) followed by observation, landmarks obtained from publication; 5, AstraZeneca data on file - Simulacrum[45]; 6, AstraZeneca data on file.[146]

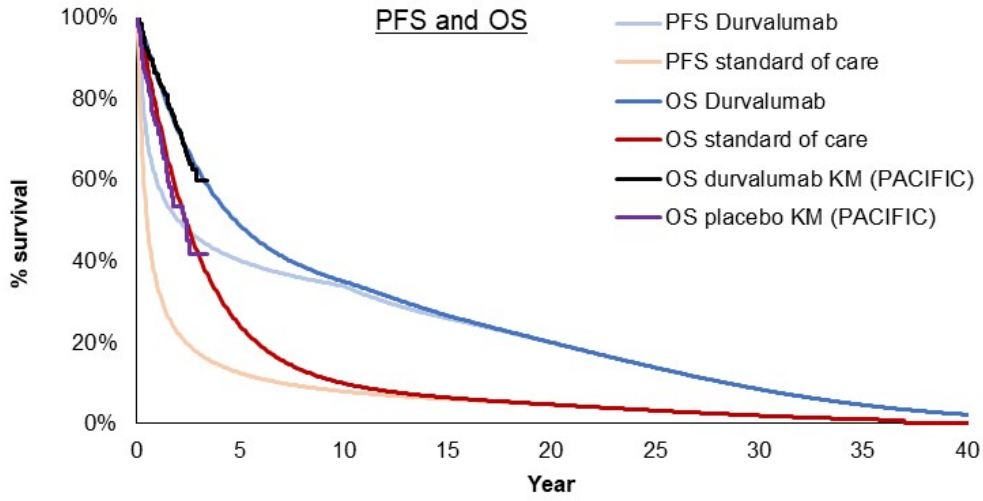
Table 35: Comparison of modelled OS versus NICE-accepted predicted OS gains for immunotherapies in advanced metastatic NSCLC

TA	Treatment	Setting	1 year	2 years	3 years	4 years	5 years	10 years	15 years
ID1175	Durvalumab	Stage III unresectable, PD-L1 ≥ 1%	86%	73%	63%	55%	49%	36%	27%
	Standard of care		77%	57%	42%	32%	24%	10%	7%
TA521[151]	Pembrolizumab	1L metastatic disease	~70%	~52%	-	-	-	-	-
	Standard of care		~55%	~35%	-	-	8–11%	-	-
TA428[26]	Pembrolizumab[a]	2L metastatic disease	~55%	-	-	-	10%	1%	-
	Standard of care[a]		~40%	~35%	<5%	<5%	<5%	<1%	<1%
TA483 / TA484[27, 86]	Nivolumab[b]	2L metastatic disease, squamous	42–43%	23–24%	12–16%	6–12%	3–10%	0–5%	0–3%
	Standard of care		24%	8%	6%	<5%	<5%	<1%	<1%
	Nivolumab[b]	2L metastatic disease, non-squamous	47–52%	27–28%	14–19%	7–14%	4–10%	0–4%	0–2%
	Standard of care		~40%	~10%	~5%	<5%	<5%	<1%	<1%
TA520[130]	Atezolizumab[c]	2L metastatic disease	-	29–30%	16–19%	8–13%	4–10%	-	-
	Standard of care		-	16–17%	7%	3–4%	1–2%	-	-

Key: - Not available (figures either not stated or redacted in NICE documents); 1L, first line; 2L, second line; ERG, Evidence Review Group; PD-L1, programmed cell death ligand 1; NICE, National Institute for Health and Care Excellence; OS, overall survival; NSCLC, non-small cell lung cancer; TA, technology appraisal.
Notes: All figures approximate.
[a]Company base case shown as NICE accepted values not stated explicitly.
[b]Range shown ERG estimates to company estimates (committee preferred intermediary curve between the two).
[c]Range shown ERG/committee estimates to company estimates.

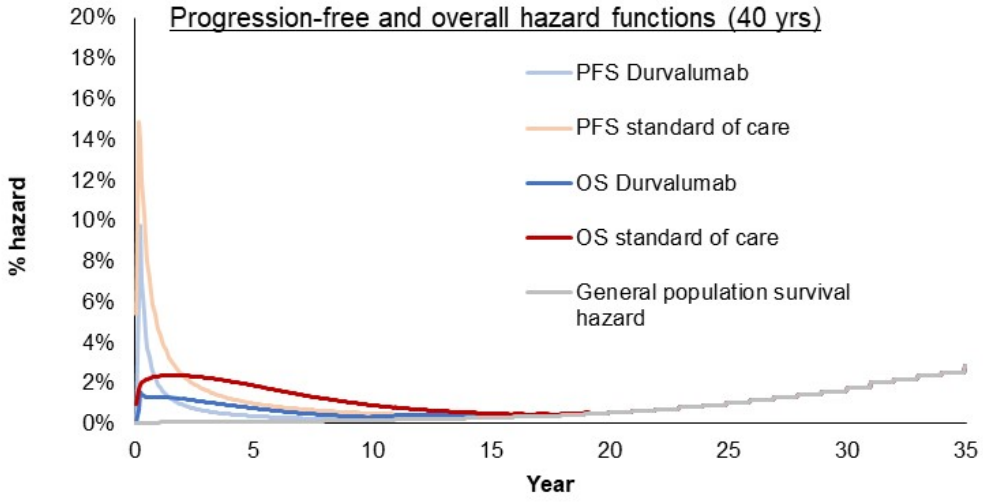
Figure 38 shows the final predicted survival (PFS and OS). Figure 39 shows the PFS and OS hazard functions (capturing the instantaneous rate of occurrence of the event conditional on having survived [for OS], or not progressed or died [for PFS], up until that point). Declining hazards for PFS indicate that the longer a patient has been progression-free, the less likely they are to experience disease progression. Similarly, declining hazards for OS indicate that the longer a patient has been alive, the less likely they are to die from cancer-related mortality. As can be seen from Figure 39, after 15−20 years, death is driven by general population mortality rates rather than within-trial predictions driven primarily by cancer deaths.

Figure 38: Predicted survival curves (40 years)



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

Figure 39: Predicted hazard functions (40 years)



Key: OS, overall survival; PFS, progression-free survival.

Adverse events (AEs)

Following assessment of PACIFIC data, a shortlist of key AEs was identified for inclusion in the economic model. Adverse events were chosen if they had a frequency of ≥2% in either arm in the PACIFIC study (PD-L1 ≥1% group), or if they were judged to have a sizable impact on either costs or HRQL. The final list of AEs included in the economic model is provided in Table 36. AE rates in the economic analysis were based on number of events (rather than number of patients, as is the case for data presented in Section B.2.10).

Table 36: Summary of adverse events considered in the economic model

Adverse event	Reason for inclusion	Number of events over study period (n)		Incidence per cycle (2-week), %	
		Durvalumab	SoC	Durvalumab	SoC
Anaemia	≥2% frequency, CTCAE Grade 3 or 4 in PACIFIC	6	4	0.001	0.002
Haemoptysis		0	2	0.000	0.001
Hypokalaemia		4	5	0.001	0.003
Pneumonia		12	5	0.003	0.003
Pneumonitis		6	1	0.001	0.001
Radiation pneumonitis		5	3	0.001	0.002
Endocrinopathy	High impact on cost	1	0	0.000	0.000

Key: CTCAE, common terminology criteria for adverse events; DCO, data cut-off; SoC, standard of care.
Source: PACIFIC PD-L1 subgroup analyses, 22 March 2018 DCO.[92]

AEs are modelled as a per-cycle occurrence while patients are on treatment. The likelihood of occurrence during each model cycle is based on the number times each AE occurred in the PACIFIC trial (see Table 36) and the total treatment years per arm (183.6 and 66.2 years, for durvalumab and placebo, respectively).

In the base case analysis, only the costs of AEs were included, since the utility data was sourced from the PACIFIC trial and would include any impact of AEs that occurred during the treatment phase. This assumption was tested in a sensitivity analysis (Section B.3.8).

B.3.4. Measurement and valuation of health effects

Health-related quality-of-life (HRQL) data from the PACIFIC study

Data from the health state utility questionnaire EQ-5D-5L were collected in PACIFIC study every 8 weeks for the first 48 weeks, and every 12 weeks thereafter until confirmed disease progression.

The EQ-5D is a standardised measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal.[152] The EQ-5D-5L descriptive system comprises the following five dimensions: mobility (MO), self-care (SC), usual activities (UA), pain / discomfort (PD) and anxiety / depression (AD). Each dimension has five response levels – no problems (1), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5) – that reflect increasing levels of difficulty.[153] The EQ-5D-5L is an expansion of the ED-5D-3L questionnaire, which had the option of three response levels, rather than five.

To derive utility scores for the economic model, analysis was conducted in three stages:

- **Exploratory analysis**: utility summaries were performed to determine the effect on utility of each covariate individually and to identify covariates to be considered for regression analysis. The following potential prognostic factors were explored using descriptive summaries:
  - Treatment (durvalumab or placebo)
  - Analysis Visit (Baseline, Week 4, Week 8, Week 16, etc.)
  - Age (<65 years or ≥ 65 years)
  - Health state (pre-progression or post-progression)[y]
  - Time to death (or censored date), defined based on the OS date (≤30 days, 30–179 days, 180–359 days, ≥ 360 days)

[y] Pre-progression includes all observations prior to date of progression or death (baseline utility observations were excluded from pre-progression summaries). Post-progression includes observations on and after date of progression or death; records on and after a censored date of progression are not used in some analyses (the inclusion or exclusion of these records are specified for each analysis). Progression was defined based on BICR assessment of PFS.

- **Mixed effects modelling**: mixed effects models were derived to estimate utilities adjusted for covariates, and for repeated measures within subjects.
  - A random effect for patients was also included in the models to adjust for the correlation between multiple observations from the same patient. The model selection process explored simple models (including only one covariate) through to the most complex models, including interaction terms of all covariates present in the model. This process continued until all covariates in the model were significant at a 5% level.
- **Selection of final utility mixed effects model**: Appropriate mixed effects utility models were selected as inputs for the economic model.

The results of the exploratory analysis and mixed effects modelling are shown in Appendix P. Results were mapped from EQ-5D-5L to EQ-5D-3L values (see below). A scenario analysis is presented that looks at the impact of using the EQ-5D-5L utilities on the cost effectiveness results. The final utility values used in the economic model are detailed below.

Mapping (EQ-ED-5L to EQ-5D-3L)

The PACIFIC study collected HRQL data using EQ-5D-5L. The 3-level version (EQ-5D-3L) and the UK time trade-off value set are the reference case for HTA submissions, as defined by NICE. If EQ-5D-5L is collected, NICE recommend applying the mapping function developed by Van Hout *et al*. to convert it to the EQ-5D-3L for the reference-case analyses.[154, 155] Therefore, PACIFIC EQ-5D-5L data were mapped to EQ-5D-3L using the Van Hout mapping function.

Patient responses from the EQ-5D-5L questionnaire were combined using the Van Hout crosswalk mapping algorithm, to obtain utility values mapped to the EQ-5D-3L. The Van Hout crosswalk mapping algorithm is a non-parametric model that maps responses from the EQ-5D-5L to the EQ-5D-3L using the probability of the response to each question on the 5L being equivalent to the 3L.[154] For example, if a patient has answered 2 for mobility on the 5L questionnaire, the probability of this being equivalent to a response of 1 on the 3L is 0.18; to a response of 2 in the 3L, 0.82; and to a response of 3 on the 3L, a probability of 0. The product of the probabilities of each 5L question's response being mapped to the responses on the 3L gives the probability of

each of the 3,125 5L response combinations or health states reporting each of the 243 3L health states. The 5L utility value is calculated by multiplying the 243 transition probabilities by their corresponding 3L utility values and summing them. Each 5L health state can be linked with each 3L health state, and a 3,125 by 243 matrix of transition probabilities is created. A tool is available at https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation/crosswalk-index-value-calculator/ that applies the mapping to 3L responses and then uses the UK valuation set to produce the corresponding utility values.

To produce UK utility values, the tool was merged on to the PACIFIC EQ-5D-5L dataset. Only records collected after randomisation in the initial treatment phase were included in analysis.

Health-related quality-of-life (HRQL) data from other sources

An SLR was conducted to identify any other relevant health state utility data from the published literature on locally-advanced, unresectable, Stage III NSCLC patients, or advanced metastatic Stage IV NSCLC patients. The SLR was thus broader in scope that the decision problem for this appraisal. It was appropriate to expand the population of interest since the economic model includes health states reflecting disease progression from locally-advanced Stage III NSCLC to advanced metastatic NSCLC.

The SLR was conducted in two stages. An original search was conducted in October 2016, and captured published health state utility data in adults with locally-advanced, unresectable, Stage III NSCLC who had received CRT. An SLR update was conducted in March 2018, which aimed to:

- Identify evidence published since the original review was conducted.
- Extend the scope of the review to include adults with locally-advanced, unresectable, Stage III NSCLC, or advanced metastatic Stage IV NSCLC, with **no** restriction to patients treated with CRT.

Full details of the search methodology and a summary of the included studies are provided in Appendix H.

In summary, 53 publications were included across the original review and the March 2018 update, with 49 reporting utility data [22, 26-28, 35, 72, 85, 86, 123-126, 129, 130, 156-188] and four studies reporting mapping algorithms.[189-192] None of the included publications were exactly aligned with the population of interest, as detailed in Table 1.

Of the 29 unique studies published as journal articles (in 35 publications), four were conducted exclusively in UK populations [158, 164, 171, 186]. Two studies that were conducted internationally reported utilities based on UK weights applied to the EQ-5D, [163] or reported utilities for the UK population only [170]. In addition, 14 HTA submissions identified as part of the cost-effectiveness review (reporting on eight unique indications) reported relevant utility data and were included for completeness [26-28, 32, 35, 85, 86, 122-126, 129, 130]. Altogether, 49 eligible publications (associated with 37 unique studies / indications) were included in the review.[22, 26-28, 32, 35, 72, 85, 86, 122-126, 129, 130, 156-188] Key published utility studies from the SLR, which have been used in previous STA submissions to NICE are shown in Table 37. Full details of the search methodology and a summary of the included studies are provided in appendix H.

Table 37: Key published utility and disutility studies identified by the review and/or included in previous STA submissions†

Study / population	Methods	Country	Utility values reported [SD] (SEM)	Relevance for economic model
Chouaid 2013 [163] [Results initially reported in abstract, Chouaid 2012 [183]] Patients with Stage IIIB or IV NSCLC [Data used in TA347 [35] TA403 [129], and TA520 [130]]	EQ-5D (based on UK weights [193])	Multinational (Australia, Belgium, Canada, France, Italy, Sweden, Turkey, the Netherlands and the UK)	Overall sample (n=263) 0.66 [0.29] Progression free (n=190) 0.70 [0.25] Progressed disease (n=64) 0.58 [0.32] 1st-line progression free (n=115) 0.71 [0.24] 2nd-line progression free (n=44) 0.72 [0.18] 3rd/4th- line progression free (n=24) 0.62 [0.29] 1st-line progressed disease (n=26) 0.67 [0.20] 2nd-line progressed disease (n=17) 0.59 [0.34]	Possible alternative value for utility after progression

Study / population	Methods	Country	Utility values reported [SD] (SEM)	Relevance for economic model
			3rd/4th-line progressed disease (n=21) 0.46 [0.38]	
Doyle 2008 [164] Patients with advanced, metastatic NSCLC [Data used in TA483 [27] and TA484 [86]]	EQ-5D	UK	Treatment response, 0.712 Stable disease, 0.626 Stable disease with cough, 0.580 Stable disease with dyspnoea, 0.576 Stable disease with pain, 0.557 Stable disease with cough, dyspnoea, and pain, 0.461	Not suitable as an alternative value for utility after progression as assumes all patients have become metastatic
Nafees 2008 [171] [Results initially reported in abstract, Nafees 2006 [184]] Patients with metastatic NSCLC receiving second-line treatment [Data used in TA124 [127], TA181 [39], TA190 [128], TA347 [35], TA402 [32], TA403 [129], TA447/ID1349 [28] [85], TA483 [27], TA484 [86], and TA520 [130]]	Interview and SG	UK	Stable disease with no toxicity, 0.653 (0.02) Progressive disease with no toxicity, 0.473; utility decrement from stable disease, -0.180 (0.022) Responsive disease with no toxicity, 0.673; utility decrement from stable disease, -0.019 (0.007) Disutility Neutropenia, -0.090 (0.015) Febrile neutropenia, -0.090 (0.016) Fatigue, -0.073 (0.002) Nausea and vomiting, -0.048 (0.016) Diarrhoea, -0.047 (0.015) Hair loss, -0.045 (0.018) Rash, -0.032 (0.011)	Not suitable as an alternative value for utility after progression as it relates to second line treatment in metastatic setting

Key: EQ-5D, EuroQol 5-Dimension; NSCLC, non-small cell lung cancer; SD, standard deviation; SEM, standard error of the mean; SG, standard gamble; TA, technology appraisal.
Note: †NICE TA190 [128] used the health state utility values from the decision framework reported in Berthelot 2000[194] in a scenario analysis. However, only treatment-related health state utility values for each chemotherapy regimen being evaluated are reported in Table 2 of the publication.

Adverse events' impact on health state utility (HSU)

The overall impact of AEs on HRQL in this patient group is expected to be relatively small compared to the impact of progression. Moreover, any HSU impact of AEs

associated with durvalumab and SoC is expected to be accounted for in the health state utilities estimated from the PACIFIC study. Therefore, in the base case, no separate dis-utilities for AEs were considered. The impact of including AEs explicitly was tested in a sensitivity analysis (section B.3.8).

Health state utility (HSU) data used in the cost-effectiveness analysis

The base case analysis used EQ-5D-3L utility values derived from the PACIFIC study. This was considered the most robust and applicable source of utility data for this population. Furthermore, this was the only source of data available for the population of interest while in the PF health state. A variety of models including different covariates were constructed and tested (Appendix P). Models with progression only, as well as time to death together with progression, were considered viable options. In the base case analysis, the mixed model including progression only was included. This was based on:

- Progression being the key clinical factor most affecting patient's HRQL (section B.1.3), and the most significant variable in the mixed effect modelling.
  - Note: EQ-5D-5L data was only collected up to 30 days following progression.

- Using utility values dependent on progression only being a conservative approach (that overestimates the ICER). In reality, HRQL is likely to continue to decline further following disease progression, as patients will progress on subsequent treatments and experience worsening health and symptom burden. In an immunotherapy appraisal in the advanced metastatic NSCLC setting, HSU was reported to decline from 0.653−0.753 in the PF state on 1L metastatic treatments to 0.473−0.664 in the PD state.[26]

Sensitivity analysis was conducted using time to death and progression utility mixed effects modelling. Health state utility values used in the base case analysis are presented below in Table 38.

Table 38: HSU values used in the base case analysis; PACIFIC mixed effects model – by progression status

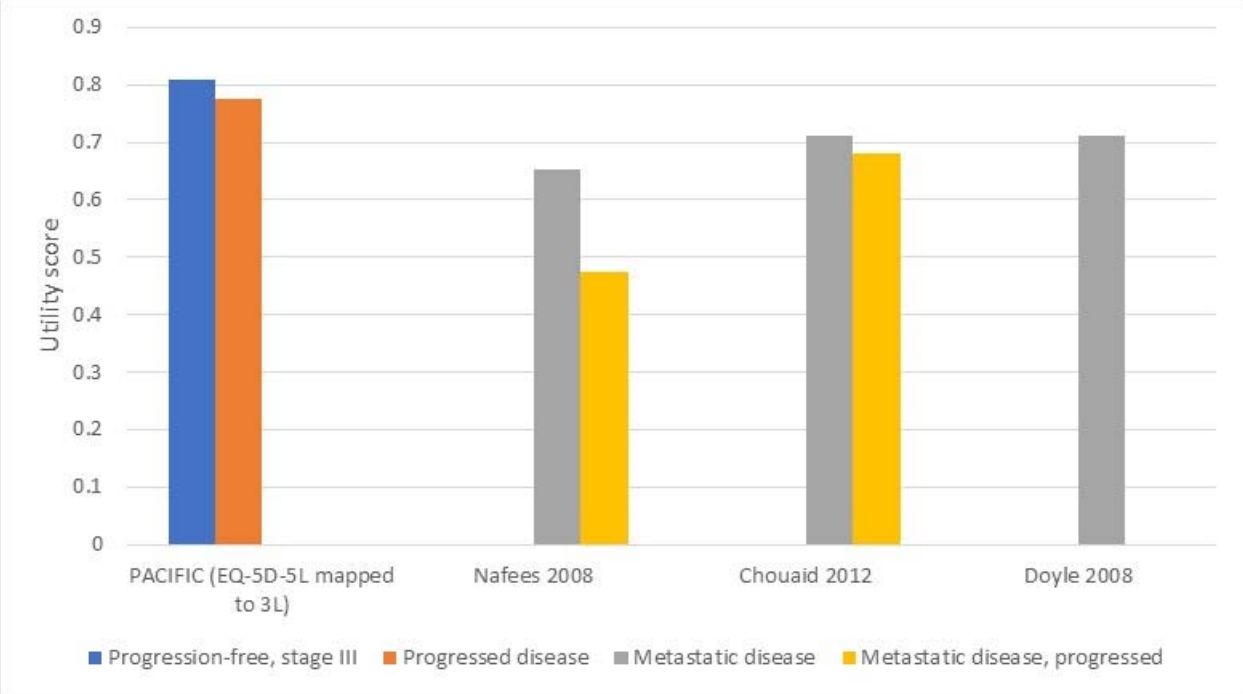
	Progression (BICR)	
	Estimate	SE
Intercept	0.810	0.009
Post-progression	-0.034	0.009

Key: BICR, blinded independent central review; HSU, health state utility; SE, standard error.

Comparison of PACIFIC utility values against other sources

Figure 40 shows an illustrative comparison of the utility values derived from PACIFIC alongside values identified from other clinical trials in the advanced metastatic NSCLC setting. There is broad consistency with the values reported for advanced metastatic disease, with the post-progression utility value for PACIFIC being above (but close to) reported those reported for advanced metastatic disease. This is aligned with the fact that not all patients who experienced disease progression in the PACIFIC study developed metastatic disease.

Figure 40: Comparison of PACIFIC utility values against published sources



Key: EQ-5D-3L, EuroQol 5-dimension, 3-level health state utility index; EQ-5D-5L, EuroQol 5-dimension, 5-level health state utility index.

In addition, we compared the values from the PACIFIC study against general population norms from Kind 1999.[195] The comparable general population norm reported in Kind 1999 is 0.79 (for someone aged 55–64 years; average patient age in PACIFIC = 63 years). This is slightly below the utility reported for the PF health state from PACIFIC (0.81). On face value this does not make sense since the HSU of patients with locally-advanced Stage III NSCLC is expected to be lower than the general population. However, it should be noted that values from Kind 1999 are over 20 years old, and the HSU of the general population is expected to have increased over time, in line with better health and life expectancy. Kind 1999 is also based on EQ-5D-3L values, whereas values from PACIFIC are based on EQ-5D-5L mapped to 3L.

To test the impact of alternative utility values, sensitivity analysis was conducted capping the utility values at the general population figures (similar to ERG analysis in the pembrolizumab 1L advanced metastatic NSCLC appraisal[28, 85]). Another scenario was also explored, assuming a utility decrement of 20% from PF state to PD state (Section B.3.8).

B.3.5. Cost and healthcare resource use identification, measurement, and valuation

Please refer to Appendix I for details of how relevant cost and healthcare resource data were identified for use in the model. Costs in the economic model consisted of:

- Costs associated with treatment
  - Drug acquisition costs (including any subsequent therapies)
  - Drug administration costs (including any subsequent therapies)
  - Costs associated with treatment-related AEs
- Costs associated with disease management and patient observation
- Costs associated with end-of-life care.

An SLR was conducted to identify published resource use and costs data associated with the treatment and management of patients with locally-advanced, unresectable, Stage III NSCLC who had completed platinum-based CRT. None of the studies identified through the SLR reported cost or resource use data relevant to the decision

problem. See appendix I for full details of how relevant cost and healthcare resource data were identified.

Intervention and comparators' costs and resource use

Drug acquisition cost

- **Durvalumab:** Durvalumab is administered via (60 minute) IV infusion at a dose of 10 mg/kg Q2W. This dosage is aligned to the anticipated EMA Marketing Authorisation for durvalumab. Durvalumab is supplied in 120mg and 500mg vials. The proposed list price of durvalumab is £592 per 120mg vial and £2,466 per 500mg vial. In line with the PACIFIC study design, AstraZeneca propose that a treatment duration cap of 12 months is applied to durvalumab treatment in any NICE recommendation.

  In the model, the average cost per infusion was calculated by multiplying the cost per mg by the average body weight in the PD-L1 ≥1% group in the PACIFIC study (71.1kg) and dosage (10 mg/kg). The base case analysis assumes that vial sharing is adopted (i.e. centres are able to optimise administration of durvalumab and other chemotherapies so that no drug is wasted). This is aligned with policy initiatives for immuno- and chemo-therapy treatments put in place by NHS England.[196, 197] The impact of no vial sharing (i.e. total wastage) was tested in a sensitivity analysis (Section B.3.8).

  Acquisitions cost were applied in line with how treatment long was received for in the PACIFIC study (i.e. using TTD KM curves, which were fully mature at the latest, 22 March 2018 DCO).
- **SoC**: The model assumes zero acquisition cost for SoC. This was considered reasonable as concomitant medication use was similar in durvalumab and placebo arms of the PACIFIC study.

Drug administration cost

There is no NHS reference cost or payment-by-results (PbR) tariff specific to the cost of administrating durvalumab. Therefore, the cost of administration was based on NHS reference cost code SB12Z (total healthcare resource groups [HRGs], cost of administering simple chemotherapy).[198] This is aligned to assumptions made in previous NICE technology appraisals and accepted by the respective committees.[130,

[199-201] The cost of administering treatment was also applied in line with how long treatment was received for in the study (i.e. using TTD KM-curve). No administration costs were applied to SoC, given this is active follow-up only.

A summary of drug related acquisition and administration costs are presented below in Table 39.

Table 39: Summary of drug related costs

Items	Durvalumab	Rational	SoC
Dosing per administration	10mg/kg	Draft SmPC (see Appendix C)	NA
Frequency of administration	Q2W	Draft SmPC (see Appendix C)	NA
Total dose per administration	711mg	Mean patient weight in PACIFIC PD-L1 ≥1% group: 71.1kg * 10 mg/kg	NA
Treatment cost per 120mg vial	£592	Anticipated list price	£0
Treatment cost per 500mg vial	£2,466	Anticipated list price	£0
Treatment cost per cycle (Q2W)	£3,507	711*(£2,466/500)	£0
Total mean treatment cost	[redacted]	£3,507*(30/14)*(average treatment duration of [redacted] months [from PACIFIC])	£0
Administration cost per cycle (Q2W)	£241.07	Total HRGs SB12Z[198] Same source as approved NICE TAs[130, 199-201]	£0

Key: HRG, healthcare resource group; NA: not applicable, NICE, National Institute for Health and Care Excellence; PD-L1, programmed cell death ligand 1; Q2W, every 2 weeks; SmPC, summary of product characteristics; SoC: Standard of care, TA: technology appraisal.

Time to treatment discontinuation (TTD)

TTD KM-curves were used to determine the duration of treatment, as well as drug acquisition and administration costs for patients on treatment (Section B.2.6). TTD in the PACIFIC study is defined as: *end date of treatment – start date of treatment + 1*. As per the study protocol, all patients were discontinued from treatment at or before 12 months. TTD data were fully mature and no extrapolation was required; the KM data were used directly in the model. The mean TTD was [redacted] and [redacted] for durvalumab and placebo arms, respectively.

PD-L1 testing costs

It is expected that PD-L1 tests will be conducted prior to initiating treatment with durvalumab, to confirm pre-CRT PD-L1 expression on ≥1% of TCs (per the anticipated EMA Marketing Authorisation for durvalumab in this patient population). Therefore, the economic model includes a cost per patient associated with PD-L1 testing. It is estimated that, to identify one patient eligible for durvalumab, 1.89 patients would need to be tested (Table 40).

In the base case analysis, we included the full cost of testing in the durvalumab arm and no cost of testing in the SoC arm. This is a conservative assumption, because:

- For some patients, PD-L1 tests are conducted at staging or diagnosis as part of standard practice in the NHS (referred to as "reflex testing"), in which case there is no need to test again before the patient initiates treatment with durvalumab (section B.1.3)
- PD-L1 testing is currently available and funded within the NHS as part of SoC for Stage IV disease. Even if not tested before, some patients in the SoC arm would go on to receive subsequent immunotherapy upon disease progression. These patients would be tested for PD-L1 / PD-L1 expression as part of UK clinical practice (24.2% of patients in the placebo arm received subsequent immunotherapy in the PACIFIC study PD-L1 ≥1% group) (Table 10).

Table 40 shows the costs associated with PD-L1 testing applied in the model. PD-L1 testing cost was applied as a one-off cost at the beginning of the modelled time horizon and therefore, was not discounted.

Table 40: PD-L1 testing costs used in the model

Parameter	Value	Reference
Proportion of patients who have not progressed§	95%	UK clinical expert opinion[89]
Proportion of patients with evaluable tissue rate	83%	PACIFIC data*
Proportion of tissue with PD-L1 expression on ≥1% TCs	67%	PACIFIC data*
Proportion of patients eligible for durvalumab treatment	53%	Calculation (0.83*0.67)
Number of patients needed to test to identify one eligible patient	1.89	Calculation (1/0.53)
Cost of PD-L1 test	£40.50	As reported in NICE TA 531 [85]
Total testing cost per eligible patient	**£76.68**	**-**

Key: CRT, chemoradiation therapy; ITT, intention to treat; NICE, National Institute for Health and Care Excellence; PD-L1, programmed cell death ligand 1; TA, technology appraisal; TC, tumour cell. **Note:** §Starting from pool of patients who receive curative-intent CRT; *Out of the full ITT population in PACIFIC, 545 patients had tissue obtained, 451 had evaluable samples for PD-L1 testing, and 303 had pre-CRT PD-L1 expression on ≥1% of TCs.

Cost of subsequent therapy (upon disease progression)

In line with the PACIFIC study and UK clinical practice, patients in the model who experience disease progression go on to receive further treatment and / or end-of-life care. These patients can be treated with immunotherapy if they meet the criteria required for treatment.

24.2% of patients in the placebo arm (PACIFIC PD-L1 ≥1% group) went on to receive subsequent immunotherapy. This is broadly reflective of UK clinical practice- clinical experts estimate that ~30% of locally-advanced, unresectable, Stage III NSCLC patients receive subsequent immunotherapy upon disease progression following treatment with overlapping CRT (Section B.1.3).[44] A greater proportion of patients in the placebo arm received nivolumab, compared to pembrolizumab, in subsequent lines of therapy. 2L treatments for advanced metastatic NSCLC are commonly-used in upon disease progression for patients who progress within 12 months of completing CRT.[44] Nivolumab may have been preferred since PD-L1 / PD-L1 biomarker testing is not necessary for treatment initiation.[1]

Since durvalumab is only available in the UK through the EAP ([redacted][5] there is no real-world data to validate subsequent immunotherapy use after durvalumab. However, when clinical experts were asked to predict subsequent immunotherapy use after durvalumab, once it became available, their responses were broadly similar to the levels reported in the PACIFIC study (mean of 14 responses = 2% [range 0−15%]).[44] Therefore, no formal adjustment for treatment switching was included in the economic model for the base case analysis. Sensitivity analysis was conducted looking at different levels of immunotherapy use (Section B.3.8).

Subsequent therapies were included in the model if they were used in more than 3% of patients in either treatment arm in the PACIFIC study. The included list of subsequent therapies and the proportion of patients who received each therapy is presented below in Table 41. The percentages can be more than 100% due to use of combination treatments and multiple lines of treatment. Chemotherapy was the most commonly-used subsequent treatment modality in both durvalumab and placebo groups, which is aligned with clinical expert opinion of UK real-world practice.[44]

Table 41: Proportion of patients receiving subsequent treatment

	PD-L1 ≥1% group		Patients in PD-L1 ≥1% group who experienced disease progression	
Subsequent treatment	**Durvalumab (N=212)**	**SoC (N=91)**	**Durvalumab (n=86)**	**SoC (n=57)**
Immunotherapy				
Nivolumab	13 (6%)	18 (20%)	13 (15%)	18 (32%)
Pembrolizumab	4 (2%)	4 (4%)	4 (5%)	4 (7%)
Durvalumab (re-treatment)	6 (3%)	0%	6 (7%)	0%
Other commonly-used subsequent therapies				
Radiotherapy	31 (15%)	20 (22%)	31 (36%)	20 (35%)
Docetaxel	19 (9%)	4 (4%)	19 (22%)	4 (7%)
Erlotinib	5 (2%)	6 (7%)	5 (6%)	6 (11%)
Carboplatin	29 (14%)	17 (19%)	29 (34%)	17 (30%)
Pemetrexed	18 (9%)	7 (8%)	18 (21%)	7 (12%)
Gemcitabine*	18 (8%)	10 (11%)	18 (21%)	10 (18%)
Cisplatin	8 (4%)	6 (7%)	8 (9%)	6 (11%)

	PD-L1 ≥1% group		Patients in PD-L1 ≥1% group who experienced disease progression	
Subsequent treatment	**Durvalumab (N=212)**	**SoC (N=91)**	**Durvalumab (n=86)**	**SoC (n=57)**
Paclitaxel	8 (4%)	8 (9%)	8 (9%)	8 (14%)
Afatinib	5 (2%)	3 (3%)	5 (6%)	3 (5%)

Key: IO, immune-oncology; PD-L1, programmed cell death ligand 1; SOC, Standard of care.

Notes: * Include treatment coded as gemcitabine and gemcitabine hydrochloride. Treatments could be given individually or in combination.

Source: PACIFIC DCO 22nd March 2018 table 11.1.18.1.B, [202]

Once patients progress in the model, a one-off cost for subsequent treatment is accrued. This cost is informed by the type of treatment, the required treatment dose (Table 42), the dosing schedule, the unit drug cost (based on acquisition costs shown in

Table 43 and assuming vial sharing), and the duration of treatment.

Due to lack of data on serum creatinine and glomerular fibrillation rate (GFR) data required in estimating the required dose of carboplatin from the PACIFIC study, the analysis uses a dose of 500mg from a previous NICE technology appraisal[39], which included carboplatin-containing regimens (Table 42). Pembrolizumab is available as a fixed dose formulation in 1L metastatic NSCLC, while a weight-based formulation is recommended 2L metastatic NSCLC.[26, 28, 85] The majority of pembrolizumab use is expected in 1L metastatic setting as an immediate subsequent IO treatment; therefore, costs of the fixed dose regimen was applied throughout (Table 42).

The NHS reference cost-code 'total HRGs SB12Z' (£241.07)[198] was used in calculating the costs associated with administering all subsequent therapies delivered intravenously (i.e. the same approach as was used for durvalumab). Pembrolizumab, nivolumab, afatinib, and erlotinib are all associated with confidential discounts. Their list prices were used in the base-case analysis (

Table 43); alternative prices were tested in sensitivity analyses.

Table 42: Drug dosages used in calculating the costs of subsequent therapies

Treatment	Dose
Durvalumab	10 mg/kg
Pembrolizumab	200 mg
Paclitaxel	200 mg/m^2
Carboplatin	AUC=5; 500mg dose assumed
Gemcitabine	1000 mg/m^2
Cisplatin	75 mg/m^2
Pemetrexed	500 mg/m^2
Nivolumab	240 mg
Docetaxel	75 mg/m^2
Erlotinib	150 mg
Afatinib	40 mg
Radiotherapy	N/A
Key: AUC, area under the curve; N/A, not applicable.	

Table 43: Subsequent treatment acquisition costs

Treatment	Dose	Frequency	Unit size (mg)	Unit cost (no discount)	Source / comment
Durvalumab	10 mg/kg	Day 1 of 14-day cycle	500	£2,466	AstraZeneca, anticipated list price
			120	£592	
Pembrolizumab	200mg	Day 1 of 21-day cycle	50	£1,315	MIMS[203]
			100	£2,630	
Nivolumab	240 mg	Day 1 of 14-day cycle	100	£1,097	MIMS (Opdivo)[203]
			200	£2,633	
Paclitaxel	200 mg/m^2	Day 1 of 21-day cycle	30	£3.44	eMIT 2018[204]
			100	£10.85	
			150	£10.52	
			300	£19.68	
Carboplatin	AUC=5; 500mg dose assumed	Day 1 of 21-day cycle	50	£3.18	eMIT 2018[204]
			150	£6.35	
			450	£18.73	
			600	£28.24	
Gemcitabine	1000 mg/m^2	Day 1 and 8 of 21-day cycle	200	£3.55	eMIT 2018[204]
			1000	£11.97	
			2000	£16.32	
Cisplatin	75 mg/m^2	Day 1 of 21-day cycle	10	£1.84	eMIT 2018[204]
			50	£4.48	
			100	£10.13	

Treatment	Dose	Frequency	Unit size (mg)	Unit cost (no discount)	Source / comment
Pemetrexed	500 mg/m^2	Day 1 of 21-day cycle	100	£160	MIMS (Alimta)[203]
			500	£800	
Docetaxel	75 mg/m^2	Day 1 of 21-day cycle	20	£3.85	eMIT 2018[204]
			80	£14.74	
			160	£46.75	
Erlotinib	150 mg	Daily dose	30	£1,631.53	MIMS (Tarceva)[203]
Afatinib	40 mg	Daily dose	20	£2023.28	MIMS (Giotrif)[203]
			30	£2023.28	
			40	£2023.28	
			50	£2023.28	
Radiotherapy	NA	NA	NA	£2,801.62	NHS reference costs[203] *

Key: AUC, area under the curve; eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities; NA, not applicable; NHS, National Health Service; SOC, Standard of care;
Note: * Assumed 8% of patients receiving CHARD, and 92% receiving radical radiotherapy based on RCR data[53]: Cost for CHART is a sum of NHS reference costs code IP SC54Z (1x £428.47), IP SC22Z (35x £146.86) and IP SC23Z (1x £278.45). Cost for radical radiotherapy is a sum of NHS reference costs OP SC45Z (1x £362.59), OP SC22Z (19x £107.46) and OP SC23Z (1x £132.40). Resource use was based on NICE CG121 (2011).[40]

Duration of treatment was assumed to be 3.30 months for chemotherapies, taken from TA428[26]; 11 months for erlotinib and afatinib based on a previous NICE technology appraisal,[36] and 3.9 months, 6.1 months and 4.9 months for durvalumab, nivolumab, and pembrolizumab, respectively, based on data from PACIFIC[202]). It is worth noting that PACIFIC data were not fully mature at the 22 March 2018 DCO, and some patients were still undergoing treatment with immunotherapy. Therefore, these durations may be an underestimation. The impact of longer subsequent immunotherapy treatment durations was assessed in sensitivity analysis (section B.3.8).

A summary of costs associated with commonly-used subsequent therapies is provided in Table 44.

Table 44: Subsequent treatment regimen costs applied in the model

Subsequent treatment	Dose (mg) per administration	Weeks per administration	Duration of treatment (weeks)	Acquisition cost per administration	Administration cost	Total one-off cost per patient
Durvalumab	711	2	17.11	£3,504	£241	£32,056
Pembrolizumab	200	3	21.40	£5,260	£241	£39,241
Nivolumab	240	2	26.33	£2,633	£241	£37,832
Paclitaxel	366	3	14.35	£24	£241	£1,268
Carboplatin	500	3	14.35	£21	£241	£1,253
Gemcitabine	1830	1.5	14.35	£15	£241	£2,449
Cisplatin	137	3	14.35	£12	£241	£1,212
Pemetrexed	915	3	14.35	£1,464	£241	£8,155
Docetaxel	137	3	14.35	£25	£241	£1,274
Erlotinib	150	0.14	47.83	£54	£0	£18,209
Afatinib	40	0.14	47.83	£51	£0	£16,935
Radiotherapy	NA	NA	NA	NA	£0	£2,802
Key: NA, not applicable						

The average cost of subsequent treatment was determined using the distribution of patients across the various subsequent treatments used in the PD-L1 ≥ 1% group of the PACIFIC study (Table 41). The one-off total subsequent treatment cost for the durvalumab arm and placebo arm are [redacted] and [redacted], respectively.

Health-state unit costs and resource use

In addition to the drug acquisition and administration costs, the economic model takes into consideration the cost of resource use associated with patient observation and disease management in both PF and PD health states. Resource use and associated costs are applied to all patients based on their treatment arm, treatment status, and disease progression status. These resources are applied in addition to the cost of administering durvalumab (detailed above).

The SLR conducted did not identify any UK-specific data for costs or resource use associated with the observation and management of the population of interest. There were however published resource use and costs associated with the management of patients in the first-line (1L) advanced metastatic setting (i.e. following disease progression) in TA531.[85] Therefore, the model used resource use and cost identified and accepted in TA531 for the PD health state (see Table 45).

For the PF state, it was assumed that patients on SoC would receive outpatient oncology visits and scans in line with ESMO guidelines[46] and clinical expert opinion.[139] For durvalumab, we assumed patients would be scanned every two months, in line with the PACIFIC study design (section B.2.3), and that patients would receive a blood test every visit to monitor treatment-related AEs[1], based on clinical expert opinion.[139] No costs of outpatient visits or clinical nurse specialist visits were included, as these are expected to be captured in the cost of administering durvalumab (detailed above).

The associated unit costs are taken from the PSSRU 2017[205] and NHS reference costs 2016–17[198] (

Table 46). Combining these data gives the patient monitoring cost per week (Table 47).

Table 45: Resource use estimates (per year), monitoring and management of patients on / after durvalumab and placebo (standard-of-care)

Additional resources required	Durvalumab		SoC	PD	Source
	PF - on treatment	PF – off treatment	PF - off treatment		
Outpatient oncologist visit	0	1st year: 5 2nd year: 3 Years 3−4: 2	1st year: 5 2nd year: 3 Years 3−5: 2	9.61	PF: based on draft SmPC, clinical expert opinion,[139] and ESMO guidelines PD: Big Lung Trial[206], TA531[85]
Chest radiography	0	1st year: 2 2nd year: 0 Years 3−4: 2	1st year: 2 2nd year: 0 Years 3−5: 2	6.79	
Blood test	24	0	0	0	PF: based on draft SmPC, clinical expert opinion, and ESMO guidelines PD: NA
CT scan (chest)	6	1st year: 3 2nd year: 3 Years 3−4: 0	1st year: 3 2nd year: 3 Years 3−5: 0	0.62	PF: based on draft SmPC, clinical expert opinion, and ESMO guidelines PD: Big Lung Trial[206], TA531[85]
CT scan (Other)	0	0	0	0.36	
ECG	0	0	0	1.04	
Community nurse visit	0	0	0	8.7	PF: based on draft SmPC, clinical expert opinion, and ESMO guidelines PD: Appendix 1, NICE CG81[207], Marie Curie Report[208], TA531[85]
Clinical nurse specialist	0	0	0	12	PF: based on draft SmPC, clinical expert opinion, and ESMO guidelines PD: Appendix 1, NICE CG81[207], TA531[85]
GP surgery visit	0	0	0	12	

Key: CT, computed tomography; ECG, electrocardiography; GP, general practitioner; PF, progression free; PD, progressed disease; SmPC, summary of product characteristics; SoC, standard of care.

Table 46: Resource unit costs associated with monitoring and management of patients on / after durvalumab and placebo (standard-of-care)

Resources required	Unit cost	Reference (unit cost)
Outpatient oncologist visit	£161.13	NHS reference costs 2016–2017[198] (Total Outpatient Attendances → 370 Medical Oncology
Chest radiography	£47.78	NHS reference costs 2016–2017[198]

Resources required	Unit cost	Reference (unit cost)
		(Total outpatient attendances → Diagnostic imaging [code: 812])
Blood test	£3.06	NHS reference costs 2016–2017[198] (Total other currencies → DAPS05)
CT scan (chest)	£112.33	NHS reference costs 2016-2017[198] (IMAG → RD24Z, outpatient)
CT scan (other)	£122.51	NHS reference costs 2016-2017[198] (IMAG → RD26Z, outpatient)
ECG	£201.72	NHS reference costs 2016-2017[198] (OPROC → 800, EY51Z)
Community nurse visit	£44.00	PSSRU 2017[205], table 10.1: Nurses, Band 6, per hour
Clinical nurse specialist	£53.00	PSSRU 2017[205], table 10.1: Nurses, Band 7, per hour
GP surgery visit	£37.00	PSSRU 2017[205], table 10.3b: GP contact lasting 9.22 minutes, including direct care staff costs, including qualification costs.
Key: CT, computed tomography; ECG, electrocardiography; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit, TA; Technical Appraisal.		

Table 47: Resource costs (per week) associated with the monitoring and management of patients treated with durvalumab or placebo

Status	Cost per cycle
Progression-free (durvalumab)	
On-treatment	£62.28
Off-treatment, year 1	£103.18
Off-treatment, year 2	£68.37
Off-treatment, years 3−4	£34.82
Off-treatment, year 4+	£0.00
Progression-free (SoC)	
Off-treatment, year 1	£103.18
Off-treatment, year 2	£68.37
Off-treatment, years 3−5	£34.82
Off-treatment, year 5+	£0.00
Progressed disease	**£304.94**
Key: SoC, standard of care.	

Adverse event (AE) unit costs and resource use

The types and rates of AEs used in the model are documented in section B.3.3. Once an AE occurs, a one-off cost (taken from the NHS reference costs[198]) is applied (Table

48), which gives a total per-cycle cost for each arm. This is applied to the duration that patients are on assigned treatment (

Table 49).

Table 48: Adverse event (AE) unit costs

AE	Cost	Reference
Anaemia	£753.02	NHS reference costs 2016-2017[198] (Total HRGs; weighted average of SA03G−SA05J)
Hypertension	£388.81	NHS reference costs 2016−2017[198] (NES; EB04Z)
Haemoptysis	£391.98	NHS reference costs 2016−2017[198] (NES; weighted average of DZ19H−DZ19N)
Hypokalaemia	£151.69	NHS reference costs 2016−2017[198] (134 total outpatient general medicine [service code 300])
Pneumonia	£1,851.16	NHS reference costs 2016-2017[198] (Total HRGs; weighed average DZ11K−DZ11V)
Pneumonitis	£391.98	NHS reference costs 2016-2017[198] (NES; weighted average of DZ19H−DZ19N)
Radiation Pneumonitis	£391.98	Same cost assumed as for pneumonitis (since no HRG available) NHS reference costs 2016−2017[198] (NES; weighted average of DZ19H−DZ19N)
Endocrinopathy	£443.46	NHS reference costs 2016−2017[198] (NES weighted average of KA08A−KA08C)
Key: HRG, healthcare resource group; NEL, non-elective inpatients; NES, non-elective short stay; NHS, National Health Service.		

Table 49: Per cycle adverse event (AE) costs by treatment arm (while patients are on assigned treatment)

AE	Durvalumab	SoC
Anaemia	£0.96	£1.80
Hypertension	£0.00	£0.00
Haemoptysis	£0.00	£0.46
Hypokalaemia	£0.13	£0.46
Pneumonia	£4.79	£5.56
Pneumonitis	£0.50	£0.23
Radiation Pneumonitis	£0.41	£0.70
Endocrinopathy	£0.09	£0
Total per cycle cost	**£6.88**	**£9.20**
Key: AE, adverse event; SoC, standard of care.		

End-of-life palliative care costs

A one-off cost of £3,577 is applied in the model when a patient dies, to reflect the cost of terminal care. This cost reflects resource use in various care settings, and is based on the values accepted in a NICE multiple technology appraisal for erlotinib and gefitinib (TA374).[34] These costs were also used and accepted by the NICE committee in recent nivolumab and pembrolizumab appraisals. The model assumes that end-of-life palliative care costs is the same for patients on both treatment arms (Table 50).

Table 50: Unit costs of terminal (end-of-life) care

Resource	Unit cost	Resource use	Proportion of patients in each care setting[209]	Total cost	Reference (resource use)	Reference (unit cost)
Community nurse visit (per hour)	£62.00	28	27%	£468.72	PD: Appendix 1, NICE CG81[207], Marie Curie Report[208], TA531[85]	PSSRU 2017[205], table 10.1
GP home visit	£37.00	7	27%	£69.93	Marie Curie Report[208], TA531[85]	PSSRU 2017[205], table 10.3b
Macmillan nurse (per hour)	£41.35	50	27%	£558.28	Marie Curie Report[208], TA531[85]	TA374[34], section 2, table 47

Resource	Unit cost	Resource use	Proportion of patients in each care setting[209]	Total cost	Reference (resource use)	Reference (unit cost)
Drugs and equipment (average)	£270.11	1	27%	£72.93	Marie Curie Report[208], TA531[85]	TA374[34], section 2, table 47. Inflation corrected[1]
Terminal care in hospital (per patient, 8.93 days)	£3,116.28	1	56%	£1,745.11	-	TA374[34], section 2, table 47. Inflation corrected[2]
Terminal care in hospice (per patient, 8.93 days)	£3,895.34	1	17%	£662.21	-	TA374[34], section 2, table 47
Total cost (applied as one-off cost in the model)				**£3,577.18**		

Key: GP, general practitioner; PD, progressed disease; PSSRU, Personal Social Services Research Unit; TA, Technical Appraisal.
Notes: [1]Inflation from 2009/2010 applied £240*(302.3/268.6) PSSRU 2017 table 16.3[205], [2]Inflation from 2009/2010 applied (2716.53+0.84*232.9)*(302.3/282.5) PSSRU 2017 table 16.3[205]

B.3.6. Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A summary of the key variables included in the model are provided in appendix R.

Assumptions

A summary of the model assumptions is provided in Table 51.

Table 51: Overall summary of assumptions in the model

Assumption	Rationale	Model element	Related sensitivity analysis
The time horizon was set to 40 years in the base case	Forty years is sufficient duration to capture the differences in costs and QALYs between durvalumab and SoC	Model structure	N/A
Progression definition - BICR	Aligned with primary endpoint in PACIFIC	PFS extrapolation	N/A

Assumption	Rationale	Model element	Related sensitivity analysis
Extrapolation for PFS based on independent models	Data indicates proportional hazards assumption does not hold	PFS extrapolation	Gompertz, with treatment covariate as predictor*
Durvalumab PFS curve: generalised gamma	Good visual fit, most clinically plausible outcomes and best statistical fit, aligned with function for SoC	PFS extrapolation	Gompertz
SoC PFS curve: generalised gamma	Good visual fit, most clinical plausible outcomes, and best statistical fit	PFS extrapolation	Gompertz
Treatment effect of durvalumab becomes equal to SoC at 10 years	Based on long-term treatment effect for other IOs	Treatment effect	Effect up to 3 years, 5 years, and lifetime
PPS assumed the same for both treatment arms	Conservative assumption, supported by PPS data from PACIFIC	PPS extrapolation	N/A
Natural mortality: PFS and OS hazards are not allowed to go below natural mortality (based on UK lifetable)	To account for long-term mortality trends not captured in the clinical trial period	Natural mortality	N/A
Utilities driven by progression only in base case analysis	Most straightforward and conservative approach, based on statistically significant variables	Utilities	Time to death, inclusion of age parameter, capped at general population levels, include AE dis-utilities, clinical expert opinion
Vial sharing for all IV treatments	Aligned with policy initiatives for chemotherapy and immunotherapy in place by NHS England[196, 197]	Costs	No vial sharing included
Resource use	Based on standard sources and values accepted in other NICE appraisals	Costs	Alternative costs and durations of subsequent therapies

Key: AE, adverse event; BICR, blinded independent central reviewed; IV, intravenous; NSCLC, non-small cell lung cancer; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PPS, post progression survival; QALY, quality adjusted life year; SoC, standard of care.
Note: *Proportional hazards, generalised gamma was also considered for sensitivity analysis, but showed inadequate fit to placebo arm (Appendix M).

B.3.7. Base-case results

Base-case incremental cost-effectiveness analysis

Total costs, life years gained (LYG), QALYs, and incremental cost per QALY gained for durvalumab versus SoC are presented in Table 52. In the base case analysis, durvalumab generates 2.94 incremental QALYs and [redacted] incremental costs over a 40-year time horizon compared with SoC alone, resulting in an ICER of £19,320 per QALY gained.

Table 52: Base-case results

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	--	--	--	--	--
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**3.61**	**2.94**	**£19,320**	**£19,320**

Key: LYG, life years gained; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

B.3.8. Sensitivity analyses

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) was run for 1,000 iterations for the base case analysis (durvalumab versus SoC). Results from the PSA are presented in Table 53. The probabilistic ICER is £21,221 per QALY gained, which compares well with £19,320 in the deterministic analysis.

Table 53: Average results based on the probabilistic sensitivity analysis (1000 iterations)

Treatment	Total costs (£)	QALYs	Incremental Costs (£)	Incremental QALYs	ICER per QALY gained (£)
Durvalumab	[redacted]	[redacted]	[redacted]	2.69	£21.221
SoC	[redacted]	[redacted]			

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

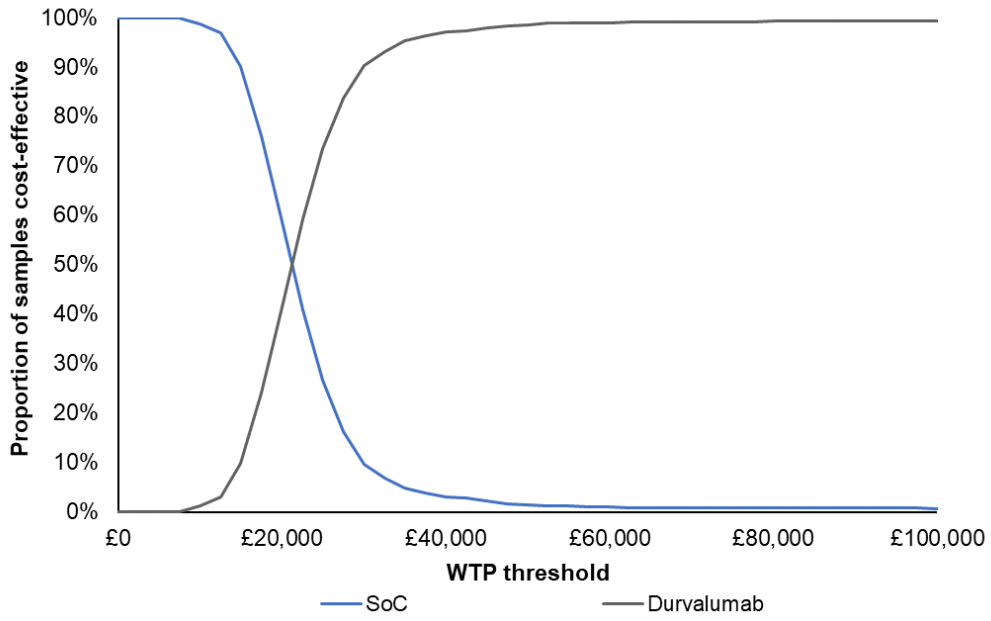
The cost-effectiveness plane and cost-effectiveness acceptability curve for durvalumab versus SoC are presented in Figure 41 and Figure 42, respectively. At a

cost-effectiveness threshold of £50,000 and £30,000, durvalumab has a 99% and 88% probability, respectively, of being cost-effective compared with SoC.

Figure 41: Cost-effectiveness plane for durvalumab versus standard of care

Key: QALY, quality adjusted life year; WTP, willingness to pay.

Figure 42: Cost-effectiveness acceptability curve for durvalumab versus standard of care



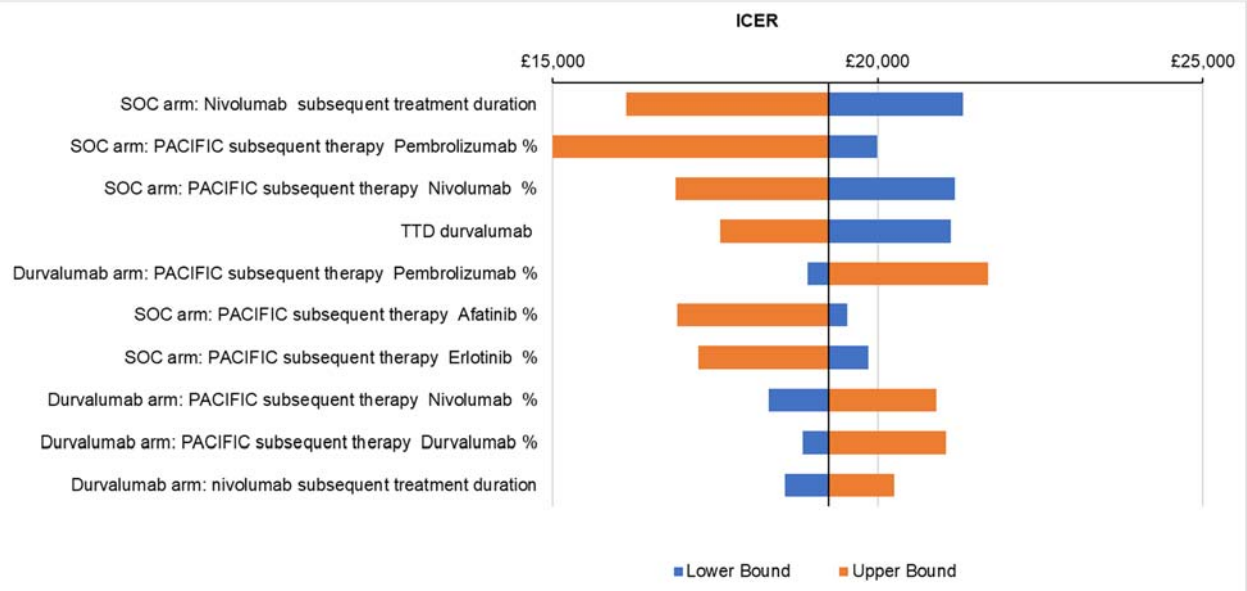
Key: SoC, standard of care; WTP, willingness to pay.

Deterministic sensitivity analysis

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 15 parameters are presented in Figure 43.

Overall, the results show that the ICER is most sensitive to the duration of subsequent immunotherapy use, the level (%) of subsequent immunotherapy use, and the time to discontinuation of durvalumab.

Figure 43: Tornado diagram



Key: ICER, incremental cost-effectiveness ratio; SOC, standard of care; TTD, time to discontinuation.

Scenario analysis

The results of the scenario analysis are shown in Table 54.

Scenario analysis conducted showed that the ICERs were consistent under differing assumptions. ICERs ranged between £11,298 and £30,534, excluding time horizon analyses.

Table 54: Results of scenario analyses conducted

Scenario	Values	Source / rationale	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Base case	-	-	[redacted]	**2.94**	**£19,320**
Time horizon	10 years	-	[redacted]	1.43	£39,161
	20 years	-	[redacted]	2.45	£23,099
	30 years	-	[redacted]	2.84	£20,001
PSM approach	PFS and OS as per base case; PSM approach to calculate	-	[redacted]	2.94	£19,320
Alternative PFS distributions (details in Appendix J)	Independent models; Gompertz	PACIFIC, section B.3.3	[redacted]	2.49	£23,237
	Proportional hazards; Gompertz	PACIFIC, Appendix M	[redacted]	2.87	£20,003
Alternative PPS distributions (details in appendix J)	Weibull	PACIFIC, section B.3.3	[redacted]	2.97	£19,175
Treatment waning cut-off	3 years	Minimum possible cutoff (PACIFIC data captured up to ~3 years)	[redacted]	1.94	£30,534
	5 years	Cut-off accepted by NICE for immunotherapy in advanced metastatic NSCLC setting[130]	[redacted]	2.40	£24,326
	Lifetime	Maximum possible durability	[redacted]	3.06	£18,372
Subsequent treatment	Alternative PPS curve (START / KEYNOTE-024) + 24% subsequent IO use	• Alternative method of estimating PPS (page 143, Appendix N) • Same level of subsequent IO use as in PACIFIC	[redacted]	2.98	£19,099
	Alternative PPS curve (START / KEYNOTE-024) + no subsequent IO use in either arm	• Alternative method of estimating PPS (page 143, Appendix N) • Tests impact of no subsequent IO use in either arm	[redacted]	2.98	£21,240

Scenario	Values	Source / rationale	Incremental Costs	Incremental QALYs	ICER (£/QALY)
	Alternative PPS curve (START / KEYNOTE-024) + 20% subsequent IO use in both arms	• Alternative method of estimating PPS (Appendix N) • Tests impact of 20% subsequent IO use in both arms±	[redacted]	2.98	£20,569
	Alternative PPS curve (START / KEYNOTE-024) + 30% subsequent IO use in SoC arm and 2% in durvalumab arm	• Alternative method of estimating PPS (Appendix N) • Tests impact of subsequent IO use predicted by clinical experts± [44]	[redacted]	2.98	£18,261
	Alternative PPS curve (START / KEYNOTE-024) + 60% subsequent IO use in SoC arm, 2% in durvalumab arm	• Alternative method of estimating PPS (Appendix N) • Tests impact of 60% subsequent IO use in SoC§, 2% IO use in durvalumab arm (as predicted by clinical experts)± [44]	[redacted]	2.98	£15,140
Utility approach	Time to death and progression	Appendix P	[redacted]	2.95	£19,236
	Inclusion of age parameter	Appendix P	[redacted]	3.10	£18,292
	PF utilities capped at general population levels (PF = 0.79, PD = 0.76)	-	[redacted]	2.86	£20,442
	Include AE dis-utilities	Appendix P	[redacted]	2.86	£19,920
	20% decrease in HRQL upon progression (PF = 0.81, PD = 0.65)	-	[redacted]	3.00	£18,922
	PACIFIC PF EQ-5D-5L data (PF = 0.818)	PACIFIC, EQ-5D-5L	[redacted]	2.97	£19,107
Vial sharing	No vial sharing	-	[redacted]	2.94	£22,979
Subsequent treatment costs	50% discount for all subsequent treatments, where applicable	-	[redacted]	2.94	£20,702

Scenario	Values	Source / rationale	Incremental Costs	Incremental QALYs	ICER (£/QALY)
	(pembrolizumab nivolumab, erlotinib, afatinib)				
Subsequent immunotherapy duration	Pembrolizumab and nivolumab: two years duration	Maximum possible treatment duration	[redacted]	2.94	£11,298

Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; PPS, post-progression survival; PSM, partition survival model; QALY, quality-adjusted life year; SoC, Standard of care.
Note: *Proportional hazards, generalised gamma was also considered for sensitivity analysis but showed inadequate fit to placebo arm (Appendix M). ±Assumed pembrolizumab use in calculating treatment costs. §In excess of subsequent IO use in RFSTM scenario (described in Section B.2.6) where everyone who received subsequent anticancer treatment in placebo arm (55%), had immunotherapy in first line.

B.3.9. Subgroup analysis

No subgroups were explored as part of the analysis.

B.3.10. Validation of cost-effectiveness analysis

The model was reviewed by health economists within AstraZeneca. The review included an assessment of the face validity of the model, and third-party validation of the workings and data sources used in the model. The Markov trace was independently checked, and any discrepancies identified in the model calculations were corrected. A range of extreme value and logic tests were conducted to examine the behaviour of the model and ensure that the results were logical.

In addition, the model was checked thoroughly by an independent third-party vendor. This quality control process involved checks of basic validity of model outcomes, application and sources of costs and utilities, clinical inputs, model settings, sensitivity analyses and macros, as well as review by a senior health economist.

Finally, the model structure and approach (semi-Markov versus partition survival) was reviewed by a well-known health economics expert (member of the ISPOR task force), who advised on most appropriate methodology in this setting.

B.3.11. Interpretation and conclusions of economic evidence

A *de novo* economic analysis was developed to evaluate the incremental cost-effectiveness of durvalumab compared to active follow-up in the treatment of patients with locally-advanced, unresectable, Stage III NSCLC whose tumours express PD-L1 on ≥1% of TCs and whose disease has not progressed after ≥2 overlapping cycles of platinum-based CRT.

The three health states in the model were PF, PD, and death. This health state structure (i.e. 3-states) has been extensively validated and applied in previous technology assessments in NSCLC. Furthermore, it captures the clinically important aspects relating to the treatment of these patients.

A semi-Markov approach was chosen to evaluate PFS and OS over the modelled time horizon. This approach was chosen as it best reflected the clinical trial data, while maintaining the structural relationship between PFS and OS (which would be violated if a PSM was used).

Model data were sourced primarily from the PD-L1 ≥1% group in the PACIFIC study, a well-designed, double-blind, international Phase III RCT in the relevant patient population. The results of the trial and associated economic evaluation are considered generalisable to clinical practice in the UK.

Data from PACIFIC were available up to ~three years. Predictions of long-term survival used in the economic model were extensively validated against published literature, as well as UK real-world data and clinical expert opinion. In addition, there was a clear rationale for choosing the parametric distributions used in the base case: generalised gamma distribution for PFS (reflecting clinical opinion that risk of progression would initially increase and then decrease over time[115]), and exponential for PPS (reflecting previous NICE assessments for immunotherapies in the advanced metastatic NSCLC setting).

Summary of results

Results of the analysis showed that the ICER for durvalumab at list price versus SoC was £19,320, making it a cost-effective use of resources in the NHS. This was driven by the relatively short treatment duration (treatment cap of 12 months, mean treatment

duration of [redacted] months), and the durable, significant, and sustained treatment effect observed in the PACIFIC study (OS HR = 0.53 [95% CI 0.36, 0.77], section B.2.6).

The modelled life years gained with durvalumab over a patient's lifetime was 3.61, which translated into a QALY gain of 2.94 (associated with durvalumab). This level of QALY gain is rarely seen in economic evaluations and is far greater than that achieved with immunotherapies currently approved in the advanced metastatic NSCLC setting.[z]

To put this figure in context, the product criteria for a "transformative medicine" for the Accelerated Access Collative is "*substantial incremental QALY gains at a population level or individual incremental QALY gains perhaps greater than, for example, 2 QALYs*".[107] Durvalumab would more than meet this criteria. Moreover, all of the QALY gain was driven by PFS (appendix J), for which data are relatively mature.

Scenario analysis showed that the ICERs were consistent under differing assumptions: scenarios showed a range of ICERs between £11,298 and £30,534, excluding time horizon analyses (as a lifetime time horizon is in line with the NICE reference case). In addition, probabilistic analysis showed that the probability of durvalumab being cost-effective at a willingness to pay of £50,000 and £30,000 was 98% and 85% respectively, demonstrating a high level of certainty in the results.

Limitations of current analyses

These analyses were based on a group of patients from the PACIFIC study, whose tumours express PD-L1 on ≥1% of cells (in-line with the anticipated EMA Marketing Authorisation for durvalumab in this patient population).

[z] Pembrolizumab first-line metastatic PD-L1 ≥50% NSCLC, TA531 (versus SoC, including platinum-based combinations with either gemcitabine or paclitaxel, and a platinum-based combination with pemetrexed): base case incremental QALYs (adjusted for crossover) = 1.27; base case incremental QALYs (unadjusted for crossover) = **0.96**.[85]
Pembrolizumab second-line advanced PD-L1 ≥1% NSCLC, TA428 (versus docetaxel): base case 1 incremental QALYs = 0.614; base case 2 incremental QALYs = **0.606**.[26]
Nivolumab second-line, advanced, squamous NSCLC, TA483 (versus docetaxel): base case incremental QALYs = **0.76**.[27]
Nivolumab second-line, advanced or metastatic, non-squamous NSCLC, TA483 (versus docetaxel): base case incremental QALYs = **0.73**.[86]
Atezolizumab second-line advanced or metastatic NSCLC, TA520 (versus docetaxel and nintedanib plus docetaxel): base case incremental QALYs (versus docetaxel) = 0.66; base case incremental QALYs (versus nintedanib plus docetaxel) = 0.49; base case incremental QALYs (PD-L1 positive subgroup) = **0.28**.[130]

PACIFIC is a well-designed, double-blinded RCT. OS data from the study are still immature due to the step-change benefit observed in the durvalumab arm. Although current OS extrapolations are based on the best available evidence, and show good consistency with historical data in this setting, UK real-world evidence, and clinical expert opinion, these estimates may change as OS data from PACIFIC mature. For example, PPS was assumed to be equal between the treatment arms in the economic model; however, preliminary data show a small separation of the curves after 13 months in favour of durvalumab, which may increase as these data mature.

In addition, the level of subsequent immunotherapy use may increase in the UK over time, meaning that there would be additional costs for the SoC arm that are not considered in the economic model: nivolumab and atezolizumab are currently available through the CDF, and may move into baseline commissioning in the next few years.[27, 86, 130]

Finally, there are limited data on the use of health care resources in patients with Stage III NSCLC, as identified in the SLR. Currently, the model relies on resource use estimates from previous technology appraisals and clinical expert opinion. Further research into the resource use of patients with Stage III NSCLC would improve the precision of the results of the evaluation, although it is unlikely to change the conclusion from this analysis surrounding the use of durvalumab in this population.

Extensive sensitivity analyses were conducted to inform the uncertainties around the above limitations, which helped in understanding the key variables that have a major impact on the cost-effectiveness results. Collectively, these analyses demonstrated that durvalumab remains cost-effective in nearly all the scenarios considered.

Since the modelling approaches applied were primarily conservative, the results presented here support the conclusion that, particularly within the context of innovative end-of-life therapies, durvalumab is a clinically- and cost-effective therapeutic option for the treatment 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 platinum-based CRT.

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Single technology appraisal

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID1175]

Dear Astrazeneca UK Ltd,

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 31 August 2018 from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Tuesday 9 October.** Your response and any supporting documents should be uploaded to NICE Docs [embed NICE DOCS LINK].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Stephen Robinson, Technical Lead (Stephen.Robinson@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

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Section A: Clarification on effectiveness data

Literature searching

A1. **Priority question:** Please confirm whether one single clinical effectiveness search was conducted simultaneously across all databases for MEDLINE, MEDLINE In Process, Embase, CENTRAL, CDSR and DARE (Appendix D; p.5). If not, could you please provide the individual strategies used for each database.

A2. Please explain why durvalumab and comparator terms were not included in the clinical effectiveness database search strategy (Appendix D; p.5) when these terms were included in many of the clinical effectiveness conference searches (Appendix D; p.9-11).

PACIFIC trial

A3. **Priority question:** According to Table 4, most participants included in the PACIFIC trial received two or more overlapping cycles of definitive chemotherapy and radiotherapy. However, according to personal communication with Dr Susan Harden, [redacted].

a. Given this discrepancy, please explain how the results of the PACIFIC trial are applicable to the UK population.

b. Currently, [redacted] patients were not yet confirmed for type of CRT received. If possible, please identify the type of CRT received by these [redacted] patients.

A4. **Priority question:** Please provide definitions of “best supportive care” (BSC)/ “active follow-up”/ “Standard of care”/ “Placebo”/ “Active surveillance”, i.e. by referring to relevant guidelines. Please discuss potential differences in these definitions between centres or countries.

A5. **Priority question:** Please provide the complete version of the CSR (currently reference 75) and the CSR appendices (currently reference 92) for the PACIFIC trial. This should include all tables and figures.

A6. **Priority question:** Page 39 of the CS includes a reference to the CSR to support a statement regarding concomitant treatments in the PACIFIC trial. The CSR (reference 75 of the CS) includes a section on “pre-study, concomitant, and post-study treatment(s)”. However, the short text in that section refers to another section of the CSR which has not been provided.

a. Please provide this section as part of the complete CSR, as detailed in question A5.

b. Please provide details of concomitant and subsequent treatments in the PACIFIC trial for both, the overall trial population as well as the PD-L1 sub-population, and discuss the generalisability to UK clinical practice.

c. Please provide further details on the “re-treatment” with Durvalumab (mentioned in Table 42 of the CS), e.g. whether this is in line with UK clinical practice. Please discuss any potential impact on the findings and the generalisability of the PACIFIC trial.

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A7. **Priority question:** Further details on the analyses should be provided.

a. Please confirm whether all PD-L1 analyses were pre-specified. If not, please list the analyses which were not pre-specified.

b. For all analyses that were not pre-specified, please provide further details. Furthermore, please discuss any potential limitations to the generalisability of these analyses.

A8. **Priority question:** Please provide details of the definitions of the outcomes and statistical analysis methods used for time to progression (TTP) and post-progression survival (PPS) as these were not pre-specified outcomes in the PACIFIC trial. In line with question A7, please discuss any potential limitations to the generalisability of these analyses as well as of the definitions used. Finally, please also provide details on patient characteristics in both treatment arms within the TTP and PPS analyses.

A9. The CS states that "the final summary of product characteristics (SmPC) and European Public Assessment Report (EPAR) are not available at the present time (24 August 2018)". If these documents are available now, please share them. If not, could you please give an indication on when these documents can be expected.

A10. According to Table 2, "[redacted]" while text on page 38 states that PACIFIC "included eight UK patients across three centres (all eight were randomised to durvalumab treatment)". Please provide results for all sets of patients for all outcomes.

A11. Some of the results presented in Table 6 for PACIFIC are from the data cut-off of 22 March 2018.

a. Are more recent OS and PFS data available? If so, please re-do all analyses using these latest data.

b. If not, please clarify when updated results will be available?

c. When will the PACIFIC trial be completed and final results be available?

A12. Please provide definitions of progression-free survival (using BICR assessments according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as well as PFS2.

A13. Please provide details on adverse events related to treatment with durvalumab. These should at least cover the adverse events listed in section 5 of the FDA assessment,[1] i.e. "Immune-Mediated Pneumonitis", "Immune-Mediated Hepatitis", "Immune-Mediated Colitis", "Immune-Mediated Endocrinopathies", "Immune-Mediated Nephritis", "Immune-Mediated Dermatologic Reactions", any " Other Immune-Mediated Adverse Reactions" as well as "Infection", "Infusion-Related Reactions" and "Embryo-Fetal Toxicity".

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Section B: Clarification on cost-effectiveness data

Literature searching

B1. **Priority question:** Please provide the 2018 HRQoL searches for MEDLINE and Embase. The strategies provided in Appendix H; p.183-7 are the same as those used for the cost and healthcare resource use searches in Appendix I; p.206-10.

B2. Please confirm whether the 2016 Embase searches reported for cost-effectiveness (Appendix G; p.58), HRQoL (Appendix H; p.171) and cost and healthcare resource use (Appendix I; p.197) were joint searches for MEDLINE and Embase. If not, please provide the MEDLINE search strategies. If they were joint searches, please clarify if the Embase searches were a single search conducted simultaneously over both, the Embase and MEDLINE individual databases, or whether they were a single search of Embase conducted with the understanding that this database now contains all records from MEDLINE.

B3. Please explain the choice of comparator intervention terms used in the cost-effectiveness search strategies (Appendix G), and how this list was deemed to be complete.

B4. Were searches conducted on CDSR, CENTRAL, DARE and the Cochrane Methodology Register, as listed in Appendix G; p.57, Appendix H; p.171 and Appendix I; p.196? If so, please provide the strategies used (2016 and 2018 searches).

B5. Please provide any search strategies used to identify conference proceedings in the 2018 update searches for cost-effectiveness, HRQoL and cost and healthcare resource use.

Model structure

B6. **Priority question:** The use of a state transition model instead of a partitioned survival analysis model was justified by the crossing of extrapolated overall survival (OS) and progression-free (PFS) curves. This issue does not appear to be resolved with the chosen approach to state transition modelling: in the model, a fix was necessary because the probability of progression exceeded that of the probability of progression or death after 2.3 years into the model time horizon for durvalumab and 5.5 years for standard of care. This indicates that progression and survival curves cross. If such a fix was necessary in the state transition modelling approach, it is unclear how this approach was an improvement over partitioned survival analysis, where such a fix could have also been applied. Furthermore, when the trial data are OS and PFS, according to NICE DSU Technical Support Document (TSD) 19,[2] the use of state transition modelling is associated with significant challenges and potential biases.

a. Please comment on how the chosen approach of state transition modelling addressed the problem of crossing OS and PFS curves.

b. TSD 19 recommends that when trial data are in the form of OS and PFS (as in the PACIFIC study), to obtain data for a state transition model, three different survival analyses are necessary: 1. Time to death from progression-free state (progression events censored), 2. Time to progression from progression-free state (death events censored) and 3. Time to death from progressed disease state. Only analyses 2 and 3 were performed. Please explain why analysis 1

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was not performed and comment on the validity of the extrapolations and the state transition model approach in light of this omission.

c. The PPS analysis is potentially biased because groups are no longer balanced (see TSD 19).[2] More specifically, this analysis uses data from early progressors, who may have different survival to patients with later progression. Moreover, the PPS data include more patients treated with placebo (who progress earlier), introducing additional bias. Please comment on these biases and reflect on the superiority of the state transition modelling approach over a partitioned survival analysis approach.

d. Please supply a revised model file, enabling partitioned survival analysis as a scenario.

B7. **Priority question:** Disease progression was considered to be a clinically important and patient-relevant endpoint in the model. According to the CS, progressed patients experience deterioration in HRQoL, worsening of symptoms and the possibility of cure is lost. Although patients can progress in two main ways, locally, or to advanced metastatic disease, there is only one progressed disease health state.

a. Please explain what is meant by a loss of possibility of cure upon progression, given that a proportion of patients in both arms are still treated with subsequent immunotherapy post-progression.

b. Please provide more information on why local progression and advanced metastatic progression are modelled in one health state and reflect on how these two types of progression may differ regarding HRQoL, costs, symptoms and subsequent treatment.

c. If the state transition modelling approach is viewed as most appropriate, please provide a scenario including four health states in which progressed disease is split into local progression and advanced metastatic disease.

Treatment effectiveness

B8. **Priority question:** The selected extrapolated PFS and PPS curves pass either through or above the plateau at the end of the Kaplan-Meier (KM) curve (CS Figures 32, 33, 36). It is noteworthy that the KM curves exhibit long tails but the estimated survival probabilities at the end of the curves are affected by censoring as the numbers at risk are low (e.g. [redacted] for placebo at 24 months in Figure 8 of the CS). The choice of any parametric survival distribution that lies above these tails will probably over-estimate survival.

a. Please explain the extrapolation methods, especially whether the data in the KM tails were used for the curve fitting.

b. Please justify the choice of parametric survival model (generalised gamma for PFS, which is associated with the highest expected longer-term survival for durvalumab; and exponential for PPS, which crosses the KM tail at its very end) in the light that these may over-estimate survival as observed in PACIFIC. If, on reflection, it is considered that survival might be over-estimated then please amend the choice of survival model.

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c. Please provide an analysis in which parametric survival models were fitted to data excluding patient numbers at risk < 5, to reduce the uncertainty about the impact of these estimates on the extrapolation results, as recommended by Tremblay et al. 2015.[3]

B9. **Priority question:** There are concerns about the treatment waning effect incorporated in the model, including the cut-off point and its implementation.

a. There is no evidence supporting the use of a 10-year cut-off point. The data used for validation come from company submissions in a different treatment setting. Please comment on whether experts were consulted, and whether any other efforts were made to validate both the cut-off point and the shape of the survival curve (or proportion of patients alive and not progressed) from that time onwards. Please provide supporting evidence of the validation methods.

b. Please comment on the appropriateness of incorporating a treatment waning effect by setting the hazard (for progression and pre-progression deaths) for durvalumab equal to the hazard for placebo. Please also comment on the alternative method, which is setting the durvalumab PFS and TTP curves equal to those for placebo at the cut-off point, to reflect the same survival at this time, and amend your choice of method, if necessary.

B10. **Priority question:** General population mortality is applied to PFS and PPS by capping PFS and PPS at general population survival. In addition, it is subtracted from the transition probability from the progression-free to the progressed disease health state (only in a fix taking effect at 2.3 years for durvalumab and 5.5 years for standard of care). This would lead to fewer people transitioning to progression, whilst the number of people in the progression-free health state is not reduced by background mortality. Please amend this in the model.

B11. **Priority question:** PPS extrapolations are pooled for both treatment arms.

a. Please comment on whether this is appropriate, given that patients on placebo progressed sooner.

b. Please provide details on any efforts to validate the extrapolated PPS using expert opinion.

c. Please provide a scenario analysis in which PPS was fitted separately per treatment arm.

B12. The START and KEYNOTE-024[4] studies were used to inform scenario analysis on PPS.

a. Please provide more detail on the selection of these studies. In particular, explain how KEYNOTE-024 was selected (not included in the SLR) and whether there were no other relevant studies that could have been used to inform this.

b. Please also comment on the generalisability to the post-progression survival setting in terms of the comparability of patient characteristics in the PACIFIC post-progression population and the START and KEYNOTE populations.

B13. Please provide some information on and justification for how age calculations were performed in the model (using the distribution of age obtained from PACIFIC), and

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comment on the possible implications for model outcomes, through general background mortality and age dependent utilities.

B14. With regards to subsequent treatments, assumptions were made about the proportion of metastatic patients and those who receive immuno-oncological (IO) treatment. Please comment on:

a. Whether the proportions of metastatic patients (37%; CS page 146) were equal in both treatment arms. If not, please provide the proportions for each treatment arm.

b. The proportions of metastatic patients receiving an IO treatment, were lower for durvalumab than for placebo (6% versus 24%; CS Table 55 and model file). Please provide details of the source for these proportions (in the model an advisory board is cited, but Table 55 of the CS refers to PACIFIC). Please also comment on whether these proportions were obtained in patients with metastatic progression.

c. Whether these IO treatment proportions are representative of UK clinical practice.

Adverse events

B15. As only grade 3/4 AEs are considered in the model, a substantial number of pneumonias (those < grade 3 according to tables 19 and 20 of the CS) are not accounted for. Please justify the assumption that these < grade 3 pneumonias were not associated with any relevant treatment costs.

Health-related quality of life

B16. **Priority question:** There are concerns regarding the face validity of the health-state utility scores. The utility score for the progression-free health state is higher than for the general population. In the CS it is stated that general population norms may be outdated, and that they were based on EQ-5D-3L while PACIFIC used EQ-5D-5L. However, more recent population norms by Szende et al. (taken from EuroQoL group website) for the UK-England population (2008)[5] are not substantially higher (i.e. 0.81 for age 55-64) and Ara and Brazier 2011 report a similar score of around 0.802 for age 63 and according to this same publication, persons with a history of cancer had a substantially lower utility score (0.73 for age 65-70).[6] In addition, the SLR for utility scores identified a paper by Chouaid et al. 2013 on stage IIIb/IV NSCLC reporting a utility score of 0.71.[7]

a. In light of the above, please comment on the face validity of utility values used in the model, particularly the health state utility for PF of 0.81, and comment on the potential use of the Chouaid et al. 2013 utility value.[7]

b. For comparison and reference, please provide also 5L utilities based on the algorithm by Devlin et al 2018.[8]

B17. **Priority question:** With the utility values used being high, the ERG considers it important to adjust the utilities by population norms. Please include general population level utility decrements in the base-case analysis.[8]

B18. The base-case economic model does not apply utility decrements for AEs as these are assumed to be incorporated in the utilities as observed. However, as treatment is not

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a factor in the mixed utility model (Table 39), any differences in QoL between treatment arms caused by AEs will not be incorporated in the QALY results. To explore the possible impact of AEs:

a. Alternative to the base-case mixed model, please provide ICER results using a mixed model with treatment included as a factor.

b. Alternative to the scenario using PACIFIC EQ-5D-5L mapped utilities, please provide results using average utility scores per treatment arm (instead of overall scores).

Costs and resource use

B19. **Priority question:** Base-case health-state resource use is calculated using data from TA531[9] and clinical expert opinion, as per reference 139[10]. After inspection of reference 139, the ERG cannot find any reason for monitoring and management cost in PF to be zero after the 5th year, as long-term management did not seem to be a topic in the clinical consultation meeting.

a. Please justify the zero-cost assumption.

b. Furthermore, please add the results using only TA447 data for resource use (the button in cell D121 of the model's controls worksheet) to the list of scenarios in table 55 and discuss the relevance of both approaches.

B20. **Priority question:** Resource use in PD management and monitoring were based on TA531,[9] where these were estimated for patients with metastatic disease. However, in the PACIFIC ITT population only 37% of all progression events were metastatic (CS page 146).

a. Please justify that using TA531 as the sole source for health-state costs in progressed disease is not overestimating costs for those patients with local disease progression.

b. In addition, please explore the impact of lower costs for patients with local disease progression in a scenario analysis.

B21. Table 48 of the CS states that costs are 'per week' (also CS page 169) and 'per cycle' (column header) but after inspection of the model they appear to be monthly. Please confirm whether the costs are weekly or monthly, and amend the analysis, if necessary.

B22. The model base-case assumes perfect vial sharing (0% wastage). Please justify that perfect vial sharing is feasible in clinical practice, given the fact that the number of patients eligible for treatment with durvalumab in England and Wales is expected to be [redacted] annually (CS page 32).

B23. The cost of subsequent treatment is higher for the placebo arm, because more patients in the placebo arm received IO therapy compared to durvalumab. However, PPS is assumed to be the same between treatment arms. Please justify the different assumptions for costs (differential costs per treatment strategy with higher costs in placebo) and treatment effectiveness (equality).

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Sensitivity analyses

B24. A probabilistic sensitivity analysis (PSA) was run for 1,000 iterations for the base-case analysis (durvalumab versus SoC). The CS report, appendix and model file appear contradictory in terms of what is and what is not included in the PSA.

a. Please provide a corrected overview of what is and is not included in the PSA. Specifically provide more detail on the inclusion of PFS, TTP and PPS parameters. Please provide a model enabling a PSA that incorporates all relevant parameters.

b. Patient characteristics (age, body surface area [BSA], proportion male) appear to be included in the PSA (model file), although they are considered first order uncertainty and typically not reflected in PSAs. Please exclude these parameters from the PSA.

c. Please provide the correct number for incremental costs in Table 54 of the company submission.

d. Compared with the deterministic base-case results, probabilistic incremental QALYs are lower. Please comment on how this difference occurred.

Errors in the model file

B25. **Priority question:** The ERG noted the following errors in the model file and requests a correction.

a. Please correct age calculations for standard of care on the PF_BSC worksheet (column CU), to match the calculations for durvalumab on the PF_Durvalumab worksheet column CU.

b. The utility decrement used for the scenario “Include age-related utility decrement” on Controls worksheet cell D129, is an addition of a positive number, resulting in even higher utility values.

Scenario analyses

B26. **Priority question:** Not all scenarios discussed in Table 55 of the CS are enabled in the submitted model file. For other scenarios, buttons on the control sheet are not working and the ICERs are not reproducible.

a. Please provide a description of how to implement all scenarios in the model.

b. Please correct the following issues in the model file:

i. In Controls worksheet row 47, changing the setting of Extrapolation method used results in a “Value” error message.

ii. In Controls worksheet row 68, the Model metastatic survival? buttons do not work.

c. It was not possible to reproduce the results in Table 55 of the CS for the following scenarios:

I. “PF utilities capped at general population levels”

II. “Include AE disutilities”

III. “PACIFIC EQ-5D-5L data”. Please also provide the values applied for both PF and PD, as the PD value is missing in table 55 and the PF

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value of 0.818 does not match the overall PF utility as reported in appendix P (table 41) but is the utility of both PF and PD taken together.

IV. The scenario using a partitioned survival analysis was not supplied. Note that the reported ICER in Table 55 of the CS is exactly the same as the base-case ICER and appears erroneous.

d. Please provide a revised model file with details of the changes and scenarios.

Validation

B27. The assumptions used in the economic model for long-term survival outcomes, subsequent treatments, and health-state management costs rely quite heavily on clinical expert opinion. As the documents provided to substantiate these opinions appear quite concise, please provide full minutes of the expert meetings.

Section C: Textual clarifications and additional points

C1. Table 26 of the CS defines the intervention in the PACIFIC trial as “Durvalumab 10mg/kg Q2W”, i.e. 10 mg of durvalumab given every two weeks. In contrast, Table 4 of the CS appendices lists the “consolidation / maintenance therapy as “10mg/kg via 60 minute IV once a week up to 12 weeks”. Please confirm which dosing scheme was used in the PACIFIC trial.

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References

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[9] National Institute for Health and Care Excellence. *Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer: NICE technology appraisal guidance 531 [Internet]*. London: NICE, 2018 [accessed 7.8.18] Available from: https://www.nice.org.uk/guidance/ta531

[10] AstraZeneca. Resource use associated with monitoring of patients. (DOF-IMF-006-AUG18) 28 August 2018 2018. Data on File. [PDF provided by the Company].

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Single technology appraisal

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID1175]

Dear Astrazeneca UK Ltd,

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 31 August 2018 from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Tuesday 9 October.** Your response and any supporting documents should be uploaded to NICE Docs [embed NICE DOCS LINK].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Stephen Robinson, Technical Lead (Stephen.Robinson@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Section A: Clarification on effectiveness data

Literature searching

A1. **Priority question:** Please confirm whether one single clinical effectiveness search was conducted simultaneously across all databases for MEDLINE, MEDLINE In Process, Embase, CENTRAL, CDSR and DARE (Appendix D; p.5). If not, could you please provide the individual strategies used for each database.

A2. Please explain why durvalumab and comparator terms were not included in the clinical effectiveness database search strategy (Appendix D; p.5) when these terms were included in many of the clinical effectiveness conference searches (Appendix D; p.9-11).

PACIFIC trial

A3. **Priority question:** According to Table 4, most participants included in the PACIFIC trial received two or more overlapping cycles of definitive chemotherapy and radiotherapy. However, according to personal communication with Dr Susan Harden, most UK patients receive sequential rather than overlapping treatment. Therefore, the efficacy and safety of durvalumab was not evaluated after sequential CRT.

a. Given this discrepancy, please explain how the results of the PACIFIC trial are applicable to the UK population.

b. Currently, [redacted] patients were not yet confirmed for type of CRT received. If possible, please identify the type of CRT received by these [redacted] patients.

A4. **Priority question:** Please provide definitions of “best supportive care” (BSC)/ “active follow-up”/ “Standard of care”/ “Placebo”/ “Active surveillance”, i.e. by referring to relevant guidelines. Please discuss potential differences in these definitions between centres or countries.

A5. **Priority question:** Please provide the complete version of the CSR (currently reference 75) and the CSR appendices (currently reference 92) for the PACIFIC trial. This should include all tables and figures.

A6. **Priority question:** Page 39 of the CS includes a reference to the CSR to support a statement regarding concomitant treatments in the PACIFIC trial. The CSR (reference 75 of the CS) includes a section on “pre-study, concomitant, and post-study treatment(s)”. However, the short text in that section refers to another section of the CSR which has not been provided.

a. Please provide this section as part of the complete CSR, as detailed in question A5.

b. Please provide details of concomitant and subsequent treatments in the PACIFIC trial for both, the overall trial population as well as the PD-L1 sub-population, and discuss the generalisability to UK clinical practice.

c. Please provide further details on the “re-treatment” with Durvalumab (mentioned in Table 42 of the CS), e.g. whether this is in line with UK clinical practice. Please discuss any potential impact on the findings and the generalisability of the PACIFIC trial.

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A7. **Priority question:** Further details on the analyses should be provided.

a. Please confirm whether all PD-L1 analyses were pre-specified. If not, please list the analyses which were not pre-specified.

b. For all analyses that were not pre-specified, please provide further details. Furthermore, please discuss any potential limitations to the generalisability of these analyses.

A8. **Priority question:** Please provide details of the definitions of the outcomes and statistical analysis methods used for time to progression (TTP) and post-progression survival (PPS) as these were not pre-specified outcomes in the PACIFIC trial. In line with question A7, please discuss any potential limitations to the generalisability of these analyses as well as of the definitions used. Finally, please also provide details on patient characteristics in both treatment arms within the TTP and PPS analyses.

A9. The CS states that "the final summary of product characteristics (SmPC) and European Public Assessment Report (EPAR) are not available at the present time (24 August 2018)". If these documents are available now, please share them. If not, could you please give an indication on when these documents can be expected.

A10. According to Table 2, "[redacted]" while text on page 38 states that PACIFIC "included eight UK patients across three centres (all eight were randomised to durvalumab treatment)". Please provide results for all sets of patients for all outcomes.

A11. Some of the results presented in Table 6 for PACIFIC are from the data cut-off of 22 March 2018.

a. Are more recent OS and PFS data available? If so, please re-do all analyses using these latest data.

b. If not, please clarify when updated results will be available?

c. When will the PACIFIC trial be completed and final results be available?

A12. Please provide definitions of progression-free survival (using BICR assessments according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as well as PFS2.

A13. Please provide details on adverse events related to treatment with durvalumab. These should at least cover the adverse events listed in section 5 of the FDA assessment,[1] i.e. "Immune-Mediated Pneumonitis", "Immune-Mediated Hepatitis", "Immune-Mediated Colitis", "Immune-Mediated Endocrinopathies", "Immune-Mediated Nephritis", "Immune-Mediated Dermatologic Reactions", any " Other Immune-Mediated Adverse Reactions" as well as "Infection", "Infusion-Related Reactions" and "Embryo-Fetal Toxicity".

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Section B: Clarification on cost-effectiveness data

Literature searching

B1. **Priority question:** Please provide the 2018 HRQoL searches for MEDLINE and Embase. The strategies provided in Appendix H; p.183-7 are the same as those used for the cost and healthcare resource use searches in Appendix I; p.206-10.

B2. Please confirm whether the 2016 Embase searches reported for cost-effectiveness (Appendix G; p.58), HRQoL (Appendix H; p.171) and cost and healthcare resource use (Appendix I; p.197) were joint searches for MEDLINE and Embase. If not, please provide the MEDLINE search strategies. If they were joint searches, please clarify if the Embase searches were a single search conducted simultaneously over both, the Embase and MEDLINE individual databases, or whether they were a single search of Embase conducted with the understanding that this database now contains all records from MEDLINE.

B3. Please explain the choice of comparator intervention terms used in the cost-effectiveness search strategies (Appendix G), and how this list was deemed to be complete.

B4. Were searches conducted on CDSR, CENTRAL, DARE and the Cochrane Methodology Register, as listed in Appendix G; p.57, Appendix H; p.171 and Appendix I; p.196? If so, please provide the strategies used (2016 and 2018 searches).

B5. Please provide any search strategies used to identify conference proceedings in the 2018 update searches for cost-effectiveness, HRQoL and cost and healthcare resource use.

Model structure

B6. **Priority question:** The use of a state transition model instead of a partitioned survival analysis model was justified by the crossing of extrapolated overall survival (OS) and progression-free (PFS) curves. This issue does not appear to be resolved with the chosen approach to state transition modelling: in the model, a fix was necessary because the probability of progression exceeded that of the probability of progression or death after 2.3 years into the model time horizon for durvalumab and 5.5 years for standard of care. This indicates that progression and survival curves cross. If such a fix was necessary in the state transition modelling approach, it is unclear how this approach was an improvement over partitioned survival analysis, where such a fix could have also been applied. Furthermore, when the trial data are OS and PFS, according to NICE DSU Technical Support Document (TSD) 19,[2] the use of state transition modelling is associated with significant challenges and potential biases.

a. Please comment on how the chosen approach of state transition modelling addressed the problem of crossing OS and PFS curves.

b. TSD 19 recommends that when trial data are in the form of OS and PFS (as in the PACIFIC study), to obtain data for a state transition model, three different survival analyses are necessary: 1. Time to death from progression-free state (progression events censored), 2. Time to progression from progression-free state (death events censored) and 3. Time to death from progressed disease state. Only analyses 2 and 3 were performed. Please explain why analysis 1

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was not performed and comment on the validity of the extrapolations and the state transition model approach in light of this omission.

c. The PPS analysis is potentially biased because groups are no longer balanced (see TSD 19).[2] More specifically, this analysis uses data from early progressors, who may have different survival to patients with later progression. Moreover, the PPS data include more patients treated with placebo (who progress earlier), introducing additional bias. Please comment on these biases and reflect on the superiority of the state transition modelling approach over a partitioned survival analysis approach.

d. Please supply a revised model file, enabling partitioned survival analysis as a scenario.

B7. **Priority question:** Disease progression was considered to be a clinically important and patient-relevant endpoint in the model. According to the CS, progressed patients experience deterioration in HRQoL, worsening of symptoms and the possibility of cure is lost. Although patients can progress in two main ways, locally, or to advanced metastatic disease, there is only one progressed disease health state.

a. Please explain what is meant by a loss of possibility of cure upon progression, given that a proportion of patients in both arms are still treated with subsequent immunotherapy post-progression.

b. Please provide more information on why local progression and advanced metastatic progression are modelled in one health state and reflect on how these two types of progression may differ regarding HRQoL, costs, symptoms and subsequent treatment.

c. If the state transition modelling approach is viewed as most appropriate, please provide a scenario including four health states in which progressed disease is split into local progression and advanced metastatic disease.

Treatment effectiveness

B8. **Priority question:** The selected extrapolated PFS and PPS curves pass either through or above the plateau at the end of the Kaplan-Meier (KM) curve (CS Figures 32, 33, 36). It is noteworthy that the KM curves exhibit long tails but the estimated survival probabilities at the end of the curves are affected by censoring as the numbers at risk are low (e.g. <5 for placebo at 24 months in Figure 8 of the CS). The choice of any parametric survival distribution that lies above these tails will probably over-estimate survival.

a. Please explain the extrapolation methods, especially whether the data in the KM tails were used for the curve fitting.

b. Please justify the choice of parametric survival model (generalised gamma for PFS, which is associated with the highest expected longer-term survival for durvalumab; and exponential for PPS, which crosses the KM tail at its very end) in the light that these may over-estimate survival as observed in PACIFIC. If, on reflection, it is considered that survival might be over-estimated then please amend the choice of survival model.

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c. Please provide an analysis in which parametric survival models were fitted to data excluding patient numbers at risk < 5, to reduce the uncertainty about the impact of these estimates on the extrapolation results, as recommended by Tremblay et al. 2015.[3]

B9. **Priority question:** There are concerns about the treatment waning effect incorporated in the model, including the cut-off point and its implementation.

a. There is no evidence supporting the use of a 10-year cut-off point. The data used for validation come from company submissions in a different treatment setting. Please comment on whether experts were consulted, and whether any other efforts were made to validate both the cut-off point and the shape of the survival curve (or proportion of patients alive and not progressed) from that time onwards. Please provide supporting evidence of the validation methods.

b. Please comment on the appropriateness of incorporating a treatment waning effect by setting the hazard (for progression and pre-progression deaths) for durvalumab equal to the hazard for placebo. Please also comment on the alternative method, which is setting the durvalumab PFS and TTP curves equal to those for placebo at the cut-off point, to reflect the same survival at this time, and amend your choice of method, if necessary.

B10. **Priority question:** General population mortality is applied to PFS and PPS by capping PFS and PPS at general population survival. In addition, it is subtracted from the transition probability from the progression-free to the progressed disease health state (only in a fix taking effect at 2.3 years for durvalumab and 5.5 years for standard of care). This would lead to fewer people transitioning to progression, whilst the number of people in the progression-free health state is not reduced by background mortality. Please amend this in the model.

B11. **Priority question:** PPS extrapolations are pooled for both treatment arms.

a. Please comment on whether this is appropriate, given that patients on placebo progressed sooner.

b. Please provide details on any efforts to validate the extrapolated PPS using expert opinion.

c. Please provide a scenario analysis in which PPS was fitted separately per treatment arm.

B12. The START and KEYNOTE-024[4] studies were used to inform scenario analysis on PPS.

a. Please provide more detail on the selection of these studies. In particular, explain how KEYNOTE-024 was selected (not included in the SLR) and whether there were no other relevant studies that could have been used to inform this.

b. Please also comment on the generalisability to the post-progression survival setting in terms of the comparability of patient characteristics in the PACIFIC post-progression population and the START and KEYNOTE populations.

B13. Please provide some information on and justification for how age calculations were performed in the model (using the distribution of age obtained from PACIFIC), and

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comment on the possible implications for model outcomes, through general background mortality and age dependent utilities.

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a. Whether the proportions of metastatic patients (37%; CS page 146) were equal in both treatment arms. If not, please provide the proportions for each treatment arm.

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a. In light of the above, please comment on the face validity of utility values used in the model, particularly the health state utility for PF of 0.81, and comment on the potential use of the Chouaid et al. 2013 utility value.[7]

b. For comparison and reference, please provide also 5L utilities based on the algorithm by Devlin et al 2018.[8]

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a factor in the mixed utility model (Table 39), any differences in QoL between treatment arms caused by AEs will not be incorporated in the QALY results. To explore the possible impact of AEs:

a. Alternative to the base-case mixed model, please provide ICER results using a mixed model with treatment included as a factor.

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Costs and resource use

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a. Please justify the zero-cost assumption.

b. Furthermore, please add the results using only TA447 data for resource use (the button in cell D121 of the model's controls worksheet) to the list of scenarios in table 55 and discuss the relevance of both approaches.

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a. Please justify that using TA531 as the sole source for health-state costs in progressed disease is not overestimating costs for those patients with local disease progression.

b. In addition, please explore the impact of lower costs for patients with local disease progression in a scenario analysis.

B21. Table 48 of the CS states that costs are 'per week' (also CS page 169) and 'per cycle' (column header) but after inspection of the model they appear to be monthly. Please confirm whether the costs are weekly or monthly, and amend the analysis, if necessary.

B22. The model base-case assumes perfect vial sharing (0% wastage). Please justify that perfect vial sharing is feasible in clinical practice, given the fact that the number of patients eligible for treatment with durvalumab in England and Wales is expected to be 367 annually (CS page 32).

B23. The cost of subsequent treatment is higher for the placebo arm, because more patients in the placebo arm received IO therapy compared to durvalumab. However, PPS is assumed to be the same between treatment arms. Please justify the different assumptions for costs (differential costs per treatment strategy with higher costs in placebo) and treatment effectiveness (equality).

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Sensitivity analyses

B24. A probabilistic sensitivity analysis (PSA) was run for 1,000 iterations for the base-case analysis (durvalumab versus SoC). The CS report, appendix and model file appear contradictory in terms of what is and what is not included in the PSA.

a. Please provide a corrected overview of what is and is not included in the PSA. Specifically provide more detail on the inclusion of PFS, TTP and PPS parameters. Please provide a model enabling a PSA that incorporates all relevant parameters.

b. Patient characteristics (age, body surface area [BSA], proportion male) appear to be included in the PSA (model file), although they are considered first order uncertainty and typically not reflected in PSAs. Please exclude these parameters from the PSA.

c. Please provide the correct number for incremental costs in Table 54 of the company submission.

d. Compared with the deterministic base-case results, probabilistic incremental QALYs are lower. Please comment on how this difference occurred.

Errors in the model file

B25. **Priority question:** The ERG noted the following errors in the model file and requests a correction.

a. Please correct age calculations for standard of care on the PF_BSC worksheet (column CU), to match the calculations for durvalumab on the PF_Durvalumab worksheet column CU.

b. The utility decrement used for the scenario “Include age-related utility decrement” on Controls worksheet cell D129, is an addition of a positive number, resulting in even higher utility values.

Scenario analyses

B26. **Priority question:** Not all scenarios discussed in Table 55 of the CS are enabled in the submitted model file. For other scenarios, buttons on the control sheet are not working and the ICERs are not reproducible.

a. Please provide a description of how to implement all scenarios in the model.

b. Please correct the following issues in the model file:

i. In Controls worksheet row 47, changing the setting of Extrapolation method used results in a “Value” error message.

ii. In Controls worksheet row 68, the Model metastatic survival? buttons do not work.

c. It was not possible to reproduce the results in Table 55 of the CS for the following scenarios:

I. “PF utilities capped at general population levels”

II. “Include AE disutilities”

III. “PACIFIC EQ-5D-5L data”. Please also provide the values applied for both PF and PD, as the PD value is missing in table 55 and the PF

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value of 0.818 does not match the overall PF utility as reported in appendix P (table 41) but is the utility of both PF and PD taken together.

IV. The scenario using a partitioned survival analysis was not supplied. Note that the reported ICER in Table 55 of the CS is exactly the same as the base-case ICER and appears erroneous.

d. Please provide a revised model file with details of the changes and scenarios.

Validation

B27. The assumptions used in the economic model for long-term survival outcomes, subsequent treatments, and health-state management costs rely quite heavily on clinical expert opinion. As the documents provided to substantiate these opinions appear quite concise, please provide full minutes of the expert meetings.

Section C: Textual clarifications and additional points

C1. Table 26 of the CS defines the intervention in the PACIFIC trial as “Durvalumab 10mg/kg Q2W”, i.e. 10 mg of durvalumab given every two weeks. In contrast, Table 4 of the CS appendices lists the “consolidation / maintenance therapy as “10mg/kg via 60 minute IV once a week up to 12 weeks”. Please confirm which dosing scheme was used in the PACIFIC trial.

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References

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Submission from Roy Castle Lung Cancer Foundation, for consideration by NICE, in their review of Durvalumab for maintenance treatment of unresectable non small cell lung cancer after platinum based chemoradiation [ID1175]

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 10%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of non small cell lung cancer (nsclc).

General Points

1. Locally advanced (stage III) lung cancer, is divided in to Stage IIIA and Stage IIIB. In the National Lung Cancer Audit Report 2017 (patients diagnosed in 2016), Stage IIIA accounted for 12% and Stage IIIB for 4% of cases. The Report showed that the one year survival for all Stage III patients was only 42.5% (including surgical cases). The current standard of care for patients with unresectable Stage III disease is chemotherapy and radiation, followed by active surveillance to monitor progression. We understand that in this patient group, after chemoradiation, only about 15% of patients are alive at 5 years. There is obvious unmet need.

2. The relatively recent addition of targeted therapies and immunotherapy, in the treatment of nsclc, has ensured active therapy options for many with nsclc. However, overall outcomes for many of this patient population remains poor. The availability of new targets and therapy choices being of key future importance.

3. Improving survival, extension of life and improving quality of life is of obvious importance in this patient group.

This Product

1. Mechanism

   Durvalumab is a monoclonal antibody, directed against PD-L1, blocking PD-L1 interaction with PD-1 and CD80 on T cells. This counters the tumour's immune-evading tactics, thus inducing an immune response.

2. Well tolerated

   Duvalumab is administered as a one hour two weekly intravenous infusion.

   The most common side effects associated with Durvalumab include fatigue, shortness of breath, decreased appetite, cough, nausea, musculoskeletal pain, peripheral oedema and constipation. More serious side effects, though uncommon, can occur if the immune system attacks healthy tissues in the body, such as the lungs, colon, liver, kidneys or hormone producing glands. In the anecdotal patient experience reported to us, these immunotherapeutic agents appear to be fairly well tolerated.

3. Outcome of treatment

   We do not have any additional data, beyond that publically available.

   We note, however, the results of the PACIFIC trial - a randomised double-blind, placebo controlled trial, conducted in 713 patients with unresectable, Stage III nsclc. Patients had completed concurrent platinum-based chemotherapy and radiation within 42 days prior to study drug administration. The median PFS was 16.8 months in the Durvalumab arm and 5.6 months in the placebo arm. Thus, in patient terms, half of those tumours not treated with immunotherapy, had begun to grow again within six months, whilst half of those, who had received Durvalumab, remained stable or in remission at almost one year and five months.

Our observations come from a combination of one-to-one discussion with lung cancer patients, published research, on line patient contact and our patient information helpline.

In summary

Durvalumab maintenance represents a new option in this Stage III nsclc patient group, with high unmet need.

[redacted], **Medical Director, RCLCF.**

March 2018.

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Professional organisation submission

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID1175]

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-NCRI-RCP-ACP-RCR**

3. Job title or position	**RCP registrar**
4. Are you (please tick all that apply):	
5a. Brief description of the organisation (including who funds it).	
5b. 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?	The main aim of treatment would be to delay / prevent relapse of locally advanced non-small cell lung cancer (NSCLC) after primary chemo-radiotherapy treatment and hence improve quality of life and survival.
7. What do you consider a clinically significant treatment response?	Improved median progression free survival of 8 months and median overall survival of 4 months.
8. In your view, is there an unmet need for patients and	Yes, the best study results for stage III NSCLC treated with primary chemoradiotherapy suggest median survivals of around 28 months with 25 – 30% of patients alive at 5 years (‘cured’) can be achieved using

healthcare professionals in this condition?	modern staging / treatment practices. In a less selected population typical of patients currently treated in the UK current median survivals are likely to be in the range of 20 – 24 months with 15 – 20% of patients alive at 5 years [1]. 1. Robinson SD et.al Radical radiotherapy for Non-Small Cell Lung Cancer (NSCLC): Real world outcomes for two accelerated fractionation schedules. Lung Cancer 115 Suppl 1S 71:163;2018.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The majority of new lung cancer cases are non-small cell lung cancer (NSCLC), which now accounts for 85-90% of lung cancers with almost 38,000 new cases diagnosed in the UK during 2015. Despite recent advances in the surgical management of lung cancer but a significant number of patients still present with disease that is too advanced for surgery or have significant co-morbidities that make them inoperable at diagnosis. Therefore, radical radiotherapy (RT) remains a mainstay of treatment particularly in locally advanced (stage III) disease. However, local relapses after radiotherapy are common with 85% of repeat bronchoscopies after radical RT demonstrating persistent tumour. Improving local control remains an important goal particularly as successful local control has been found to correlate with improved survival. Strategies that have improved local control include the addition of chemotherapy as a radio-sensitizer, the acceleration of the RT schedule and dose escalation. Concurrent chemo-radiotherapy (CTRT) is the current standard of care for locally advanced stage III lung cancer with the recent RTOG 0617 trial [1] showing we can expect median survival rates of approximately 27.8 months for patients with PET staged III disease in the control arm of 60 Gy given in 30 fractions. However, this study has acted as a reminder that concurrent CTRT can be extremely taxing for the patient and the majority of patients may not be suitable for the concurrent approach because of their age [2], co-morbidities and poorer performance status. A national survey of CTRT practice, the majority of Clinical Oncologists supported this suggesting that clinicians felt that less than 30% of stage III NSCLC patients were suitable for the concurrent chemo-radiotherapy approach [3] and would use sequential CTRT or radiotherapy alone for the majority of patients assessed. Alternative strategies employed in UK practice to improve local control intensify the anti-tumour effect through the acceleration of the RT schedule. The best example of this approach is provided by the Continuous Hyper-

	fractionated Accelerated Radiation Therapy (CHART) schedule [4]. However, CHART needs weekend treatments and patient hospitalization, and implementation proved challenging as recognized in the 2011 National Institute of Clinical Excellence (NICE) guidelines for the management of lung cancer and the recommendation for CHART is qualified and allows a RT regime with a biologically equivalent dose (BED) can be used. In the UK the commonest dose/fractionation used is an accelerated hypofractionated regimen of 55Gy in 20 fractions over 4 weeks [5] which still shortens the overall treatment time which is felt to be important in combating tumour repopulation. 1. Bradley JD, Paulus R, Komaki R, Master G, Blumenschein G, Child S, *et al*. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015; 16(2):187-99. 2. Miller ED et al. The addition of chemotherapy to radiation therapy improves survival in elderly patients with stage III NSCLC. JTO 2018;13:426-435 3. Helbrow J, MacNicoll F, Bayman N, Faivre-Finn C. Concurrent chemoradiotherapy (cCTRT) for locally advanced unresectable non-small cell lung cancer (LA-NSCLC): A national survey of current practice. Lung Cancer. 2012; 75(1):S50-S51. 4. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M, for the CHART Steering Committee. Continuous hyperfractionated accelerated radio-therapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: A randomised multicentre trial. Lancet. 1997; 350:161–165. 5. Prewett SL, Aslam S, Williams MV, Gilligan D. The management of lung cancer: A UK survey of Oncologists. Clin Oncol. 2012; 24:402-9
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	National Institute of Clinical Excellence. The Diagnosis and Treatment of Lung Cancer. April 2011. (Currently being updated with draft versions expected Autumn 2018). Scottish Intercollegiate Guidelines Network - 137 Management of lung cancer guideline, 2014. ASCO / ASTRO Definitive and Adjuvant Radiotherapy in Locally Advanced Non–Small-Cell Lung, 2015.
• Is the pathway of care well defined? Does it vary or are there	The patients will come through lung cancer MDTs which will oversee the diagnostic and referral pathways to appropriate specialists for treatment. This process will also include an assessment of fitness to undergo multi-modality treatment with systemic treatments (chemotherapy, immunotherapy or targeted agents), radiotherapy and surgery. Locally advanced Stage III NSCLC encompasses a wide

differences of opinion between professionals across the NHS?	range of clinical scenarios which means individualisation of treatment is important and does mean there is a variation of treatment practice across the UK which is documented through the National Lung Cancer Audit.
• What impact would the technology have on the current pathway of care?	There would be an impact with the addition of an immunotherapy treatment given 2 weekly for one year following the completion of standard concurrent chemo-radiotherapy treatment. However, numbers of patients receiving concurrent chemo-radiotherapy for stage III NSCLC will be relatively small making impact modest.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Immunotherapy is a standard of care treatment for stage IV NSCLC (ID 811, 840, 970, 990) with agents targeting PD-L1 pathways. The administration requirements and side effect profile of durvalumab will be very similar to the PD-L1 inhibitiors in routine use. The adoption of the technology would be an addition workload on departments but would not require any adaption of current treatment pathways.
• How does healthcare resource use differ between the technology and current care?	As above
• In what clinical setting should the technology be used?	Chemotherapy assessment / treatment clinics in secondary care.
• What investment is needed to introduce the technology?	The training requirements for adoption of durvalumab maintenance treatment will be very small but there is an additional workload for chemotherapy units with a requirement for pre-treatment assessment, pharmacy preparation, treatment (chair) time and management of toxicities.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the Pacific study results point towards clinically significant survival benefits for maintenance durvalumab following concurrent chemoradiotherapy. International opinion suggests this combination is being adopted as the new standard of care and will serve as the control arm for future studies.
• Do you expect the technology to increase length of life more than current care?	Yes, the progression free survival difference reported is clinically meaningful. In addition the mature data from studies in more advanced NSCLC cancer consistently point towards an increase in the tail of long term survivors for patients received PD-L1 directed immunotherapy. The lower incidence of metastatic disease reported for the Durvalumab arm I see as indicator that there is a reasonable expectation that the increased tail will be present for this drug and stage of disease.
• Do you expect the technology to increase health-related quality of life more than current care?	We are not aware of any published quality of life data from the Pacific trial but would expect to see improvement related to better progression free survival as it is well documented that quality of life worsens when cancer recurs / progresses. The toxicity data reported is consistent with levels seen with other PD-L1 inhibitors and manageable.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Our experts would be cautious about use in patients with driver mutations (eg EGFR), number entering the Pacific study was small.
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.	The technology could be considered standard for NHS chemotherapy units and the difficulty faced would be of increased workload.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will be evaluated regularly through treatment with clinical assessment and radiological imaging including CT and MRI. This would follow the standard of care guidance for current chemotherapy / immunotherapy.
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?	NO

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 improve the way that current need is met?	The innovation is taking immunotherapy into a new cohort of patients with less advanced disease where gain may be more significant than those described for patients treated with stage IV NSCLC.
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Yes there is a need to improve outcomes for locally advanced NSCLC lung cancer which currently accounts for about a third of cases.
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?	The side-effects are well documented for PD-L1 inhibitors and the levels reported in the Pacific study are in keep with those we are seeing in day to day practice. In practice quality of life of patients is generally related to disease recurrence and persistent effects of combined chemo-radiotherapy treatment.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The improvement seen in progression free survival, reduction in level of metastatic disease and relative low levels of toxicity.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The trial has reported with short follow up, which will mean uncertainty when modelling overall survival.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware of.

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	We are not aware of real data on the use of maintenance immunotherapy following concurrent chemo-radiotherapy.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

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

- Outcomes for patient treated with chemo-radiotherapy for stage III NSCLC remain disappointing.
- immunotherapy with PD-L1 inhibitors is a standard of care treatment for stage IV NSCLC.
- Durvalumab maintenance can extend the benefits seen in stage IV NSCLC to those with less advanced stage III disease
- The side profile of durvalumab is consist with that seen in current practice using other NICE approved PD-L1 inhibitors
-

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 [ID1175]

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	**British Thoracic Society**

3. Job title or position	**Deputy Chief Executive**
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 British Thoracic Society (BTS) is the professional society for respiratory medicine and related health care professions. The Society exists to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care. It is a registered charity and a company limited by guarantee.
5b. 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 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.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The British Thoracic Society supports this appraisal. There is an urgent need more treatment options for patients with advanced lung cancer given the very poor prognosis.
What is the expected place of the technology in current practice?	
9. How is the condition 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.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology 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 the technology and current care?	
• In what clinical setting should 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.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these 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?	
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	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
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?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	

20. How do data on real-world experience compare with the trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

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

-
-
-
-
-

Thank you for your time.

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

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Patient organisation submission

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID1175]

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	NLCFN
3. Job title or position	Macmillan Lung Cancer Nurse Specialist
4a. Brief description of the organisation (including who funds it). How many members does it have?	The NLCFN is a proactive national forum made up of Specialist Lung Cancer and Mesothelioma Nurses. We have approximately 250 members. It is funded via income from educational events and sponsorship from pharmaceutical and law firms
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients and carers frequently feedback (formal and informal routes) experiences of treatments to lung cancer specialist staff. We as a forum share such information. I regularly attend oncology clinics; so speak to patients about their experience of treatments and assess side effects and effectiveness of oncological treatments. I have worked with patients to enable them to share their experience of living with Lung cancer (patient stories); and had the opportunity to present 'patient Stories' at local, national and international conferences.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lung Cancer is a distressing condition to live with. Patients frequently have numerous complex symptoms. Many have other co-morbidities which impact on performance status and quality of life. Any treatment which can improve side effects and quality of life is a bonus. Carers often describe feeling helpless.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is an acknowledgement of hope; as new treatments for lung cancer are evolving. They are always looking for new treatments which will improve symptoms, improve survival without having a negative impact on their quality of life. Very few lung cancer are diagnosed at an early stage; any treatment that potentially can extend their life is beneficial. Side effects and quality of life are always a consideration but more so when a cure is not possible. These treatments are seen as a life line.
8. Is there an unmet need for patients with this condition?	Definitely

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	There is an acknowledgement of hope; as new treatments for lung cancer are evolving. Patients and carers always welcome the development of treatments. These treatments are seen as a life line.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Not to my knowledge**
Other issues	
13. Are there any other issues that you would like the committee to consider?	Treatments for lung cancer remain very limited; it is refreshing to see these new technologies being considered. Any treatment which has the potential to improve survival, reduce the risk of recurrent disease and improve quality of life; should be available for the appropriate patient group
Key messages	

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

- This drug group appears to be well tolerated and appears to reduce recurrent disease for this sub group of patients
- Drug does appear to have survival benefit
- Please always consider new treatments that have potential to improve survival for lung cancer patients
-

-

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

Clinical expert statement

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID1175]

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

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

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

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Matthew Hatton**
2. Name of organisation	**Weston Park Hospital**

3. Job title or position	**Consultant and Honorary Professor in Clinical Oncology**
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.
5. Do you wish to agree with your nominating organisation's submission?	Yes, I agree with it
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.)	Minor modifications made.
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The main aim of treatment would be to delay / prevent relapse of locally advanced non-small cell lung cancer (NSCLC) after primary chemo-radiotherapy treatment and hence improve quality of life and survival.

or prevent progression or disability.)	
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improved median progression free survival of 8 months and median overall survival of 4 months.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the best study results for stage III NSCLC treated with primary chemoradiotherapy suggest median survivals of around 28 months with 25 – 30% of patients alive at 5 years ('cured') can be achieved using modern staging / treatment practices. In a less selected population typical of patients currently treated in the UK current median survivals are likely to be in the range of 20 – 24 months with 15 – 20% of patients alive at 5 years [1]. 1. Robinson SD et.al Radical radiotherapy for Non-Small Cell Lung Cancer (NSCLC): Real world outcomes for two accelerated fractionation schedules. Lung Cancer 115 Suppl 1S 71:163;2018.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The majority of new lung cancer cases are non-small cell lung cancer (NSCLC), which now accounts for 85-90% of lung cancers with almost 38,000 new cases diagnosed in the UK during 2015. Despite recent advances in the surgical management of lung cancer but a significant number of patients still present with disease that is too advanced for surgery or have significant co-morbidities that make them inoperable at diagnosis. Therefore, radical radiotherapy (RT) remains a mainstay of treatment particularly in locally

	advanced (stage III) disease. However, local relapses after radiotherapy are common with 85% of repeat bronchoscopies after radical RT demonstrating persistent tumour. Improving local control remains an important goal particularly as successful local control has been found to correlate with improved survival. Strategies that have improved local control include the addition of chemotherapy as a radio-sensitizer, the acceleration of the RT schedule and dose escalation. Concurrent chemo-radiotherapy (CTRT) is the current standard of care for locally advanced stage III lung cancer with the recent RTOG 0617 trial [1] showing we can expect median survival rates of approximately 27.8 months for patients with PET staged III disease in the control arm of 60 Gy given in 30 fractions. However, this study has acted as a reminder that concurrent CTRT can be extremely taxing for the patient and the majority of patients may not be suitable for the concurrent approach because of their age [2], co-morbidities and poorer performance status. A national survey of CTRT practice, the majority of Clinical Oncologists supported this suggesting that clinicians felt that less than 30% of stage III NSCLC patients were suitable for the concurrent chemo-radiotherapy approach [3] and would use sequential CTRT or radiotherapy alone for the majority of patients assessed. Alternative strategies employed in UK practice to improve local control intensify the anti-tumour effect through the acceleration of the RT schedule. The best example of this approach is provided by the Continuous Hyper-fractionated Accelerated Radiation Therapy (CHART) schedule [4]. However, CHART needs weekend treatments and patient hospitalization, and implementation proved challenging as recognized in the 2011 National Institute of Clinical Excellence (NICE) guidelines for the management of lung cancer and the recommendation for CHART is qualified and allows a RT regime with a biologically equivalent dose (BED) can be used. In the UK the commonest dose/fractionation used is an accelerated hypofractionated regimen of 55Gy in 20 fractions over 4 weeks [5] which still shortens the overall treatment time which is felt to be important in combating tumour repopulation. 1. Bradley JD, Paulus R, Komaki R, Master G, Blumenschein G, Child S, *et al*. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015; 16(2):187-99. 2. Miller ED et al. The addition of chemotherapy to radiation therapy improves survival in elderly patients with stage III NSCLC. JTO 2018;13:426-435

	3. Helbrow J, MacNicoll F, Bayman N, Faivre-Finn C. Concurrent chemoradiotherapy (cCTRT) for locally advanced unresectable non-small cell lung cancer (LA-NSCLC): A national survey of current practice. Lung Cancer. 2012; 75(1):S50-S51. 4. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M, for the CHART Steering Committee. Continuous hyperfractionated accelerated radio-therapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: A randomised multicentre trial. Lancet. 1997; 350:161–165. Prewett SL, Aslam S, Williams MV, Gilligan D. The management of lung cancer: A UK survey of Oncologists. Clin Oncol. 2012; 24:402-9
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	National Institute of Clinical Excellence. The Diagnosis and Treatment of Lung Cancer. April 2011. (Currently being updated with draft versions expected Autumn 2018). Scottish Intercollegiate Guidelines Network - 137 Management of lung cancer guideline, 2014. ASCO / ASTRO Definitive and Adjuvant Radiotherapy in Locally Advanced Non–Small-Cell Lung, 2015.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS?	The patients will come through lung cancer MDTs which will oversee the diagnostic and referral pathways to appropriate specialists for treatment. This process will also include an assessment of fitness to undergo multi-modality treatment with systemic treatments (chemotherapy, immunotherapy or targeted agents), radiotherapy and surgery. Locally advanced Stage III NSCLC encompasses a wide range of clinical scenarios which means individualisation of treatment is important and does mean there is a variation of treatment practice across the UK which is documented through the National Lung Cancer Audit.
• What impact would the technology have on the current pathway of care?	There would be an impact with the addition of an immunotherapy treatment given 2 weekly for one year following the completion of standard concurrent chemo-radiotherapy treatment. However, numbers of patients receiving concurrent chemo-radiotherapy for stage III NSCLC will be relatively small making impact modest.
11. Will the technology be used (or is it already used) in	Immunotherapy is a standard of care treatment for stage IV NSCLC (ID 811, 840, 970, 990) with agents targeting PD-L1 pathways. The administration requirements and side effect profile of durvalumab will be very

the same way as current care in NHS clinical practice?	similar to the PD-L1 inhibitiors in routine use. The adoption of the technology would be an addition workload on departments but would not require any adaption of current treatment pathways.
• How does healthcare resource use differ between the technology and current care?	As above
• In what clinical setting should the technology be used?	Secondary care through the established Lung Oncology clinics in teaching and general hospitals.
• What investment is needed to introduce the technology?	The training requirements for adoption of durvalumab maintenance treatment will be small but there is an additional workload for chemotherapy units with a requirement for pre-treatment assessment, pharmacy preparation, treatment (chair) time and management of toxicities.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the Pacific study results point towards clinically significant survival benefits for maintenance durvalumab following concurrent chemoradiotherapy. International opinion suggests this combination is being adopted as the new standard of care and will serve as the control arm for future studies. The side effect profile is different to standard chemotherapy treatment, generally auto-immune but did not require dose interruptions or modifications in the majority of patients. Therefore, some (relatively minor) modifications will be required for treatment assessment and follow up with a training requirement so that staff becomes familiar with the management of the side effect profile. This is currently occurring as other drugs in this class have been introduced into clinical practice.
• Do you expect the technology to increase	Yes, the progression free survival difference reported is clinically meaningful. In addition the mature data from studies in more advanced NSCLC cancer consistently point towards an increase in the tail of long term

length of life more than current care?	survivors for patients received PD-L1 directed immunotherapy. The lower incidence of metastatic disease reported for the Durvalumab arm I see as indicator that there is a reasonable expectation that the increased tail will be present for this drug and stage of disease.
• Do you expect the technology to increase health-related quality of life more than current care?	We are not aware of any published quality of life data from the Pacific trial but would expect to see improvement related to better progression free survival as it is well documented that quality of life worsens when cancer recurs / progresses. The toxicity data reported is consistent with levels seen with other PD-L1 inhibitors and is manageable.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I would be cautious about use in patients with driver mutations (eg EGFR), number entering the Pacific study was small. Pre-existing auto-immune disease
The use of the technology	
14. 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	The technology could be considered standard for NHS chemotherapy units and the difficulty faced would be of increased workload.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will be evaluated regularly through treatment with clinical assessment and radiological imaging including CT and MRI. This would follow the standard of care guidance for current chemotherapy / immunotherapy.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The innovation is taking immunotherapy into a new cohort of patients with less advanced disease where gain may be more significant than those described for patients treated with stage IV NSCLC.
• Is the technology a 'step-change' in the management of the condition?	Yes, see above
• Does the use of the technology address any particular unmet need of the patient population?	Yes there is a need to improve outcomes for locally advanced NSCLC lung cancer which currently accounts for about a third of cases.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side-effects are well documented for PD-L1 inhibitors and the levels reported in the Pacific study are in keep with those we are seeing in day to day practice. In practice quality of life of patients is generally related to disease recurrence and persistent effects of combined chemo-radiotherapy treatment.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The improvement seen in progression free survival, reduction in level of metastatic disease and relative low levels of toxicity.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The trial has reported with short follow up, which will mean uncertainty when modelling overall survival.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA406, TA181, TA190, TA402]	No
22. How do data on real-world experience compare with the trial data?	I am not aware of real world data on the use of maintenance immunotherapy following concurrent chemo-radiotherapy.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	

Key messages

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

- Outcomes for patient treated with chemo-radiotherapy for stage III NSCLC remain disappointing.
- immunotherapy with PD-L1 inhibitors is a standard of care treatment for stage IV NSCLC.
- Durvalumab maintenance can extend the benefits seen in stage IV NSCLC to those with less advanced stage III disease
- The side profile of durvalumab is consist with that seen in current practice using other NICE approved PD-L1 inhibitors
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID1175]

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Carol A Davies**

2. Name of organisation	NLCFN
3. Job title or position	Macmillan Lung Cancer Nurse Specialist
4a. Brief description of the organisation (including who funds it). How many members does it have?	The NLCFN is a proactive national forum made up of Specialist Lung Cancer and Mesothelioma Nurses. We have approximately 250 members. It is funded via income from educational events and sponsorship from pharmaceutical and law firms
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients and carers frequently feedback (formal and informal routes) experiences of treatments to lung cancer specialist staff. We as a forum share such information. I regularly attend oncology clinics; so speak to patients about their experience of treatments and assess side effects and effectiveness of oncological treatments. I have worked with patients to enable them to share their experience of living with Lung cancer (patient stories); and had the opportunity to present 'patient Stories' at local, national and international conferences.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lung Cancer is a distressing condition to live with. Patients frequently have numerous complex symptoms. Many have other co-morbidities which impact on performance status and quality of life. Any treatment which can improve side effects and quality of life is a bonus. Carers often describe feeling helpless.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is an acknowledgement of hope; as new treatments for lung cancer are evolving. They are always looking for new treatments which will improve symptoms, improve survival without having a negative impact on their quality of life. Very few lung cancer are diagnosed at an early stage; any treatment that potentially can extend their life is beneficial. Side effects and quality of life are always a consideration but more so when a cure is not possible. These treatments are seen as a life line.
8. Is there an unmet need for patients with this condition?	Definitely

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	There is an acknowledgement of hope; as new treatments for lung cancer are evolving. Patients and carers always welcome the development of treatments. These treatments are seen as a life line.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Not to my knowledge**
Other issues	
13. Are there any other issues that you would like the committee to consider?	Treatments for lung cancer remain very limited; it is refreshing to see these new technologies being considered. Any treatment which has the potential to improve survival, reduce the risk of recurrent disease and improve quality of life; should be available for the appropriate patient group
Key messages	

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

- This drug group appears to be well tolerated and appears to reduce recurrent disease for this sub group of patients
- Drug does appear to have survival benefit
- Please always consider new treatments that have potential to improve survival for lung cancer patients
-

-

Thank you for your time.

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

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Robert Wolff, Deputy Director, Kleijnen Systematic Reviews Ltd, UK Sabine Grimm, Health Economist, Maastricht UMC Thea van Asselt, Health Economist, Maastricht UMC Willem Witlox, Health Economist, Maastricht UMC Nigel Armstrong, Health Economics Manager, KSR Ltd Gill Worthy, Statistician, KSR Ltd Annette Chalker, Systematic Reviewer, KSR Ltd Titas Buksnys, Health Economist, KSR Ltd Lisa Stirk, Information Specialist, KSR Ltd Manuela Joore, Health Economist, Maastricht UMC Jos Kleijnen, Director, KSR Ltd; Professor of Systematic Reviews in Health Care, Maastricht University
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Date completed	08/11/2018 updated 20/02/2019

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Declared competing interests of the authors
None.

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None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence 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. Thea van Asselt, Willem Witlox, Titas Buksnys, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker and Titas Buksnys acted as a systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission 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

1-L	First-line
2-L	Second-line
AACR	American Association for Cancer Research
AE	Adverse event
AIC	Akaike information criterion
AiC	Academic in confidence
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
BIC	Bayesian information criterion
BICR	Blinded independent central review
BSC	Best supportive care
BTOC	British Thoracic Oncology Group
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CRF	Case report form
CRT	Chemoradiation therapy
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed Tomography
CTx	Chemotherapy
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DCR	Disease control rate
DoR	Duration of response
DSA	Deterministic sensitivity analysis
EAP	Early access program
EGFR	Epidermal growth factor receptor
ELCC	European Lung Cancer Conferences
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire
EORTC	European Organisation for Research and Treatment of Cancer quality of life questionnaire and lung cancer module
eMIT	Electronic Market Information Tool
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
EQ-5D-5L	European Quality of Life-5 Dimensions, five-level scale
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
EuroQOL SC	EuroQOL self-classifier
EuroQOL VAS	EuroQOL visual analogue scale
FE	Fixing errors
FV	Fixing violations
HR	Hazard ratio
HRG	Healthcare Resource Group

HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IDMC	Independent data monitoring committee
IO	Immuno-oncological
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
kg	Kilogram
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LY	Life year
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MIMS	Monthly Index of Medical Specialities
MJ	Matters of judgements
N/A	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
ORR	Objective response rate
OS	Overall survival
OS24	Overall survival after 24 months
PD	Progressed disease
PD-L1	Programmed death-ligand 1
PF	Progression-free
PFS	Progression-free survival
PFS12	Progression-free survival after 12 months
PFS18	Progression-free survival after 18 months
PFS2	Time from randomisation to second progression or death
PPS	Post-progression survival
PRESS	Peer review of electronic search strategies
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q2W	Every two weeks
QALY(s)	Quality-adjusted life year(s)
RCR	Royal College of Radiologists
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RT	Radiotherapy
SAP	Statistical analysis plan
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
UK	United Kingdom
UMC	University Medical Centre
TC	Tumour cell
TFTS	Time to first or subsequent therapy or death
TNM	Tumour-node-metastasis

TSD	Technical support document
TSST	Time to second subsequent therapy or death
TTDM	Time to death or distant metastasis
TTF	Time to treatment failure
TTP	Time to progression
UK	United Kingdom
US	United States
WCLC	World Conference on Lung Cancer
WHO	World Health Organization

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1. Summary

1.1 Critique of the decision problem in the company's submission

The population defined in the company submission (CS) is adults with locally-advanced, unresectable, stage III non-small cell lung cancer (NSCLC) whose tumours express programmed death-ligand 1 (PD-L1) on ≥1% of tumour cells (TCs) and whose disease has not progressed following platinum-based chemoradiation therapy (CRT). Compared to the National Institute for Health and Care Excellence (NICE) scope, the population is narrower, i.e. only includes patients in the relevant population whose tumours expressed PD-L1.

The intervention (durvalumab 10mg/kg every two weeks intravenously), comparator (standard of care) and outcomes are defined in line with the NICE scope.

1.2 Summary of the key issues in the clinical effectiveness evidence

The CS comprised of a systematic review of the evidence for durvalumab for the treatment of locally advanced unresectable, stage III NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based CRT. The CS and response to clarification provided sufficient details for the Evidence Review Group (ERG) to appraise the literature searches. A good range of databases and conference proceedings were searched. Of concern to the ERG was the restrictive population search, which combined NSCLC terms with disease stage and chemoradiation therapy search terms, and did not include intervention terms as an additional facet. However, this is unlikely to have greatly affected the recall of results.

The CS presented direct evidence from one randomised controlled trial (RCT), PACIFIC, which compared durvalumab to standard of care in adults with locally-advanced, unresectable, stage III NSCLC whose tumours express PD-L1 on ≥1% of TCs and whose disease has not progressed following platinum-based CRT. The population of participants receiving durvalumab represents approx. 67% of the overall population included in PACIFIC. It should be noted that randomisation was not stratified based on PD-L1 status. While reported baseline characteristics, such as age, histology, or smoking status, were balanced between the durvalumab and placebo groups, there are potential problems linked to overinterpretation of subgroup analyses which might impact on the findings.

The PACIFIC trial included only eight patients from the United Kingdom (UK). Another concern to the ERG was the applicability of durvalumab to a population receiving different types of CRT cycles. The CS notes that in the PACIFIC trial concurrent CRT was received prior to beginning treatment with durvalumab. However, the clinical expert highlighted that *"most UK patients receive sequential rather than overlapping treatment"* while *"the efficacy and safety of durvalumab in the PACIFIC study was evaluated after overlapping, rather than sequential, CRT"*. The response to request for clarification suggested the cohort in the PACIFIC trial is generalisable to UK patients with locally-advanced, unresectable, stage III, NSCLC. It also suggested that survival rates might be lower amongst patients treated with sequential CRT approaches than overlapping. However, more pertinently, as the company admitted in the response to clarification, the effectiveness of durvalumab in following sequential therapy remains unknown, i.e. *"…clinicians would expect to see some benefit of durvalumab treatment after sequential CRT, although the magnitude of this remains uncertain in the absence of robust clinical evidence"*. These issues impact on the certainty regarding these findings and might limit the applicability of any findings to UK clinical practice.

The CS reported a progression-free survival (PFS) benefit with durvalumab when compared to placebo in the PD-L1 <1% and PD-L1 ≥1%, and unknown PD-L1 expression groups. Patients in the PD-L1

≥1% and unknown expression groups receiving durvalumab observed an overall survival (OS) benefit. The CS also reported the statistically significant and clinically meaningful PFS and OS benefits in the PD-L1≥1% group. However, it should be noted that these results come from an interim cut-off, i.e. not from the final analysis. Durvalumab treated patients also observed statistically-significant improvements in key secondary endpoints when compared to placebo.

Based on the PACIFIC data there appears to be a benefit in both PFS and OS for durvalumab patients compared with placebo patients, however, the data are immature and there remains substantial uncertainty about the comparative effectiveness.

Common adverse events were reported in both the durvalumab and placebo groups. The common AEs in the durvalumab patients included cough, fatigue, and radiation pneumonitis, whereas patients in the placebo group also included dyspnoea. Overall, more serious adverse events were reported for durvalumab compared to placebo (64/213 (30%) vs. 18/90 (20%)).

1.3 Summary of the key issues in the cost effectiveness evidence

Individual searches were undertaken for economic, cost and resource use and health-related quality of life (HRQoL) evidence. The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches and the 2018 update searches. A good range of databases and additional resources were searched. None of the included cost effectiveness studies were conducted from the UK perspective.

The company submission was largely in line with the NICE reference case. The modelled population, however, was narrower than that in the scope, but in line with the anticipated marketing authorisation (focussing on the subgroup with PD-L1 tumour expression ≥1%).

The company developed a de novo semi-Markov cohort state transition model. The model comprised of three health states, i.e. progression-free (PF), progressed disease (PD) and death. The company considered these health states to capture the most important clinical aspects in the treatment of stage III NSCLC patients, namely the time spent in PF and the time spent alive. The company estimated PFS, time-to-progression (TTP) and post-progression survival (PPS) to inform transitions between health states. Given the immaturity of the survival data in the PACIFIC subpopulation, the ERG had concerns about the appropriateness of the semi-Markov approach and questioned its superiority over a partitioned survival model approach. Therefore, the ERG would have liked to see both approaches appropriately explored. The company claimed that the semi-Markov approach largely avoided crossing of PFS and OS curves. However, relying on PPS to estimate survival instead of using OS drew on even fewer patients for extrapolation and potentially introduced additional bias (selection bias by relying on early progressors, with more progressions in the placebo arm than in the durvalumab arm). The magnitude and direction of any bias are unclear.

In line with its anticipated marketing authorisation, durvalumab was considered in the cost effectiveness model for the treatment of locally-advanced, unresectable, stage III NSCLC patients whose tumours express PD-L1 on ≥1% of TCs and whose disease has not progressed after ≥2 cycles of platinum-based CRT. This was a subgroup from the final scope issued by NICE, which considered the same population regardless of their PD-L1 status. However, the generalisability of PACIFIC to the United Kingdom setting was questioned, because patients in PACIFIC largely received overlapping CRT, whilst sequential CRT is standard practice in the United Kingdom. The direction and magnitude of any potential bias stemming from this could not be assessed.

Durvalumab was considered within the economic evaluation as per the anticipated licensed indication in NSCLC. Durvalumab was, in line with the dosage used in PACIFIC, modelled with a posology of 10mg/kg administered as an intravenous infusion over 60 minutes every two weeks, until disease progression or unacceptable toxicity, or a maximum of 12 months. The comparator in the economic model was described as active follow-up or standard of care (SoC), which applies up to disease progression. The intervention was implemented as per its marketing authorisation and dosage.

The analysis took an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was two weeks in the first year and four weeks thereafter with a lifetime time horizon (40 years). A half-cycle correction was applied, except to treatment and treatment administration costs.

Perspective, time horizon and discounting were in line with the NICE reference case, however, in the absence of any justification for not applying the half-cycle correction to treatment and treatment administration costs, the ERG considered this inconsistent with the calculation of resource use and other model calculations, which lowered the ICER.

The main source of evidence on treatment effectiveness used for intervention and comparators was the PACIFIC study. Only data from the subgroup of PD-L1 ≥1% patients (according to the anticipated marketing authorisation) and from the March data cut were used in the model. The ERG had concerns about the model being based on treatment effectiveness estimates derived from a post-hoc subgroup analysis and post-hoc TTP and PPS analyses, as well as in a population with mostly prior overlapping CRT instead of sequential CRT, but any bias introduced by this remained unclear.

Parametric survival curves were fitted to patient level data from PACFIC data on PFS, but instead of using the OS data from PACIFIC, the company performed survival analyses on the outcomes TTP and PPS, as explained below. The probability of remaining in the progression free (PF) state was estimated using PFS data by fitting independent parametric survival models. Based on statistical goodness of fit, the generalised gamma was selected to model PFS for both durvalumab and placebo. The Gompertz distribution was used in scenario analysis and the log-normal distribution was not used, despite the log-normal making a better fit than the Gompertz in both arms. The main concern of the ERG was that it considered durvalumab PFS to be probably over-estimated in the model, due to a model choice (generalised gamma) that resulted in PFS estimates above those observed in PACIFIC at three years, with the PACIFIC estimate notably being derived from small numbers of patients at risk. This model choice probably caused ICERs to be lower than with other model choices. It is noteworthy that any modelling choice for modelling PFS is associated with high levels of uncertainty, given the immaturity of the data, and that different PFS model choices have a large impact on the ICERs. Alternative modelling methods, such as spline-based models, remained unexplored in the CS.

The PFS curve for durvalumab was altered in the long run to reflect a potential treatment waning effect caused by stopping treatment at a maximum of 12 months. From a chosen cut-off point, which was set to 10 years in the company's base-case, a hazard ratio of one was applied to the placebo curve to model durvalumab PFS. The ERG considers this choice of time-point as highly uncertain, not appropriately validated, and potentially late, further adding to the likely over-estimation of durvalumab PFS. Furthermore, the implementation of the treatment waning effect could cause counter-intuitive results.

The probability of patients moving from the PF state to the progressed disease (PD) health state was determined by survival analysis of TTP data (PFS data with deaths treated as censored) from PACIFIC. The generalised gamma distribution was chosen in the base-case, based on best statistical fit (Akaike

information criterion; AIC and Bayesian information criterion; BIC) and to align with extrapolation of PFS.

The probability of patients moving from PD to death was estimated using survival analysis of pooled PPS data from both treatment arms in PACIFIC (choice of exponential distribution based on best statistical fit). The effectiveness of subsequent treatments was captured in the PPS to the extent that patients in the PACIFIC study received subsequent treatments. In a scenario analysis, an alternative method for extrapolating PPS was used, where PPS was informed by published data from the KEYNOTE-024 study, data from the pembrolizumab arm used for those patients in PACIFIC who received immuno-oncological (IO) treatment, and data from the chemotherapy arm used for those not receiving IO treatment. The ERG noted the uncertainty in PPS introduced by immature PPS data from PACIFIC, uncertainty about subsequent treatments and potential bias in extrapolating PPS in the light of even smaller number of patients and immature data, rather than OS. Exploratory analyses showed that any impact of this on the ICER was probably relatively small, with the main treatment benefit of durvalumab extending PFS.

The main source of evidence on treatment adverse events used for durvalumab and SoC was the PACIFIC study. Adverse events (AEs) that were of grade 3/4 and had a frequency of ≥2% in either arm of the PACIFIC study were included in the model in terms of their costs and not their impact on HRQoL. AEs were modelled as a per-cycle occurrence while patients are on treatment. Whilst AEs causally related to treatment were mostly higher for the durvalumab arm than in the placebo arm in PACIFIC, incidence of AEs in the model between treatments was comparable. It was unclear how this discrepancy occurred, likely lowering ICERs of durvalumab versus SoC. Exploratory analyses however showed that any bias caused by this would be limited.

EQ-5D-5L data were collected in PACIFIC and mapped to 3L utility scores using the crosswalk mapping algorithm as per the NICE position statement. A mixed effects model with only progression as a covariate was used to estimate utility values for the PF (0.819) and PD (0.776) health states. The ERG considered utility values for both health states to be potentially over-estimated, being comparable to those in the general population and not adjusted by general population utility estimates. The high PF utility value produces lower ICERs for durvalumab, whilst the high PD utility value produces higher ICERs for durvalumab versus SoC. Although the mapped utility scores from PACIFIC were higher in the placebo arm as compared to the durvalumab arm at almost all measurement moments, treatment was found to be statistically insignificant in the mixed effects model and therefore, equal utilities were assumed for durvalumab and SoC. The ERG was concerned that by excluding treatment as a factor in the mixed effects model, and at the same time including disutilities of a limited set of AEs only in a sensitivity analysis, the true impact of treatment with durvalumab and adverse events was not appropriately captured in the model. The exclusion of treatment as a covariate in the utility mixed effects model resulted in lower ICERs. No adverse event related disutilities were taken into account.

Costs in the model included costs for PD-L1 testing, costs associated with treatment, costs associated with disease management and patient observation, and costs associated with end of life care. Unit costs were based on the National Health Service (NHS) reference costs, Personal Social Services Research Unit (PSSRU), Monthly Index of Medical Specialities (MIMS), and the electronic Market Information Tool (eMIT). Treatment cost per durvalumab infusion was calculated based on average body weight in PACIFIC, with treatment duration taken from PACIFIC Kaplan-Meier (KM) data. No drug wastage, i.e. perfect vial sharing, was assumed. The model assumed zero acquisition and administration costs for SoC. Once patients progressed in the model, a one-off cost for subsequent treatments was accrued. This cost was informed by the type of treatment, the required treatment dose, the dosing schedule, the unit

drug cost at list prices, and the duration of treatment. Resource use for the PF state was modelled in accordance with European Society for Medical Oncology guidelines, and resource use for the PD health state was derived from NICE Technology Appraisal 531 in the metastatic setting. The frequency of occurrence of included AEs was combined with a one-off cost per AE to obtain a total per-cycle cost for each arm. The ERG considered the assumption of perfect vial sharing to be unrealistic in this setting, given the limited number of patients in England and Wales that would be eligible for treatment with durvalumab. This assumption caused the ICER of durvalumab against SoC to be lowered.

Total deterministic life years (LYs) and quality-adjusted life years (QALYs) gained were larger in the durvalumab arm compared to the SoC arm. Incremental QALYs (2.93) were mainly driven by QALY gains in the PF health state. The revised (in response to clarification letter an error was corrected) deterministic incremental cost effectiveness ratio (ICER) amounted to £19,366 per QALY gained. Compared with the deterministic results, the probabilistic sensitivity analysis (PSA) with 1,000 iterations showed lower incremental QALYs and higher incremental costs, which resulted in an increased ICER (£21,601 per QALY gained). Some deterministic sensitivity analyses (DSA) and scenario analyses significantly affected the ICER.

At the clarification stage, the ERG identified several errors in the company's base-case and scenario analyses, including several settings in the controls sheet that were not functioning, and incorrect results of scenario analyses, which were corrected by the company. The ERG was still unable to reproduce one of the company's scenarios added in response to the clarification letter and found an error in another.

Face and internal validity checks were performed by the company and a third-party provider, as well as an expert in the field. Cross validity checks were not performed. OS predictions from the model were validated against PACIFIC, other sources and expert opinion. No firm conclusion could be drawn from the external validation exercise performed by the company using alternative data sources, due to differences in population.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG made various adjustments to the company's base-case, including the fixing of errors, violations and amending the model according to its preferred assumptions (matters of judgement).

1.4.1 Fixing errors

1. Correction of age calculations
2. Correction of nivolumab and pembrolizumab vial sharing calculations
3. Correction of probabilistic utility decrements for progression and treatment

1.4.2 Fixing violations

4. Applying the half-cycle correction also to treatment and administration costs
5. Assumption of no vial sharing
6. Excluding patient characteristics from the PSA

1.4.3 Matters of judgment

7. Use of the lognormal instead of the generalised gamma distribution for modelling durvalumab PFS (and also TTP, as per company's default setting)
8. Treatment waning effect after five-year cut-off instead of 10-year cut-off
9. Applying an age-related utility decrement
10. Including treatment as a covariate in the utility mixed effects model

The probabilistic ERG base-case ICER of durvalumab versus SoC was £52,353 per QALY gained (based on 5,000 iterations). This was higher than the deterministic ERG base-case ICER of £50,238 per QALY gained. This difference was also observed in the company base-case results, and was likely caused by the skewedness of distributions used for modelling PFS.

Table 1.1: ICER resulting from ERG's preferred assumption

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			
Probabilistic ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.25	£52,353
SoC	[redacted]	[redacted]			

ERG = Evidence Review Group = ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Deterministic scenario analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. Alternative assumptions regarding PFS and treatment waning effects had the most significant impact. The scenario in which PFS distributions were changed into generalised gamma for both arms (as per the company's base-case) resulted in an ICER of £29,302 per QALY gained, whereas applying lognormal distributions for PFS in both arms drove up the ICER to £52,300 per QALY gained. Applying the company's KEYNOTE-024 PPS scenario, but with errors corrected, resulted in an ICER of £59,131 per QALY gained. The scenario exploring a treatment waning effect with three-year cut-off and using the lognormal distribution for both durvalumab and SoC PFS increased the ICER the most (to £64,531 per QALY gained). All other scenarios had a relatively modest impact (<£5,000) on the ERG base-case ICER.

In conclusion, given that the ERG base-case ICER was estimated to be substantially above £40,000 per QALY gained, and only one scenario resulting in ICERs slightly below £30,000 per QALY gained, and the large uncertainty induced by mainly the immature survival data, uncertainty around the cost effectiveness of durvalumab is substantial.

Table 1.2: Exploratory analyses undertaken by the ERG

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			
ERG base-case, no treatment waning effect (0)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.10	£60,928
SoC	[redacted]	[redacted]			
Alternative PFS distributions both arms, generalised gamma (1)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.19	£29,302

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]			
Alternative PFS distributions both arms, lognormal (2)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.27	£52,300
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as ERG base-case (3a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.35	£48,766
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as scenario 2 (3b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.04	£64,531
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as ERG base-case (4a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.25	£52,833
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as scenario 2 (4b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.41	£47,000
SoC	[redacted]	[redacted]			
PACIFIC PPS, but generalised gamma (5)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.33	£49,868
SoC	[redacted]	[redacted]			
Company's KEYNOTE-024 PPS scenario, with errors corrected (6)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.10	£59,131
SoC	[redacted]	[redacted]			
Adverse events with amended incidence and including impact on HRQoL (7)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,288
SoC	[redacted]	[redacted]			
Alternative PF utility score (8)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.42	£46,539
SoC	[redacted]	[redacted]			
Alternative PF and PD utility scores (9)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.28	£51,587
SoC	[redacted]	[redacted]			
Vial sharing possible at 30% (10)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£49,350
SoC	[redacted]	[redacted]			

ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; PD = progressed disease; PF = progression-free; PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year; SoC = standard of care

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company's submission provided sufficient details for the ERG to appraise the database searches, which were generally transparent and reproducible. An adequate number of databases were searched and a good range of additional searches were conducted for grey literature.

Study design limits to identify economic evaluations, utility data, and costs and resource use data were applied. A good range of intervention terms for durvalumab and comparators were used in the cost effectiveness strategy.

The company submission was largely in line with the NICE reference case. Utility scores were estimated using a mixed effects model based on observed EQ-5D data in the PACIFIC study.

The model was, in general, well-built and transparent. Apart from their base-case, the company provided opportunities for exploratory analyses using alternative data derived from clinical trials in similar populations.

1.6.2 Weaknesses and areas of uncertainty

The population facet for each search conducted included a limited use of synonyms, and therefore may have missed relevant literature. Given the small number of references retrieved from the search, study design filters were not essential, and may have been unnecessarily restrictive.

The population included in the PACIFIC trial is narrower than in the NICE scope and the ERG identified additional issues which might potentially limit the applicability of study results, see Section 1.1.

A substantial source of uncertainty lies in the generalisability of PACIFIC data to the UK setting, as PACIFIC pertains predominantly to prior overlapping CRT, whereas in clinical practice in the UK, mostly sequential CRT is applied. In addition, the PD-L1≥1% subgroup and TTP and PPS analyses were performed post-hoc. Furthermore, main results come from interim analysis, e.g. according to the response to the request for clarification the company *"will conduct a final analysis of OS once a maturity of 70% has been reached. OS is an event-driven endpoint; therefore, the timing of this analysis is uncertain"* which will be reached *"when 491 OS events have occurred"*. The current maturity in the relevant subgroup is 33.0% for durvalumab and 49.5% for placebo.

A main limitation was the immaturity of survival data in the PACIFIC subpopulation, and the inherent uncertainty in PFS and PPS extrapolations. The ERG particularly considers durvalumab PFS to be overestimated, even more so because the company chose to incorporate treatment waning only at 10 years. Given the immaturity of survival data, the ERG also has concerns over the appropriateness of the semi-Markov model structure, but the company did not provide an opportunity to explore a partitioned survival approach. Alternative modelling methods, such as spline-based models, remained unexplored in the CS.

Lastly, the utility scores used in the model do not seem representative of the patient population. The ERG considers the utilities for both (progression-free and progressed disease) health states to be an overestimate.

2. Background

2.1 Introduction

In this report, the ERG provides a review of the evidence submitted by AstraZeneca in support of durvalumab, trade name IMFINZI™, for the treatment of adults with locally-advanced, unresectable, stage III NSCLC whose tumours express PD-L1 on ≥1% of TCs and whose disease has not progressed following platinum-based CRT.

2.2 Background and underlying health problem

In the CS,[1] the company emphasises the prevalence of lung cancer as being the third most common cancer in the UK.[2] Lung cancer was identified as being the main cause of cancer-related death.[3]

The company describes the progression of the stages of lung cancer, through the use of the Tumour-Node-Metastasis (TNM) system according to the American Joint Committee on Cancer (AJCC).[4] This system determines the overall cancer stage in accordance with the size of the primary tumour, the regional lymph node involvement, and the presence or absence of distant metastases. The company has made stage III NSCLC the focus of the submission due to the disease's representation of a highly-heterogeneous disease stage as well as stage III occurring before the progression to metastatic stages allowing for the treatment intent to be curative.[1] The company highlights the classification of the stages across a patient population in the UK, with 20% of patients in England and Wales having stage III at the time of diagnosis.[5]

The CS identifies the symptoms experienced by patients within Stage III as including a persistent or worsening cough, difficulty breathing, pain experienced while breathing, an altered voice, and chest pain.[1] However, this burden of symptoms increases once the disease progresses to the metastatic stages. This disease progression places patients outside of the time frame to be treated with curative intent. The CS states that the increased experience of a high symptom burden also places the patient in a position to experience a decrease in HRQoL, particularly once the patient progresses to stage IV.

The CS highlights the treatment pathways according to the NICE guidelines, with surgical measures, based on suitability and fitness, being the first choice.[6] However, these guidelines emphasise if the patient is suitable for surgery, neo-adjuvant chemotherapy is not recommended, unless for the purpose of a clinical trial.[1] The CS includes a comparison of patients with stage I and stage II NSCLC, and the patients with stage III NSCLC who receive treatment with curative intent. According to the National Lung Cancer Audit (NLCA), *"81% of patients diagnosed with stage I–II (...) and a World Health Organization (WHO) performance status (PS) of 0–2 received curative-intent treatment"*.[7] In results not specific to the UK, 68%-92% of patients with stage I and 53%-60% of patients with stage II remained alive at five years.[8] This differs by the different classifications of stage III patients of which, if identified as either as stage IIIA or stage IIIB, 40% and 16% received treatment with curative intent, respectively. The CS states that 13% of Stage III patients in England and Wales had surgery.[7]

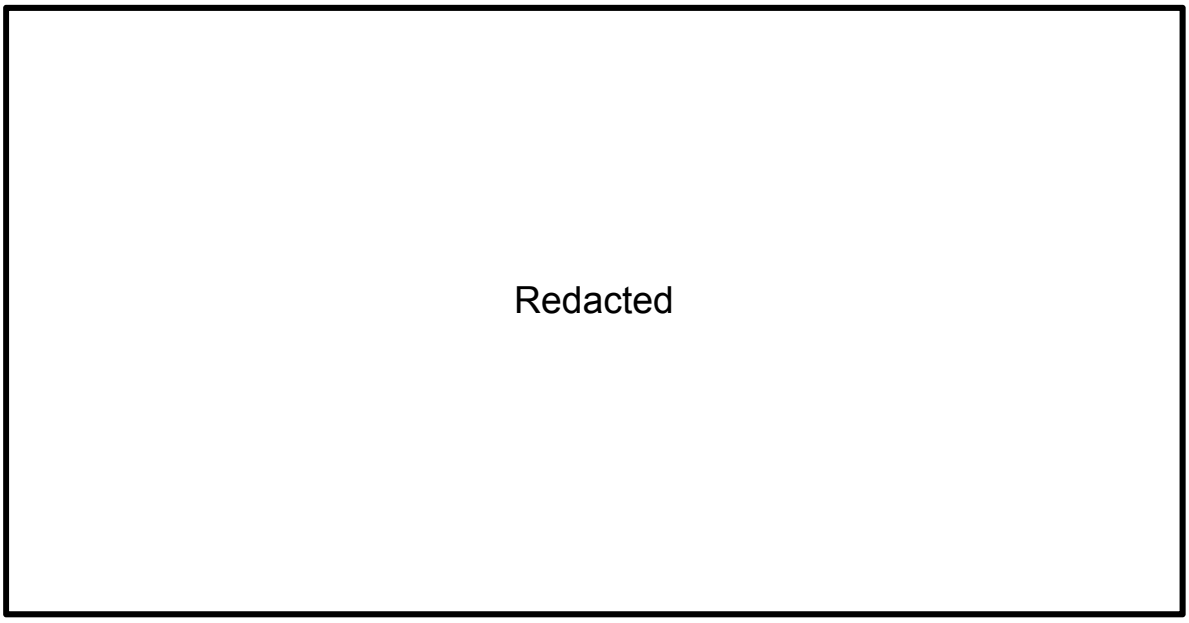
If surgery is not feasible for Stage III NSCLC patients, CRT is the standard of care.[6] Combinations of radiotherapy and chemotherapy provide better outcomes relative to radiotherapy alone.[9, 10] The CS notes that national guidelines, such as the Royal College of Radiologists and the British Thoracic Society, and regional guidelines, such as the London Cancer Alliance, which are used for the support of Stage III NSCLC patients in the UK, are in agreement with guidelines from NICE and the European Society for Medical Oncology (ESMO).[11-13] However, no new treatments have been approved for unresectable stage III NSCLC patients.[6, 14] This allows, as the company highlights, for active surveillance and best supportive care (BSC) to take place.[1] The CS emphasises that in the absence of active treatments, most

unresectable stage III NSCLC patients will experience disease progression following the completion of CRT. The CS identified several targeted therapies that have been evaluated as part of consolidation or maintenance upon completion of CRT. However, these were found to have either a moderate efficacy, while others were deemed unacceptable for integration.[15-17] During this absence of effective active treatments, disease progression within a year was experienced between 59.6% and 62.1% of Stage III patients upon completion of CRT.[18]

The CS reports that one-third of patients develop brain metastases, which can then result in poor outcomes with patients having a median overall survival (OS) of roughly four months.[19] If patients remain disease-free for a period of >12 months, they are treated with first-line (1-L) systemic drug therapies, otherwise second-line (2-L) drug therapies are utilised. Upon receiving insights from clinical experts in the UK, it is determined about 18% of Stage III patients receive further therapy after CRT. The UK clinical experts also revealed roughly 7% of Stage III patients are treated with a targeted therapy, while nearly 30% of patients receive an anti-PD-1/PD-L1 therapy.[20] The CS emphasises that during the metastatic stages the current treatment intent is palliative which identifies an unmet need for a curative treatment strategy that promotes the initial benefits achieved from CRT.[1]

The CS highlights the use of anti-PD-1/PD-L1 immunotherapy between the completion of CRT and before disease progression, which allows for *"T-cells to be reinvigorated at a time when the volume of tumour burden is low"*.[1] Anti-PD-1/PD-L1 antibodies have been reported to augment the stimulation of the immune effects from radiotherapy, resulting in an improvement of disease control.[21]

Figure 2.1: Treatment of stage III NSCLC



Source: Based on Figure 5 of the CS[1]
Footnote: ** Assumes that 95% of patients will not have experienced disease progression within six weeks or 42 days of completing CRT.
BSC = best supportive care; CRT = chemoradiation therapy; CTx = chemotherapy; NSCLC = non-small cell lung cancer; RT = radiotherapy

ERG comment: The ERG has no specific comments on the background presented in the CS.

However, it is noteworthy that no active treatment has been approved for patients with unresectable stage III NSCLC, providing a justification for the use of standard of care as comparator. The ERG also wants to direct attention to the relatively small patient population considered appropriate for treatment with durvalumab, as shown in Figure 2.1.

3. Critique of company's definition of decision problem

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose disease has not progressed after platinum-based chemoradiation therapy (CRT)	Adults with locally-advanced, unresectable, stage III NSCLC whose tumours express PD-L1 on ≥1% of tumour cells (TCs) and whose disease has not progressed following platinum-based CRT	The submission will focus on locally advanced (stage III), unresectable NSCLC patients, whose tumours express PD-L1 on ≥ 1% of TCs, to reflect the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)[§], and the anticipated Marketing Authorisation for durvalumab in this indication
Intervention	Durvalumab	Durvalumab (10 mg/kg every two weeks [Q2W] via intravenous [IV] infusion)	N/A
Comparator(s)	Best supportive care	Best supportive care (referred to as "active follow-up" throughout)	N/A

Outcomes	• Overall survival (OS)
	• Progression-free survival (PFS)
	• Response rates
	• Health-related quality of life (HRQL)
	• Adverse effects of treatment
		• PFS (primary endpoint)
		  • Secondary endpoints: proportion of patients alive and progression free at 12 and 18 months (PFS12 and PFS18)
		  • Supportive summary analysis: time to first subsequent therapy or death (TFST)
		• PFS2[*]
		  • Supportive summary analysis: time to second subsequent therapy or death (TSST)
		• Post-progression survival (PPS; *post-hoc* analysis)
			Time from randomisation to second progression or death (PFS2) and time to death or distant metastasis (TTDM) endpoints are relevant given the earlier disease setting (stage III) relative to previous immunotherapy appraisals in NSCLC (stage IV metastatic setting). They provide important information about the benefits of treatment beyond delaying disease progression:
			• PFS2 is an intermediate endpoint between PFS and OS and reflects real-life treatment decisions and patient experience. Its use is recommended by the EMA to capture potential negative impacts on next-line therapy and to demonstrate that any potential tolerability concerns are outweighed by treatment benefit.[22]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope

		• OS (primary endpoint)
		  • Secondary analysis: proportion of patients alive at 24 months (OS24)
		  • *Post-hoc* analysis: impact of subsequent immunotherapy use
		• Response rates
		• TTDM*
		• HRQL (EORTC QLQ-C30 and EORTC QLQ-LC13)
		• Adverse effects of treatment
			• TTDM captures the value of maintaining local control and delaying progression to more-advanced metastatic disease stage

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a National Health Service (NHS) and Personal Social Services perspective.	As per National Institute for Health and Care Excellence (NICE) reference case. A lifetime time horizon is appropriate in this setting to capture all differences in costs or outcomes between the technologies being compared.	N/A

Source: Based on Table 1 of the CS[1]

CHMP = Committee for Medicinal Products for Human Use; CRT = chemoradiation therapy; CS = company submission; EMA = European Medicines Agency; EORTC = European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer quality of life questionnaire and lung cancer module; HRQL =

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
health-related quality of life; IV = intravenous; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; OS = overall survival; OS24 = overall survival after 24 months; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; PFS12 = proportion of patients alive and progression free at 12 months; PFS18 = proportion of patients alive and progression free at 18 months; PFS2 = time from randomisation to second progression or death; PPS = post-progression survival; Q2W = every two weeks; TC = tumour cell; TFST = time to first or subsequent therapy or death; TSST = time to second subsequent therapy or death; TTDM = time to death or distant metastasis Footnotes: * Different from draft scope; § On 26 July 2018, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product durvalumab (IMFINZI™) as monotherapy for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of TCs and whose disease has not progressed following platinum-based CRT.[23]			

3.1 Population

The ERG identified three issues which might limit the applicability of any findings presented in the CS:

- The population defined in the CS is adults with locally-advanced, unresectable, stage III NSCLC whose tumours express PD-L1 on ≥1% of TCs and whose disease has not progressed following platinum-based CRT. Compared to the NICE scope, this definition is narrower due to the incorporation of opinions expressed by the CHMP and the EMA, i.e. included patients in the relevant population whose tumours expressed PD-L1.
- As detailed in Section B.2.3 of the CS, it is important to mention that only eight UK patients of the PACIFIC trial (the main trial identified for clinical effectiveness) were included in the trial and according to the response to request for clarification *"it was not considered appropriate to present analyses where there were <20 events in a subgroup, as this sample size is too small for meaningful analyses / interpretation of data"*.[1, 24] Therefore, outcomes data on these eight UK patients in PACIFIC were not analysed separately. As stated in clarification letter, [redacted], however, analyses of these data are not available at the moment.[24]
- Clinical expert Dr Susan Harden stated that *"most UK patients receive sequential rather than overlapping treatment"* while *"the efficacy and safety of durvalumab in the PACIFIC study was evaluated after overlapping, rather than sequential, CRT"*.[24] This issue is discussed in Section B.1.3 of the CS.[1]

3.2 Intervention

The intervention (durvalumab 10mg/kg Q2W via IV infusion is in line with the scope. However, concomitant treatments were used in the PACIFIC trial. This issue is addressed in Section B.1.1 of the CS.[1]

In July 2018, the CHMP recommended the granting of a marketing authorisation for the medical product IMFINZI™.[23] The final summary of product characteristics (SmPC) and European public assessment report (EPAR) are not available at the present time (October 2018).

3.3 Comparators

The NICE scope listed only one comparator, namely best supportive care (BSC). In the CS BSC was also defined as *"active follow-up"* and *"standard-of-care"*. These definitions were used interchangeably. Since there are no active treatment options after CRT in unresectable Stage III patients whose disease has not progressed, the comparator described in the company's clarification letter 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"* match the comparator described in the final scope.[24]

3.4 Outcomes

All of the outcomes defined in the NICE scope have been addressed in the CS.

Several measures have been included for PFS and HRQoL, as detailed in Table 3.1. Furthermore, an additional outcome, TTDM, was included.

3.5 Other relevant factors

The company describes the economic analysis as per the NICE reference case. However, the company also describe a lifetime time horizon as being appropriate for the setting.

Durvalumab is available in the UK under an Early Access Program (EAP).

4. Clinical effectiveness

4.1 Critique of the methods of the review(s)

The systematic literature review in the CS, which was used to find clinical trial data on the efficacy and safety of durvalumab when compared to active follow-up in locally-advanced, unresectable, stage III NSCLC in patients whose disease has not progressed upon completion of CRT, identified only one trial, the PACIFIC study.

4.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[25] The submission was checked against the single technology appraisal (STA) template for company/sponsor submission of evidence.[26] The ERG has presented only the major limitations of the search strategies in the main report. Further minor comments can be found in Appendix 1.

Appendix D.1 of the CS states that MEDLINE, MEDLINE in Process, Embase, Cochrane Central Register of Controlled Trials, CDSR and DARE were searched for the identification of published clinical trial data on the efficacy and safety of durvalumab.[27] The search strategy was reported in detail in Appendix D.1.[27] Searches were conducted on 24 January 2018 using the OvidSP interface from 2002, and limited to English language studies only. Results were limited to RCTs, using search terms based on the Scottish Intercollegiate Guidelines Network (SIGN) RCT search filters.

Searches were conducted and reported for conference proceedings from 2014-2017 for the following conferences: American Society of Clinical Oncology (ASCO), ESMO, European Lung Cancer Conferences (ELCC), World Conference on Lung Cancer (WCLC) and American Association for Cancer Research (AACR).

No additional search methods, such as clinical trials register searches, handsearching or reference checking were reported.

ERG comment:

- The selection of databases searched was adequate, and searches were clearly reported. The database name, host, date range and date searched were provided.
- In response to clarification the company confirmed that a single search was conducted across MEDLINE, MEDLINE in Process, Embase, Cochrane Central Register of Controlled Trials, CDSR and DARE, using the OvidSP platform. This approach has limitations when using subject heading terms which could affect recall of results. While the ERG noted the inclusion of separate trials filters designed specifically for MEDLINE and Embase, only MEDLINE subject heading terms (MeSH) were used in the population facet of the search strategy. Although simultaneous searching of Embase should automatically identify and search for equivalent Embase subject heading terms (Emtree), it is not clear if this is the case for all potentially useful Emtree terms. Given the possible limitations of this approach, the ERG considered it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in all facets of the search strategy. Reporting individual searches is also good practice in order to clarify the numbers identified on each database.

- Of concern to the ERG was that the search terms used for the population facet of the strategy were limited. The strategy combined NSCLC search terms with both disease stage and chemoradiation therapy (CRT) search terms, resulting in a very focussed strategy which may have missed relevant studies. Although the population is clearly defined in the scope, it is not possible to be sure that the search terms in the strategy will necessarily be included in the title and/or abstract of relevant references. In addition, only one MeSH term was used for NSCLC, and few synonyms were used for disease stage or CRT. Additional synonyms and subject heading terms could have been added to the strategy for NSCLC, disease stage and CRT, and use of these terms could have increased the retrieval of potentially relevant records.
- Durvalumab and comparator terms were not included in the database search strategy, although they were included in the conference searches. In response to clarification, the company stated that *"Durvalumab and comparator terms were not included in the database search strategy because we wanted to capture all possible treatments investigated in the post-chemoradiation therapy (CRT) setting"*.[24] The ERG believed that the addition of intervention and comparator terms to the database strategy as a separate facet (i.e. not combined with the other elements of the search) could have broadened the search to identify other potentially relevant studies. Given the company's awareness of relevant literature in the field and additional search methods however, this is unlikely to have greatly affected the recall of results.
- The trials filter used in the search of all included databases was unnecessary for the search of CENTRAL which contains only controlled trials. For the searches of CDSR and DARE, the trials filters will have removed all records, as these databases contain only systematic reviews. The use of a trials filter for these databases therefore risks removing potentially relevant records.
- The ERG was concerned that limiting the clinical effectiveness searches to English language may have introduced potential language bias. Current best practice states that 'Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'.[28]
- Additional search methods, such as clinical trials register searches, handsearching or reference checking might have been useful to identify additional relevant studies and grey literature.

4.1.2 Inclusion criteria

The CS provided a table illustrating the inclusion and exclusion criteria for the systematic review in order to ensure decisions were consistent (Table 4.1). The inclusion screening made distinctions between level 1 (primary) and level 2 (secondary) screening. Level 1 screening utilised a broad set of inclusion criteria in order to identify trials in which at least one CRT regimen was concurrent in unresectable, stage III NSCLC patients. During the level 2 screening, the definition used for level 1 is expanded upon to include the comparison of the outcomes of durvalumab and active follow-up, BSC, or observation. After applying the criteria, one RCT was found to be appropriate for inclusion in the systematic review. However, in the CS, the company appeared to use terms such as "best supportive care," "active follow-up," "standard of care," "placebo," and "active surveillance" interchangeably. The company amends this in their response to clarification by indicating the terms "active follow-up" and "standard of care" were meant to be used interchangeably in the CS, whereas the term "placebo" was used to refer to the control arm in the PACIFIC trial, see Table 4.2.[24]

In the CS, the outcomes used in the PACIFIC trial, time to progression (TTP) and post progression survival (PPS), were not pre-specified.[1] Upon response for clarification, the company defined TTP as the time from randomisation until the date of the first objective disease progression.[24] The company elaborates further by indicating the use of the TTP definition in this manner was consistent with to the

definition in the EMA guideline.[22] In the response for clarification, the company defines PPS as the time from objective disease progression until censoring or death due to any cause.[24] However, due to PPS not being used in regulatory approvals, there is no definition available from the EMA.

Table 4.1: Detailed inclusion/exclusion criteria for the systematic literature review

Criteria	Inclusion	Exclusion
Population	**Level 1 screening** Unresectable stage III NSCLC (≥80% of the trial population) **Level 2 screening** Unresectable stage III NSCLC patients whose disease has not progressed after completing CRT	Patient populations that do not meet the adjacent inclusion criteria (Note: clinical trials that investigated the efficacy and safety of CRT regimens in unresectable stage III NSCLC patients were initially included [at level 1] for full-text review, to ensure no relevant publications were incorrectly discarded; see **Error! Reference source not found.**)
Interventions and comparators	**Level 1 screening** CRT, including cisplatin or carboplatin in combination with: etoposide, vinblastine, vinorelbine, paclitaxel, docetaxel, or pemetrexed **Level 2 screening** CRT, as per above, followed by either durvalumab or observation / BSC only	Studies that do not meet inclusion criteria specified at each level of screening
Outcomes	**Level 1 and 2 screening:** Overall survival (OS); including hazard ratio, median, landmark survival rates PFS; including hazard ratio, median, landmark survival rates, time to progression (TTP) based on criteria reported in the relevant publication Time to death or distant metastasis (TTDM) Time to treatment failure (TTF) Time to disease progression or death on subsequent therapy (PFS2) Objective response rate (ORR), disease control rate (DCR), duration of response (DoR) based on criteria reported in the relevant publication Overall treatment discontinuation and discontinuation due to efficacy and safety reasons, respectively	Studies that do not report on any of the outcomes listed in the adjacent inclusion criteria

Criteria	Inclusion	Exclusion
	Rates of overall and treatment related grade 3–5 adverse events (AEs)	
Study design	**Level 1 screening** Clinical trials evaluating two or more CRT regimens, involving at least one concurrent regimen (e.g. head-to-head trials of concurrent CRT regimens or comparisons of concurrent and sequential protocols)* CTx used in CRT regimens were as per the inclusion criteria listed in the "intervention and comparators" section Clinical trials evaluating post-CRT maintenance / consolidation therapies **Level 2 screening** Clinical trials evaluating durvalumab or observation / BSC in unresectable stage III NSCLC patients whose disease has not progressed after completing CRT Outcomes should have been measured from randomisation (following confirmation of response / stable disease after concurrent CRT)	**Level 1 screening** Clinical trials that included CTx regimens not specified in the "intervention and comparators" section Observational studies Cases reports or editorial comments Note: studies that evaluated concurrent CRT regimens were initially included for full-text review, to ensure no relevant articles were incorrectly discarded **Level 2 screening** Clinical trials that did not meet the specified level 2 inclusion criteria Note: clinical trials where it was not possible to evaluate outcomes of interest from randomisation to durvalumab or BSC were also excluded (e.g. clinical trials that reported outcomes from initiation of CRT)
Language	Abstracts and / or full-text articles published in English	References published in any language other than English
Countries of interest	No restriction	No restriction
Date	2002 to January 24, 2018	References published outside of this date limit

Source: Table 3 of the CS appendices[27]

BSC = best supportive care; CRT = chemoradiation therapy; CS = company submission; CTx = chemotherapy; DCR = disease control rate; DoR = duration of response; NSCLC = non-small cell lung cancer; PFS = progression-free survival; PFS2 = time to disease progression or death on subsequent therapy; ORR = objective response rate; OS = overall survival; SLR = systematic literature review; TTDM = time to death or distant metastasis; TTF = time to treatment failure; TTP = time to progression

Footnotes: * trials involving at least one concurrent CRT regimen were selected to align with the SoC in unresectable Stage III NSCLC setting and the PACIFIC study population, which only included patients who had not experienced disease progression after ≥2 cycles of overlapping (i.e. concurrent) CRT

Table 4.2: Comparator terminology

Comparator Terms	Company Definitions
"Active follow-up" or "Standard-of-care"	Includes surveillance visits, history, physical examination, and chest CTs every six months for the first two years and annually thereafter to detect second primary tumours. Terms are used interchangeably.
Placebo	Refers to the control arm of the PACIFIC clinical trial or other trials.
Source: Based on response to request for clarification[24] CT = computed tomography	

ERG comment: The definition of PPS is similar to the overall survival (OS) endpoint, except it is calculated from the point of first objective disease progression, not randomisation.

4.1.3 Critique of data extraction

According to the appendices of the CS, data extraction was restricted to full publications and health technology assessments (HTAs) that were conducted from a UK perspective.[27] This resulted in one full publication and 20 HTAs being considered for data extraction. The studies selected for data extraction, were assessed by two reviewers to determine if pre-defined inclusion/exclusion criteria were met. A third-party member was involved in order to resolve any discrepancies. The data extraction was checked by a second reviewer in order to identify any inconsistencies.

ERG comment: The ERG has no further comments on this matter.

4.1.4 Quality assessment

The quality of the PACIFIC study was assessed by the company and presented in the appendices of the CS.[27] The elements that were considered in the quality assessment were appropriate randomisation, adequate concealed treatment allocation, the presence of unexpected imbalances in drop-outs between groups, any evidence suggesting the authors measured more outcomes than they reported, the inclusion of an appropriate intention-to-treat analysis, and the use of appropriate methods to account for missing data. Table 4.3 provides an overview of the quality assessment of the PACIFIC study.

Table 4.3: Quality assessment results for PACIFIC

Study question	How is the question addressed in the study?	Risk of bias
Was randomisation carried out appropriately?	Yes Treatments were assigned using the randomisation scheme in the IVRS / IWRS. One randomisation list was produced for each of the randomisation strata. A blocked randomisation was generated, and all study centres used the same list to minimise any imbalance in the number of patients assigned to each treatment group.	Low

Study question	How is the question addressed in the study?	Risk of bias
Was the concealment of treatment allocation adequate?	Yes The PACIFIC study was conducted in a double-blind manner. The reconstituted durvalumab solution and its matching placebo were identical in colour; IV bags used for administration were identical in size. The study drug was blinded using an opaque sleeve, fastened with tamper-evident tape over the IV bag.	Low*
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes Patients were stratified at randomisation based on their age (<65 versus ≥65 years), gender, and smoking history (current or former smoker versus never smoked). Patients randomised to durvalumab and placebo groups were well balanced in terms of demographics, baseline disease characteristics (including PD-L1 expression and *EGFR* mutational status), and prior anti-cancer therapy (including best response to previous concurrent CRT).	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes The PACIFIC study was conducted in a double-blind manner. The patient, the Investigator and study centre staff were blinded to study drug allocation. Only the study centre pharmacist was unblinded and prepared the durvalumab infusion or placebo for a patient, as specified by the randomisation scheme and IVRS. No member of the extended study team at AstraZeneca/MedImmune, at the investigational centres, or any Contract Research Organisation handling data had access to the randomisation scheme until the time of the final data analysis (exceptions noted in the Clinical Study Protocol[29]. Investigators were only unblinded to treatment allocation in cases of medical emergency. Note: the IDMC were provided with unblinded data for their review but AstraZeneca/MedImmune and Quintiles staff and Investigators involved in the study remained blinded.	Low

Study question	How is the question addressed in the study?	Risk of bias
Were there any unexpected imbalances in drop-outs between groups?	No At the most-recent data cut-off (interim OS analysis), 22 patients (4.6%) in the durvalumab group and 14 patients (5.9%) in the placebo group (had terminated the study by choice. One patient in the durvalumab group and no patients in the placebo group were lost to follow-up. The primary reason for study termination was death The number and reasons for discontinuations from treatment did not raise any concerns about the conduct of the study. More patients in the placebo group discontinued treatment due to worsening of the condition under investigation (49.6%, versus 31.3% in the durvalumab group), as expected given the study hypothesis.	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No Full documentation relating to the PACIFIC clinical trial methodology, analyses, and outcomes are included in the CS	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Efficacy and HRQL analyses were performed on the ITT population; standard censoring methods used to account for missing data. Note: safety analyses were performed on the Safety Analysis Set, which included all patients all patients who received at least one dose of randomised study drug and for whom any post-dose data were available	Low

Source: Based on Table 7 of the CS appendices[27]
CRT = chemoradiation therapy; CS = company submission; EGFR = epidermal growth factor receptor; HRQL = health-related quality of life; IDMC = independent data monitoring committee; ITT = intention-to-treat; IV = intravenous; IVRS = interactive voice response system; IWRS = interactive web response system; OS = overall survival; PD-L1 = programmed death ligand 1

ERG comment: In the quality assessment of the PACIFIC trial, presented in Table 7 of the CS appendices, the company identifies the PACIFIC trial as having a low risk of bias for concealment of treatment allocation.[27] The response does not describe how concealment of allocation was concealed, i.e. this question should be rated as unclear. However, describing the randomisation, the company describes that IVRS/IWRS were used which are acceptable methods of concealment of allocation.

4.1.5 Evidence synthesis

The analysis utilised in the CS was done in accordance with a comprehensive Statistical Analysis Plan (SAP). Three interim analyses were utilised.

Only one RCT, PACIFIC, was identified. Therefore, no evidence synthesis was done.

4.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Overview of the direct evidence in the submission

The CS states that the phase III PACIFIC RCT is the only study in which a direct comparison was made focusing on the clinical effectiveness of durvalumab 10mg every two week (Q2W) versus active follow-up in locally-advanced, unresectable Stage III NSCLC patients whose disease has not progressed following CRT.

The data supporting this submission is from the PACIFIC study, which is a randomised, double-blind, placebo-controlled, multicentre, international study. The main features of the PACIFIC study are summarised in Table 4.4.

The CS noted that most participants in the PACIFIC trial received two or more overlapping, or concurrent, cycles of CRT.[1] However, according to the clinical expert cited in the CS, sequential CRT is the method of treatment most often received for patients in the UK and is identified as the standard of care. While the company acknowledges this difference, they state the PACIFIC patient population is broadly general to UK patients with locally-advanced, unresectable, stage III NSCLC patients who receive curative-intent CRT treatment.

Table 4.4: Quality assessment results for PACIFIC

Trial name	**PACIFIC trial**
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	Durvalumab (n=476)
Comparator	Placebo (n=237)
Outcomes	• PFS* -PFS12, PFS18, TFST • OS* -OS24 • Adverse effects of treatment* • Response rates • PPS* • HRQL -EQ-5D* -EORTC • Time to treatment discontinuation* • TTDM • PFS2* -TSST
Study design	PACIFIC is an ongoing, randomised, double-blind, placebo-controlled, multi-centre, international, phase III study.
Duration of trial and trial phases	Randomisation completed as late as 42 days after last radiation dose.
	Durvalumab 10 mg/kg Q2W and Placebo Q2W received for up to 12 months.
	Re-treatment for patients who experienced disease control at the end of 12 months of treatment but progressed during follow-up.

Trial name	PACIFIC trial
Settings and locations where the data were collected	235 study centres in 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, UK, United States (US), and Vietnam.

Source: Table 3 and Figure 6 of the CS[1]
Footnote: * included in economic model
CRT = chemoradiation therapy; CS = company submission; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life-5 dimensions; HRQL = health-related quality of life; OS = overall survival; OS24 = proportion of patients alive at 24 months; PFS = progression free survival; PFS12 = proportion of patients alive and progression free at 12 months; PFS18 = Proportion of patients alive and progression free at 18 months; PFS2 = time to second progression or death; PPS = post-progression survival; Q2W= every 2 weeks; TFST = time to first or subsequent therapy or death; TSST = time to second subsequent therapy or death; TTDM = time to death or distant metastasis; US = United States

ERG comment: According to the response to request for clarification, *"the efficacy and safety of durvalumab in locally-advanced, unresectable, Stage III NSCLC whose disease had not progressed following sequential CRT protocols was not investigated in the PACIFIC study, and as such, robust evidence from randomised clinical trial(s) is missing in this setting"*.[24] Therefore, most participants in the PACIFIC trial received two or more concurrent cycles of CRT. However, most UK patients, according to a clinical expert, receive sequential cycles of CRT which was not included in the evaluation of durvalumab.[1] Survival rates are lower amongst patients treated with sequential CRT approaches than overlapping and this should be also taken into consideration.[24]

In the response to request for clarification, the company provided some information about clinical experts' thoughts on rationale for using durvalumab after sequential CRT.[24] Given pre-clinical data, *"clinicians would expect to see some benefits of durvalumab treatment after sequential CRT, although the magnitude of this remains uncertain in the absence of robust clinical evidence"*.[24]

4.2.2 Participants in the PACIFIC trial

In the PACIFIC study, in order to be included patients had to be adults who had histologically- or cytologically-confirmed unresectable Stage III NSCLC. The patients also had to receive at least two overlapping cycles of CRT without disease progression upon completion. In order to be included in the PACIFIC study, the last received radiation dose had to have been completed 42 days prior to the first dose of study treatment. Further inclusion criteria included the patients to have had an estimated life expectancy. Nine hundred and eighty-three patients were enrolled from 235 centres, of which 713 ITT patients were randomised to receive either durvalumab or placebo. Of the 713 ITT patients, 76.4% had biopsies available for PD-L1 analysis, which was later determined to be 303 patients had ≥1% PD-L1 expression. The table below indicates the demographics of the patients included in the PACIFIC study.

The mean age of participants in the PACIFIC study in both the durvalumab ITT group and the durvalumab PD-L1≥1% groups was 63.0 years. In the PD-L1≥1% group was comprised of 67.9% males and 32.1% females, whereas the placebo group was comprised of 71.4% males and 28.6% females. In the PD-L1≥1% group, 68.9% of the group were identified as being white, whereas in the placebo group, 65.9% identified as being white. The durvalumab and placebo groups within the identified PD-L1≥1% group appeared well balanced among the factor focusing on smoking status. The durvalumab group had 18.4% who identified as being current smokers, 72.2% identified as being former smokers, and 9.4% identified as never smoked before. The placebo group had 14.3% who identified as being current

smokers, 78.0% identified as being former smokers, and 7.7% had never smoked before. Of both the placebo and durvalumab group 99.7% received chemotherapy concurrent with radiotherapy, see Table 4.5.

Table 4.5: Patient demographics, baseline disease characteristics, and prior anti-cancer therapies

Characteristic	ITT			PD-L1 ≥1% group		
	Durvalumab (n=476)	Placebo (n=237)	Total (n=713)	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)
Demographics						
Age, mean (SD)	63.0 (8.7)	62.6 (9.6)	62.9 (9.0)	63.0 (8.4)	63.1 (8.8)	63.1 (8.5)
Age, median (range) [years]	64 (31−84)	64 (23−90)	64 (23−90)	64 (36−83)	64 (41−90)	64 (36−90)
Age groups (years), n (%)						
<50	30 (6.3)	22 (9.3)	52 (7.3)	12 (5.7)	6 (6.6)	18 (5.9)
≥50−<65	231 (48.5)	108	339	104 (49.1)	45 (49.5)	149 (49.2)
≥65−<75	178 (37.4)	88 (37.1)	266	81 (38.2)	34 (37.4)	115 (38.0)
≥75	37 (7.8)	19 (8.0)	56 (7.9)	15 (7.1)	6 (6.6)	21 (6.9)
Sex, n (%)						
Male	334 (70.2)	166	500	144 (67.9)	65 (71.4)	209 (69.0)
Female	142 (29.8)	71 (30.0)	213	68 (32.1)	26 (28.6)	94 (31.0)
Race **Race, n (%)**						
White	337 (70.8)	157	494	146 (68.9)	60 (65.9)	206 (68.0)
Black /	12 (2.5)	2 (0.8)	14 (2.0)	8 (3.8)	1 (1.1)	9 (3.0)
Asian	120 (25.2)	72 (30.4)	192	58 (27.4)	27 (29.7)	85 (28.1)
Native	1 (0.2)	1 (0.4)	2 (0.3)	0	1 (1.1)	1 (0.3)
American	4 (0.8)	5 (2.1)	9 (1.3)	0	2 (2.2)	2 (0.7)
Other	1 (0.2)	0	1 (0.1)	0	0	0
Missing	1 (0.2)	0	1 (0.1)	0	0	0
Weight, mean	71.9 (17.39)	69.4	71.1	72.6 (17.88)	67.4 (15.4)	71.1 (17.3)
Weight,	69 (34−175)	69	69	69 (34−133)	65	69 (34−133)
Weight group (kg), n (%)						
<70	243 (51.1)	124	367	107 (50.5)	54 (59.3)	161 (53.1)
≥70-≤90	174 (36.6)	93 (39.2)	267	77 (36.3)	31 (34.1)	108 (35.6)
>90	58 (12.2)	19 (8.0)	77 (10.8)	28 (13.2)	6 (6.6)	34 (11.2)
Missing	1 (0.2)	1 (0.4)	2 (0.3)	0	0	0
Smoking status, n (%)						
Current	79 (16.6)	38 (16.0)	117	39 (18.4)	13 (14.3)	52 (17.2)
Former	354 (74.4)	178	532	153 (72.2)	71 (78.0)	224 (73.9)

Characteristic	ITT			PD-L1 ≥1% group		
	Durvalumab (n=476)	Placebo (n=237)	Total (n=713)	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)
Never	43 (9.0)	21 (8.9)	64 (9.0)	20 (9.4)	7 (7.7)	27 (8.9)
Disease characteristics						
Disease Stage, n (%)						
IIIA	252 (52.9)	125	377	118 (55.7)	48 (52.7)	166 (54.8)
IIIB	212 (44.5)	107	319	89 (42.0)	42 (46.2)	131 (43.2)
Other[a]	12 (2.5)	5 (2.1)	17 (2.4)	5 (2.3)	1 (1.1)	6 (2.0)
WHO performance-status score, n (%)[b]						
0	234 (49.2)	114	348	105 (49.5)	45 (49.5)	150 (49.5)
1	240 (50.4)	122	362	106 (50.0)	46 (50.5)	152 (50.2)
Not reported	2 (0.4)	1 (0.4)	3 (0.4)	1 (0.5)	0	1 (0.3)
Tumour histological type, n (%)						
Squamous	224 (47.1)	102	326	109 (51.4)	41 (45.1)	150 (49.5)
Non-	252 (52.9)	135	387	103 (48.6)	50 (54.9)	153 (50.5)
PD-L1 status, n (%)[c]						
TC <25%	187 (39.3)	105	292	97 (45.8)	47 (51.6)	144 (47.5)
TC ≥25%	115 (24.2)	44 (18.6)	159	115 (54.2)	44 (48.4)	159 (52.5)
Unknown[d]	174 (36.6)	88 (37.1)	262	N/A	N/A	N/A
EGFR mutation status, n (%)						
Positive	29 (6.1)	14 (5.9)	43 (6.0)	17 (8.0)	4 (4.4)	21 (6.9)
Negative	317 (66.6)	165	482	180 (84.9)	84 (92.3)	264 (87.1)
Unknown[d]	130 (27.3)	58 (24.5)	188	15 (7.1)	3 (3.3)	18 (5.9)
Prior anti-cancer therapy						
Previous radiotherapy, n (%)[e]						
<54 Gy	3 (0.6)	0	3 (0.4)	2 (0.9)	0	2 (0.7)
≥54 to ≤66	442 (92.9)	217	659	193 (91.0)	86 (94.5)	279 (92.1)
>66 to ≤74	30 (6.3)	19 (8.0)	49 (6.9)	17 (8.0)	5 (5.5)	22 (7.3)
Missing[f]	1 (0.2)	1 (0.4)	2 (0.3)	0	0	0
Previous chemotherapy, n (%)[g]						
Adjuvant	3 (0.6)	1 (0.4)	4 (0.6)	2 (0.9)	0	2 (0.7)
Induction	123 (25.8)	68 (28.7)	191	49 (23.1)	21 (23.1)	70 (23.1)
Concurrent with radiation therapy	475 (99.8)	236 (99.6)	711 (99.7)	211 (99.5)	91 (100.0)	302 (99.7)
Best response to previous CRT, n (%)[h]						
Complete	9 (1.9)	7 (3.0)	16 (2.2)	3 (1.4)	2 (2.2)	5 (1.7)
Partial	232 (48.7)	111	343	[redacted]	[redacted]	[redacted]

Characteristic	ITT			PD-L1 ≥1% group		
	Durvalumab (n=476)	Placebo (n=237)	Total (n=713)	Durvalumab (n=212)	Placebo (n=91)	Total (n=303)
Stable	222 (46.6)	114	336	[redacted]	[redacted]	[redacted]
Progression	2 (0.4)	0	2 (0.3)	[redacted]	[redacted]	[redacted]
Non-	9 (1.9)	4 (1.7)	13 (1.8)	[redacted]	[redacted]	[redacted]
Not	2 (0.4)	1 (0.4)	3 (0.4)	[redacted]	[redacted]	[redacted]

Source: Based on Table 4 of the CS[1]
Key: CRT = chemoradiation therapy; CS = company submission; CSR = clinical study report; DCO = data cut-off; EGFR = epidermal growth factor receptor; ITT = intention to treat; N/A = not applicable; PD-L1 = programmed cell death ligand 1; SD) standard deviation; TC) tumour cell; WHO) World Health Organization
Note: The PD-L1 subgroup has been defined using the re-scored PD-L1 data.
Footnotes: [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 performance-status 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 2 patients in the durvalumab group changed from unknown to negative between the 13 February 2017 and 22 March 2018 DCOs, as the results for these 2 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] For the two patients with missing data, the biologically effective radiotherapy dose could not be calculated, primarily because their radiotherapy treatment planning data were neither collected nor accessible; [g] Patients may have received previous chemotherapy in more than one context; h, best response to prior therapy is based on the last therapy prior to entering the study.

ERG comment: In the PACIFIC study, randomisation was not stratified based on PD-L1 status. While reported baseline characteristics, such as age, histology, or smoking status, were balanced between the durvalumab and placebo groups, there are potential problems linked to overinterpretation of subgroup analyses which might impact on the findings.[30]

4.2.3 Efficacy outcomes

The main findings from the PACIFIC study are presented in the CS and reproduced below, see Tables 4.6 and 4.7.

Table 4.6: Key efficacy outcomes for durvalumab versus placebo from the PACIFIC RCT (ITT and PD-L1 ≥1% group; 22 March 2018 DCO)

Endpoint	ITT		PD-L1 ≥1%	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=212)	Placebo (N=91)
Primary endpoints				
PFS (13 February 2017 DCO; BICR) Median (95% CI) [months]	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)	17.8 (16.9, NR)	5.6 (3.6, 11.0)
HR (95% CI); P-value	0.52 (0.42, 0.65); P<0.001		0.44 (0.30, 0.64); *P*<0.0001	

Endpoint	ITT		PD-L1 ≥1%	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=212)	Placebo (N=91)
OS (22 Mar 2018 DCO) Median (95% CI), [months]	NR (34.7, NR)	28.7 (22.9, NR)	NR (NR, NR)	29.1 (17.7, NR)
HR (95% CI); P-value	0.68 (0.53, 0.87); *P* =0.003		0.54 (0.35, 0.81); *P*=0.003	
Updated PFS and secondary endpoints (at the time of OS interim analysis; 22 March 2018 DCO)				
PFS (BICR) Median (95% CI) [months]	17.2 (13.1, 23.9)	5.6 (4.6, 7.7)	23.9 (17.2, NR)	5.6 (3.6, 11.0)
HR (95% CI); *P*-value	0.51 (0.41, 0.63); *P*<0.0001		0.44 (0.31,0.63); *P*<0.0001	
TFST Median (95% CI) [months]	21.0 (16.6, 25.5)	10.4 (8.3, 12.5)	25.8 (18.7, 37.8)	10.0 (7.0, 17.0)
HR (95% CI); *P*-value	0.58 (0.47, 0.72); *P* <0.0001		0.51 (0.36, 0.73); *P*=0.0002	
PFS2 Median (95% CI) [months]	28.3 (25.1, 34.7)	17.1 (14.5, 20.7)	33.8 (26.7, NR)	16.5 (10.3, 22.1)
HR (95% CI); *P*-value	0.58 (0.46, 0.73); *P* <0.0001		0.44 (0.30, 0.64); *P*<0.0001	
TSST Median (95% CI) [months]	29.3 (26.0, 34.9)	18.6 (14.8, 23.9)	34.7 (28.8, NR)	17.9 (12.7, 26.2)
HR (95% CI); *P*-value	0.63 (0.50, 0.79); *P* <0.0001		0.49 (0.33, 0.71); *P*=0.0002	
Response rate ORR, % (95% CI)	30.0 (25.8, 34.5)	17.8* (13.0, 23.7)	32.5 (26.0, 39.5)	16.5 (9.3, 26.1)
P-value	*P* <0.001		*P*<0.005	
TTDM Median (95%CI)	28.3 (24.0, 34.9)	16.2 (12.5, 21.1)	NR (26.2, NR)	17.1 (9.2, 20.6)
HR (95% CI); *P*-value	0.53 (0.41, 0.68); *P* <0.0001		0.40 (0.26, 0.61); *P*<0.0001	

Source: Based on Table 6 of the CS[1]

BICR = blinded independent central review; CI = confidence interval; CRT = chemoradiation therapy; CS = company submission; CSR = clinical study report; DCO = data cut-off; HR = hazard ratio; ITT = intention-to-treat; NR = not reached; ORR = objective response, OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PFS2 = time to second progression or death; RECIST = Response Evaluation Criteria In Solid Tumours; TFST = time to first subsequent therapy or death; TSST = time to second subsequent therapy or death; TTDM = time to death or distant metastasis

* may reflect residual effect from prior CRT. The analysis of time to event endpoints 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.

Table 4.7: Semi-parametric analysis of PPS in patients with confirmed disease progression (BICR); PD-L1 ≥1% group (22 March 2018 DCO)

Post-progression survival	Durvalumab (N=86)	Placebo (N=57)
Total events, n (%)[a]	44	33
Ratio (durvalumab:placebo)	1.33	
Difference (durvalumab–placebo)	11	
Median time to event, months (95% CI)	18.6 (12.5, 26.5)	15.3 (12.5, 18.5)
Ratio (durvalumab:placebo)	1.21 (1.0, 1.4)	
Difference (durvalumab–placebo)	3.22 (0, 8)	

Source: Based on Table 13 of the CS[1]
BICR = blinded independent central review; CI = confidence interval; DCO = data cut-off; ITT = intention-to-treat; PD-L1 = programmed cell death ligand 1; PPS = post-progression survival.

ERG comment: Due to information not being presented in the initial CS, the ERG had to request further information in the request for clarification. This was needed in order to elaborate further on outcomes focusing on OS and PFS. The efficacy results reported in the CS are largely in favour of durvalumab.

However, it should be noted that some results are not yet available as PACIFIC is ongoing. According to the response to request for clarification, the company *"will conduct a final analysis of OS once a maturity of 70% has been reached. OS is an event-driven endpoint; therefore, the timing of this analysis is uncertain"* which will be reached *"when 491 OS events have occurred"*.[1, 24] A Table on page 254 of the CS appendices details the current maturity in the PD-L1≥1% subgroup[27]:

- OS: Durvalumab 33.0%, Placebo 49.5%
- PFS2: Durvalumab 39.6%, Placebo 62.6%
- PFS (BICR): Durvalumab 46.7%, Placebo 72.5%
- PPS (BICR): Durvalumab 51.2%, Placebo 57.9%

4.2.4 Adverse events (AEs)

Key AEs were identified for inclusion in the economic model, see Table 4.8. The CS noted that the incidence and severity of AEs between the durvalumab and placebo groups were comparable. The CS stated that 96.8% of patients in the durvalumab group and 94.9% of patients in the placebo group had experienced at least one AE by the latest data cut-off (DCO), durvalumab was stated to be well-tolerated and had a manageable safety profile relative to placebo. Of the patients in the durvalumab and placebo groups within the safety analysis set, 32.6% and 28.2%, respectively, experienced an AE of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4. Within the PD-L1≥1% groups, 33.8% patients in the durvalumab group experienced an AE of CTCAE Grade 3 or 4, whereas this was experienced by 23.3% of patients in the placebo group. Within the safety analysis set, serious adverse events (SAE), which included events with death as an outcome, were experienced in 29.1% of patients in the durvalumab group and 23.1% of the patients in the placebo group. In the PD-L1≥1% group, this was seen in 30.0% and 20.0% of durvalumab and placebo group patients, respectively. Within the PD-L1≥1% group the CS identifies the most common AEs among the durvalumab group as being cough, fatigue, radiation pneumonitis, dyspnoea, and diarrhoea. Whereas, the most common AEs in the placebo group were identified as being cough, dyspnoea, fatigue, diarrhoea, arthralgia, and hypothyroidism. According to the CS, of the durvalumab patients the most common AEs of CTCAE Grade 3 or 4 were identified as being pneumonia, anaemia, and pneumonitis. Whereas in the placebo group, the most

common AEs of CTCAE Grade 3 or higher were found to be pneumonia, anaemia, and hypokalemia. The CS also reports the percentage of PD-L1≥1% patients whose AEs resulted in discontinuation of the study treatment as being 36 (16.9%) of durvalumab patients and five (5.6%) of placebo patients. The CS further states the investigators identified 24 patients in the durvalumab group and two patients in the placebo group whose discontinuation was deemed to be causally related to the study treatment. According to the DCO on 22 March 2018, 15 patients in the durvalumab arm and the 10 patients in the placebo arm had died during treatment or within 90 days of the last dose. In the durvalumab group, most of the deaths were attributed to cardiac arrest, whereas in the placebo group deaths were attributed to pneumonia, haemoptysis, intestinal obstruction, and radiation pneumonitis.

Table 4.9 reports the most common AEs (>5% in any treatment group) while Table 4.10 reports HRQoL.

Table 4.8: Summary of key safety events; PACIFIC safety analysis set and PD-L1 ≥1% group (22 March 2018 DCO)

AE category, n (%)[a, b]	Safety analysis set		PD-L1 ≥1% group	
	Durvalumab (n=475)	Placebo (n=234)	Durvalumab (n=213)	Placebo (N=90)
Any AE	**460 (96.8)**	**222 (94.9)**	**205 (96.2)**	**83 (92.2)**
Any AE causally related to treatment[c]	322 (67.8)	125 (53.4)	144 (67.6)	48 (53.3)
Any AE of CTCAE Grade 3 or 4	**155 (32.6)**	**66 (28.2)**	**72 (33.8)**	**21 (23.3)**
Any AE of CTCAE Grade 3 or 4, causally related to treatment[c]	59 (12.4)	11 (4.7)	26 (12.2)	4 (4.4)
Any SAE (including events with outcome of death)	**138 (29.1)**	**54 (23.1)**	**64 (30.0)**	**18 (20.0)**
Any SAE (including events with outcome of death), causally related to treatment[c]	41 (8.6)	9 (3.8)	16 (7.5)	1 (1.1)
Any AE leading to discontinuation of study treatment	**73 (15.4)**	**23 (9.8)**	**36 (16.9)**	**5 (5.6)**
Any AE leading to discontinuation of study treatment, causally related to treatment[c]	47 (9.9)	8 (3.4)	24 (11.3)	2 (2.2)
Any AE with outcome of death	**21 (4.4)**	**15 (6.4)**	**8 (3.8)**	**4 (4.4)**
Any AE with outcome of death, causally related to treatment[b]	7 (1.5)	4 (1.7)	2 (0.9)	0
Any AE leading to dose delay[d]	203 (42.2)	72 (30.8)	96 (45.1)	27 (30.0)
Any other significant AEs[e]	0	0	0	0
Immune mediated AEs[c]	166 (34.9)	39 (16.7)	73 (34.3)	16 (17.8)
Infusion reaction AEs[c]	15 (3.2)	7 (3.0)	3 (1.4)	3 (3.3)

AE category, n (%)[a, b]	Safety analysis set		PD-L1 ≥1% group	
	Durvalumab (n=475)	Placebo (n=234)	Durvalumab (n=213)	Placebo (N=90)

Source: Based on Table 18 of the CS[1]
Note: The PD-L1 subgroup has been defined using the re-scored PD-L1 data.
Footnotes: [a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories; [b] Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first); [c] As assessed by the Investigator. Missing responses are counted as related; [d] AEs on the AE case report form with Action taken = Drug interrupted, excluding those AEs on the dosing CRF forms only leading to infusion interruptions; [e] Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as other significant AEs.
AE = adverse event; CRF = case report form; CS = company submission; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; PD-L1 = programmed cell death ligand 1; SAE = serious adverse event

Table 4.9: Most common AEs (>5% in any treatment group) by preferred term; PACIFIC PD-L1 ≥1% group (22 March 2018 DCO)

Preferred term[a]	Number of patients, n (%)[b, c]	
	Durvalumab (N=213)	Placebo (N=90)
Patients with any AE	**205 (96.2)**	**83 (92.2)**
Cough	71 (33.3)	24 (26.7)
Fatigue	60 (28.2)	19 (21.1)
Radiation pneumonitis[d]	47 (22.1)	10 (11.1)
Dyspnoea	46 (21.6)	23 (25.6)
Diarrhoea	43 (20.2)	14 (15.6)
Pruritus	36 (16.9)	4 (4.4)
Pneumonia	30 (14.1)	7 (7.8)
Pyrexia	29 (13.6)	6 (6.7)
Decreased appetite	28 (13.1)	9 (10.0)
Upper respiratory tract infection	28 (13.1)	8 (8.9)
Rash	27 (12.7)	7 (7.8)
Constipation	27 (12.7)	5 (5.6)
Arthralgia	27 (12.7)	14 (15.6)
Pneumonitis[d]	26 (12.2)	6 (6.7)
Hypothyroidism	26 (12.2)	1 (1.1)
Nausea	24 (11.3)	14 (15.6)
Headache	24 (11.3)	10 (11.1)
Asthenia	23 (10.8)	8 (8.9)
Back pain	22 (10.3)	10 (11.1)
Nasopharyngitis	22 (10.3)	5 (5.6)

Preferred term[a]	Number of patients, n (%)[b, c]	
	Durvalumab (N=213)	Placebo (N=90)
Productive cough	20 (9.4)	6 (6.7)
Vomiting	19 (8.9)	10 (11.1)
Hyperthyroidism	18 (8.5)	1 (1.1)
Anaemia	18 (8.5)	8 (8.9)
Dry skin	18 (8.5)	5 (5.6)
Oedema peripheral	17 (8.0)	5 (5.6)
Non-cardiac chest pain	16 (7.5)	12 (13.3)
Insomnia	15 (7.0)	4 (4.4)
Pain in extremity	15 (7.0)	4 (4.4)
Myalgia	14 (6.6)	5 (5.6)
Bronchitis	14 (6.6)	8 (8.9)
Musculoskeletal pain	14 (6.6)	5 (5.6)
Hypokalaemia	14 (6.6)	6 (6.7)
Dizziness	13 (6.1)	12 (13.3)
Musculoskeletal chest pain	13 (6.1)	7 (7.8)
Hypertension	11 (5.2)	4 (4.4)
Paraesthesia	11 (5.2)	5 (5.6)

Source: PACIFIC PD-L1 subgroup analyses; 22 March 2018 DCO, provided in response to request for clarification [24]

Notes: The PD-L1 subgroup has been defined using the re-scored PD-L1 data; [a] MedDRA version 19.1; [b] Includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication; [c] Patients with multiple AEs are counted once for each preferred term. Included are events that were reported in at least 5% of the patients in either group; patients with multiple events only counted once in each row; includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first); [d] Pneumonitis or radiation pneumonitis was assessed by investigators with subsequent review and adjudication by the study sponsor. In addition, pneumonitis is a grouped term that includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis.

AE = adverse event; DCO = data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; PD-L1 = programmed cell death ligand 1.

Table 4.10: Health-related quality of life of the PACIFIC trial

HRQoL parameter	Partial correlation[a]	Statistical significance
SF-36 Domains		
Physical functioning	-0.276	*P*=0.009
Bodily pain	-0.255	*P*=0.016
Mental health	-0.208	*P*=0.064
SF-36 Summed scores		
Physical component	-0.275	*P*=0.015
EuroQoL parameters		
EuroQoL SC	-0.236	*P*=0.027
EuroQoL VAS	-0.220	*P*=0.038

Source: Based on Table 34 of the CS appendices[27]
Footnotes: [a] A negative correlation coefficient indicates that the presence of metastasis worsens HRQL / utility, while a positive value indicates improvement.
CS = company submission; EuroQOL SC = EuroQOL self-classifier; EuroQOL VAS = EuroQOL visual analogue scale; HRQL = quality of life; SF-36 = 36-item Short Form health survey.

ERG comment: As detailed before, more adverse events are reported for participant treated with durvalumab compared to the placebo arm, see Table 4.9. However, as detailed in Table 4.8, this does include serious adverse events.

4.2.5 Ongoing trials

The CS mentions ongoing phases and phases due to commence in late 2018 of the PACIFIC trial. Such phases include PACIFIC-R, PACIFIC-5, and PACIFIC-6.[1] Pacific–R is a planned retrospective real-world study that will include a large group of patients with locally-advanced, unresectable, Stage III NSCLC who had been included in the EAP and treated with durvalumab. PACIFIC-5 is similar to PACIFIC in that it is also a Phase III, randomised, double-blind, placebo-controlled, multicentre study, which is assessing the efficacy and safety of durvalumab in patients with locally advanced, unresectable, Stage III NSCLC. However, PACIFIC-5 will recruit mainly recruit patients from China and will use a fixed dose of 1500mg every four weeks (Q4W) through an IV fusion rather than using a weight-based dosing system. PACIFIC-6 is a Phase II, open-label multi-centre international safety study focusing on 1500mg of durvalumab Q4W upon completion of sequential CRT. [redacted]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company submission did not present an indirect comparison and/or multiple treatment comparison.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company submission did not present an indirect comparison and/or multiple treatment comparison.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The CS comprised of a systematic review of the evidence for durvalumab for the treatment of locally advanced unresectable, Stage III NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based CRT. The presented evidence included one RCT, the PACIFIC trial.[1]

The PACIFIC trial included patients with confirmed PD-L1 expression on ≥1% of TCs. After randomisation procedures, this resulted in 476 patients in the durvalumab group and 237 patients in the placebo group. However, when focusing on only the patients with confirmed PD-L1 expression on ≥1% of TCs, there were 212 patients in the durvalumab group and 91 patients in the placebo group. While the PACIFIC trial met a multicentre, international design, only eight patients were seeking treatment in the UK. Due to the trial being identified as ongoing, some results are not yet available.

Based on the PACIFIC data there appears to be a benefit in both PFS and OS for durvalumab patients compared with placebo patients, however, the data are immature and there remains substantial uncertainty about the comparative effectiveness.

Common adverse events were reported in both the durvalumab and placebo groups. The common AEs in the durvalumab patients included cough, fatigue, and radiation pneumonitis, whereas patients in the placebo group also included dyspnoea. Overall, more serious adverse events were reported for durvalumab compared to placebo (64/213 (30%) vs. 18/90 (20%)).

Final results for PACIFIC will be published at a later date.

5. Cost effectiveness

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

This section contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes the searches for the cost effectiveness analysis review, health-related quality of life and for cost and healthcare resource identification, measurement and valuation. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[25] The submission was checked against the single technology appraisal (STA) template for company/sponsor submission of evidence.[26] The ERG has presented only the major limitations of the search strategies in the main report. Further minor comments can be found in Appendix 1.

Sections B.3.1, B.3.4 and B.3.5 of the CS state that systematic literature reviews were undertaken to identify studies reporting economic evaluations, health state utility data and cost and resource use data in adults with locally-advanced, unresectable, Stage III NSLC. The 2018 update searches extended the scope to include advanced metastatic Stage IV NSCLC with no restriction to patients treated with CRT.

Search strategies were reported in detail in Appendix G, H and I, and in the response to clarification. MEDLINE, MEDLINE In Process, Embase, EconLit, the HTA database and the NHS Economic Evaluation Database were listed as the databases searched. All databases were searched on 24/25 October 2016, with update searches conducted on 5 March 2018. Searches were limited from 2005 for the cost effectiveness and resource identification strategies, but no date limit was applied to the health-related quality of life strategies. No language limitations were applied in any searches.

Electronic searches were supplemented with hand searching reference lists of included publications and additional websites recommended by NICE, including the cost effectiveness analysis (CEA Registry) for the cost effectiveness searches. Searches were conducted and reported for conference proceedings for the following conferences: ISPOR International and European Congress, European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO) and the British Thoracic Oncology Group (BTOG).

ERG comment:

- The selection of databases searched was adequate and searches were clearly reported and reproducible. The database name, host, date range and date searched were provided. A good range of additional resources were included.
- In response to clarification, the company confirmed that 2016 Embase searches were jointly conducted for EMBASE and MEDLINE through the EMBASE.com platform. Embase.com searches were conducted as a single search simultaneously over both the Embase and MEDLINE individual databases. As the strategy used contained both MEDLINE and Embase subject heading terms, the ERG confirmed that this should be sufficient to retrieve potentially

relevant records, however the ERG was unable to assess the Embase.com searches in detail, due to lack of access to that host.

- A good range of intervention terms for durvalumab and comparators were used in the cost effectiveness strategy.
- Study design limits to identify economic evaluations, health state utility data and cost and healthcare resource data were applied. The study design filters were not referenced, so it was unclear whether the filters used were published objectively-derived filters. The filters contained a combination of subject heading terms (MeSH and Emtree) and free text terms, and the ERG deemed them to be adequate. The economic evaluation and cost facets used in the 2016 NHS EED and EconLit searches were unnecessary, however, given that these databases only contain economics literature. These limits were not applied to either database in the 2018 update searches.

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the original review on cost effectiveness studies, utilities and costs and resource use are presented in Table 8 of Appendix G, Table 17 of Appendix H and Table 20 of Appendix I of the CS, respectively.[27] To extend the scope of the review, an update was conducted in March 2017 of which the in- and exclusion criteria can be found in Table 9 of Appendix G (cost effectiveness studies), Table 18 of Appendix H (utility studies) and Table 21 of Appendix I (cost/ resource use studies).[27] Extending the scope of the review included a broader patient population (including advanced metastatic disease) and a broader range of interventions (such as immunotherapies, including nivolumab and pembrolizumab), study designs and outcomes.

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies.

5.1.3 Included/excluded studies in the cost effectiveness review

In total, three unique cost effectiveness studies met the pre-defined eligibility criteria in the original search (references not provided in the CS). However, none of these studies were conducted from a UK perspective. The updated searches related to cost effectiveness studies resulted in one full publication[31] and 20 HTA submissions (only 19 references provided in the CS).[32-50]

The original search yielded one utility study[51], and the updated search resulted in another 52 eligible utility studies (48 studies reporting utility data[32, 33, 38, 41-50, 52-80] and four studies reporting mapping algorithms[81-84]). Of all potentially relevant full publications identified by the original search for costs and resource, none reported UK-related costs or resource use data. The updated search resulted in five studies[85-89] reporting UK specific cost and resource use data.

ERG comment: The rationale for excluding cost effectiveness studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

5.1.4 Conclusions of the cost effectiveness review

The CS provided an overview of the included cost effectiveness, utility and resource use and costs studies, but no specific conclusion was formulated.

ERG comment: The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches and the 2018 update searches. A good range of databases and additional resources were searched.

Eligibility criteria were suitable for the SLR performed.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.1: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	State transition (semi-Markov) model	Partitioned survival analysis produced logical inconsistencies	B.3.2
States and events	Progression-free, progressed disease, dead	Progression is a clinically important and patient-relevant endpoint	B.3.2
Comparators	Standard of Care		B.3.2
Population	Locally advanced, unresectable, Stage III NSCLC patients whose tumours express PD-L1 on ≥1% of tumour cells	In line with anticipated marketing authorisation	B.3.2
Treatment effectiveness	Estimated based on PFS and OS data from PACIFIC		B.3.3
Adverse events	Accounted for in terms of their costs (not HRQoL), based on frequency and impact and derived from PACIFC	Utility data from PACIFIC was assumed to include impact of AEs on HRQoL	B.3.3
Health related QoL	Utilities were estimated for progression-free and progressed disease states based on EQ-5D-5L data collected in PACIFIC and mapped to EQ-5D-3L using the NICE recommended cross-walk. A mixed effects model was used to estimate utilities per health state.	In line with NICE reference case	B.3.4
Resource utilisation and costs	Drug acquisition and administration costs, costs associated with treatment-related adverse events, with disease management and patient observation and end of life care were included, based on multiple sources.	Unit prices were based on the National Health Service (NHS) reference prices, Personal Social Services Research Unit (PSSRU), Monthly Index of Medical Specialities (MIMS), and electronic Market Information Tool (eMIT), ESMO guidelines and clinical expert opinion and TA531.	B.3.5
Discount rates	Discount of 3.5% for utilities and costs	Consistent with NICE reference case	CS Table 29
Subgroups	No subgroups		
Sensitivity analysis	DSA, PSA and scenario analyses were performed.		B.3.8

	Approach	Source/Justification	Signpost (location in CS)
Source: CS[1]			
AE = adverse events; CS = company submission; DSA = deterministic sensitivity analysis; ESMO = European Society for Medical Oncology; eMIT = electronic market information tool; EQ-5D-3L/5L = EuroQol Five-Dimension Questionnaire three level / five level version; HRQoL = health-related quality of life; MIMS = Monthly Index of Medical Specialities; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = program death-ligand 1; PFS = progression-free survival; PSA = probabilistic sensitivity analysis; PSSRU = Personal Social Services Research Unit			

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.2: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Only PD-L1 tumour expression ≥1% subgroup	In line with anticipated marketing authorisation
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Yes	
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Partly	HRQoL impact of AEs excluded
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	
Synthesis of evidence in outcomes	Systematic review (SLR)	Yes	
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Yes	
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Yes	
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Partly	Patient characteristics included in PSA

AEs = Adverse events; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD-L1 = program death-ligand 1; PSA = probabilistic sensitivity analysis; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review

5.2.2 Model structure

The company developed a de novo semi-Markov cohort state transition model. The model comprised of three health states, i.e. progression free (PF), progressed disease (PD) and death. The company considered these health states to capture the most important clinical aspects in the treatment of Stage III NSCLC patients, namely the time spent in PF and the time spent alive. The company stated that disease progression impacts on patients' HRQoL, worsens symptoms, removes the possibility of cure, and was therefore also considered to be a clinically important and patient-relevant endpoint. The company's semi-Markov model used estimates of PFS, time-to-progression (TTP) and post-progression survival (PPS) to inform transitions between health states. The company considered this approach was most appropriate as there was limited evidence of the heterogenic effects of individual patient characteristics on disease course and survival (thereby ruling out an individual patient level model), and a three health state approach has been adopted in several other decision models to estimate the cost effectiveness of immunotherapies in advanced metastatic NSCLC.[32, 33, 38, 39, 41, 43, 46, 48, 50, 68]

Partitioned survival analysis was considered as an alternative by the company, however, this approach was not chosen for two reasons:

- All clinically-plausible OS and PFS curves produced logical inconsistencies where the curves crossed.
- Evidence from the PACIFIC trial suggests that prolongation of PFS is the main benefit of durvalumab and PPS is similar between both arms. Therefore, the company concluded that the data lends itself better to deriving OS from PFS and PPS data (semi-Markov approach) than independently extrapolating data for PFS and OS (as with the partitioned survival approach).

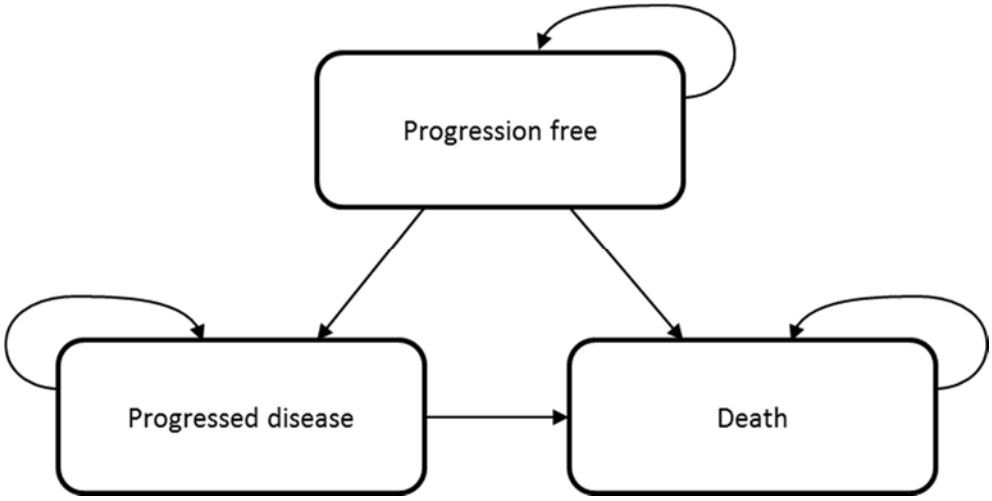
The company claimed to have conducted a partitioned survival analysis as a validation exercise, which was not included as an option in the model.

All patients entered the model in the PF health state. From there, after each cycle, they could remain progression free (modelled using PFS data), or transition to the PD (modelled using TTP data) or death states (modelled using PFS and TTP data).

Patients who experienced disease progression (i.e. local progression and/or metastatic disease) entered the progressed disease health state. The company pooled local progression and progression to

metastatic disease in the same health state. Patients could remain in the progressed disease state, or transition to death (modelled using PPS data for both arms pooled).

Figure 5.1: Model structure



Source: Based on Figure 25 of the CS[1]

ERG comment: The main concern of the ERG relates to the chosen modelling approach. The company's argument to use a semi-Markov approach over a partitioned survival analysis approach was based on the fact that the OS curve could fall below the PFS curve in partitioned survival analysis, therefore being prone to logical inconsistencies. However, in their current approach using a semi-Markov model, the ERG also observed early crossing of TTP and PFS curves as a result of extrapolating the data using the generalised gamma distribution. Furthermore, the ERG considers that the approach may be introducing bias. Survival data in PACIFIC are immature, and whilst the company is correct in pointing out that this issue persists regardless of model choice (OS or PPS), modelling PPS instead of OS is necessarily based on smaller sample sizes used for long-term extrapolation, thereby exacerbating uncertainty. Furthermore, the ERG was concerned that the PPS analysis was potentially biased because groups were no longer balanced. In Technical Support Document (TSD) 19 it is stated: *"Only those patients who have experienced a progression event within the trial follow-up will inform estimation of PPS. This could introduce bias in the extrapolation period if patients who progress within the trial are not representative of those who progress later"*.[90] More specifically, this analysis used data from early progressors, who may have different survival to patients with later progression. Moreover, the PPS data included more patients treated with placebo (who progress earlier), introducing additional bias. The ERG therefore considers that using PPS data instead of OS data may exacerbate the issue of the immaturity of the survival data. The ERG requested results of a partitioned survival analysis to assess any potential differences in results in both approaches, but this was not provided (as the company did not provide survival curves estimated using PFS and OS data from PACIFIC). The magnitude and direction of any bias are unclear.

5.2.3 Population

In line with its anticipated marketing authorisation, durvalumab was considered in the cost effectiveness model for the treatment of 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 platinum-based CRT. This was a subgroup from the final scope issued by NICE, which considered the same population regardless of their PD-L1 status.

Key patient baseline characteristics as applied in the base-case analysis can be found in Table 5.3 below.

Table 5.3: Key baseline patient characteristics of the PD-L1≥1% subgroup as applied in the CS base-case model

Variable	Value	Reference
Patient age (years)	63.1	Table 4, CS[1]
Body weight (kilograms)	71.1	PACIFIC study[91]
Patient body surface area (m^2)	1.83	KEYNOTE-024[92], TA447[68]
% male	69	Table 4, CS[1]
Source: Based on Table 57 of the CS appendices[27] CS = company submission; PD-L1 = program death-ligand 1; TA = technology appraisal		

ERG comment: The main concerns of the ERG relate to: a) modelling a subgroup of the population that was in the final scope issued by NICE, and b) the timing at which the modelled population received CRT.

a) The patient characteristics of the modelled population were comparable to the patient characteristics of the PACIFIC trial. However, in the current submission only a subgroup from the final scope issued by NICE (locally-advanced, unresectable, Stage III NSCLC patients whose tumours express PD-L1 on ≥1% of TCs and whose disease has not progressed after ≥2 cycles of platinum-based CRT) was used to address the decision problem. Nevertheless, the chosen population was in line with its anticipated marketing authorisation and therefore considered appropriate by the ERG.
b) Although sequential CRT is standard practice in the UK[1], the population in PACIFIC and therefore in the model largely received ≥2 overlapping cycles of platinum-based CRT. The potential bias introduced by this is unclear.

5.2.4 Interventions and comparators

Durvalumab was considered within the economic evaluation as per the anticipated licensed indication in NSCLC. Durvalumab was, in line with the dosage used in PACIFIC, modelled with a posology of 10mg/kg administered as an intravenous (IV) infusion over 60 minutes every two weeks (Q2W), until disease progression or unacceptable toxicity, or a maximum of 12 months.

The comparator in the economic model was described as active follow-up or SoC, which applied up to disease progression. The company provided a more comprehensive definition of SoC in its response to the clarification letter 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".*[24]

Patients who experienced disease progression in the model received further treatment and/or end-of-life care, and could be treated with immunotherapy if they met the required criteria. The company stated that subsequent therapies were included in the model if they were used in more than 3% of patients in the PACIFIC study. The list of included subsequent (immuno)therapies and the proportion of patients who received each therapy are shown in Table 41 of the CS.[1] The included immunotherapies were nivolumab, pembrolizumab and re-treatment with durvalumab, and other subsequent therapies were radiotherapy, docetaxel, erlotinib, carboplatin, pemetrexed, gemcitabine, cisplatin, paclitaxel and afatinib.

ERG comment: The intervention was implemented as per its marketing authorisation and dosage.

5.2.5 Perspective, time horizon and discounting

The analysis took an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was two weeks in the first year and four weeks thereafter with a lifetime time horizon (40 years). A half-cycle correction was applied, but not to treatment or treatment administration costs.

ERG comment: This was mostly in line with the NICE reference case, however, in the absence of any justification for not applying the half-cycle correction to treatment and treatment administration costs, the ERG considered this inconsistent with the calculation of resource use and other model components and amended this in its base-case.

5.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness used for intervention and comparators was the PACIFIC study,[91] a phase III RCT evaluating the efficacy and safety of durvalumab against placebo in all locally-advanced, unresectable, Stage III NSCLC patients regardless of PD-L1 expression levels on tumour cells. Only data from the subgroup of PD-L1 ≥1% patients (according to the anticipated marketing authorisation) and from the March data cut were used in the model. Scenarios were performed to model post-progression survival using alternative data sources namely START[93, 94] and KEYNOTE-024[92] to inform survival with subsequent treatments.

Parametric survival curves were fitted to patient level data from the (post-hoc) PACIFIC PD-L1 ≥1% subgroup and used to extrapolate survival beyond study follow-up. Instead of using the OS data from PACIFIC, the company performed survival analyses on the outcomes TTP and PPS, both post-hoc analyses. Survival analysis was also performed on the pre-specified outcome progression-free survival (PFS), however, in this subgroup this was also a post-hoc analysis.

PFS data were used to determine the number of patients staying in the alive and progression-free health state. TTP data were used to determine the number of patients transitioning to the progressed disease health state. Pre-progression mortality was calculated from PFS and TTP. Post-progression mortality was estimated separately, using PPS data.

Progression-free survival

The probability of remaining in the PF state was estimated using PFS data by fitting independent parametric survival models. The company explored whether the proportional hazard assumption was justified and found that the durvalumab and placebo curves on a log cumulative hazard plot were parallel, suggesting proportional hazards. However, the best fitting curve with this assumption showed bad visual fit to the control arm and the company therefore used independently fitted survival models. Based on statistical goodness of fit, the generalised gamma was selected to model PFS for both durvalumab and placebo. For the durvalumab arm, all other parametric models had a worse statistical fit; for the placebo arm, the log-normal distribution was relatively close. The Gompertz distribution was used in scenario analysis and the log-normal distribution was not used, despite the log-normal making a better fit than the Gompertz in both arms.

The company attempted to validate the PFS extrapolation for SoC in the model against data from the PACIFIC study, other historical RCTs and UK clinical expert opinion. The company stated that their PFS extrapolation for SoC was in line with all these data sources, although it did over-estimate PFS for durvalumab and SoC as observed in PACIFIC (CS Tables 32 and 33).[1]

The PFS curve for durvalumab was altered in the long run to reflect a potential treatment waning effect caused by stopping treatment at a maximum of 12 months. From a chosen cut-off point, which was set to 10 years in the company's base-case, a hazard ratio of one was applied to the placebo curve to model durvalumab PFS. Alternative cut-off points of five years, three years and no cut-off were explored in scenario analyses. The former two significantly drove up the incremental cost effectiveness ratios (ICERs), while the latter only decreased it marginally.

Time to progression

The rate of movement of patients moving from the PF state to the progressed disease (PD) health state was determined by survival analysis of TTP data (PFS data with deaths treated as censored) from PACIFIC. The generalised gamma distribution was chosen in the base-case, based on best statistical fit (AIC and BIC) and to align with extrapolation of PFS.

Post-progression survival

The rate of movement of patients moving from progressed disease to death was estimated using PPS data from PACIFIC, on which survival analysis was performed. The data was only 54% mature in the PD-L1 ≥1% group (CS Figure 30[1]). The analysis was not stratified by treatment arm, but instead pooled across both arms. This was implemented using tunnel states to reflect that patients entered the PF state at different time points. The company assessed that hazards were fairly constant over time based on the log-cumulative hazard plot. The exponential distribution was chosen to model PPS based on best statistical fit (AIC and BIC). The effectiveness of subsequent treatments was captured in the PPS to the extent that patients in the PACIFIC study received subsequent treatments, with chemotherapy being the most commonly used treatment modality in both durvalumab and placebo arms in the PD-L1 ≥1% group; and immunotherapy and palliative-intent radiotherapy also being commonly used in patients who experienced disease progression after treatment with placebo, whilst less frequent treatment with immunotherapies after durvalumab treatment was expected.[24]

In scenario analysis, an alternative method for extrapolating PPS was used. In this scenario, instead of using survival data from PACIFIC, PPS was informed by published data from the KEYNOTE-024 study[92], where data from the pembrolizumab arm were used for those receiving IO treatment, and data from the KEYNOTE-024 chemotherapy arm were used for those not receiving IO treatment. Published data from the START study[93, 94] would be used for predicting survival of non-metastatic patients that did not receive IO treatment, if proportions of (non-)metastatic patients were taken into account in the model (they were not in the revised base-case submitted in response to the request for clarification).[24] A weighted PPS curve was then generated. Log-logistic curves were used to extrapolate survival from KEYNOTE-024 and START, and the company claimed that this was based on best statistical fit. This analysis was changed significantly in response to clarification question B14[24]; partly, it appeared, because the proportions of patients with metastatic disease used in the model were erroneous, and partly, because the proportions of patients receiving IO treatment were estimated based on all progressors and not only those with metastatic progression. Whilst in the earlier analysis in the CS[1], patients in the progressed disease health state were split into those with advanced metastatic disease ([redacted] in durvalumab arm and [redacted] in placebo arm, based on corrected numbers provided in response to the clarification letter[24] Table 15) and those with locally-advanced disease, to reflect patient proportions eligible for subsequent IO treatment, this distinction was no longer made in the revised model based on response to request for clarification[24], and all progressed patients were deemed eligible, based on expert feedback indicating that IO treatment would be given to patients with both metastatic and local progression.[24] The proportions of progressed patients receiving IO treatment in PACIFIC were also corrected to 20% in the durvalumab arm and 39% in the placebo arm.[24]

General population mortality

General population background mortality was implemented in the model when it exceeded the predicted PFS and PPS curves. Furthermore, the company ensured that overall deaths in the model never fell below general population mortality by adapting the transition probability from the PF state to the PD state. In the case of overall deaths in the model falling below general population mortality, instead of the TTP curve, the complement of the PFS curve and general background mortality were used. This came into effect at 2.3 years in the durvalumab arm and at 5.5 years in the SoC arm in the model.

Patient age in the model was based on the age distribution as observed in the PACIFIC trial. Because mortality for each single year age cohort was calculated separately in the base case, the mean age increase reflected different mortality rates by age groups and therefore was not linear. Since the younger patients were more likely to remain alive as compared to older patients, the average age increase in each cycle was less than the exact cycle length.

ERG comment: The main concerns of the ERG relate to: a) potential indirectness caused by the model being based on treatment effectiveness estimates derived from a post-hoc subgroup analysis and post-hoc TTP and PPS analyses, as well as in a population with prior overlapping CRT instead of sequential CRT, and immaturity of survival data; b) durvalumab PFS being potentially over-estimated in the model; c) the end of the KM curves used to extrapolate survival being based on small numbers of patients at risk; d) the implementation and choice of time-point when treatment waning kicks in; e) the implementation of general population mortality; f) crossing progression and survival curves; and g) the uncertainty introduced by immature PPS data, uncertainty about subsequent treatments and methods of extrapolation.

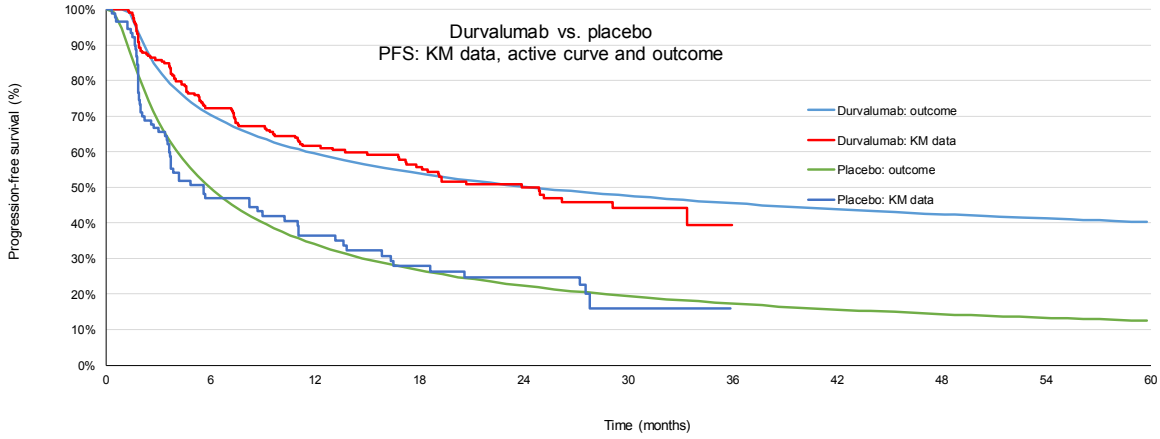
a) The treatment effectiveness in this submission was largely informed by post-hoc analyses performed on the PACIFIC study that may introduce bias in the cost effectiveness model. The subgroup analysis in patients with PD-L1 ≥1% tumour expression was a post-hoc analysis. TTP and PPS analyses were also not pre-specified. Another issue was that the PACIFIC trial may not be generalisable to the UK setting, as it included a majority of patients that received prior overlapping, instead of sequential, CRT. Furthermore, survival data were immature, with only 55% of maturity reached for PFS and 54% of maturity reached for PPS in the combined treatment arms (CS Figure 30[1]). The direction and magnitude of any potential bias stemming from this could not be assessed.
b) The ERG considers the choice of parametric model for estimating PFS (generalised gamma) to likely result in an over-estimate of durvalumab PFS in PACIFIC (see Figure 5.2) and considers all extrapolations to suffer from substantial uncertainty. This is evidenced by the vastly different PFS predictions when different models are used (CS Table 33), where even at five years into the model time horizon, PFS for SoC ranges between 15% and 1%.[1] It is noteworthy that PFS is the model aspect with the most significant impact on the ICERs. For example, in the company's analysis using one model with treatment as a factor (unstratified analysis implemented in the company's model submitted in response to the request for clarification[24]), the ICER with all other company's settings in place increases to £86,332 per QALY gained, highlighting not only the uncertainty associated with PFS, but also the impact of any modelling assumptions around this outcome on the ICER.

   The company acknowledged the potential over-estimate resulting from using the generalised gamma distribution stating *"At three years, the generalised gamma and Gompertz curves may overestimate PFS, although the data from PACIFIC is only based on one patient at this point and so caution should be taken when making comparisons"*.[24] The ERG was surprised that given this uncertainty, the only other tested model was the Gompertz model, which provided very similarly

high PFS estimates at the end of the trial period, whilst the second-best fitting and potentially more realistic lognormal distribution was omitted.

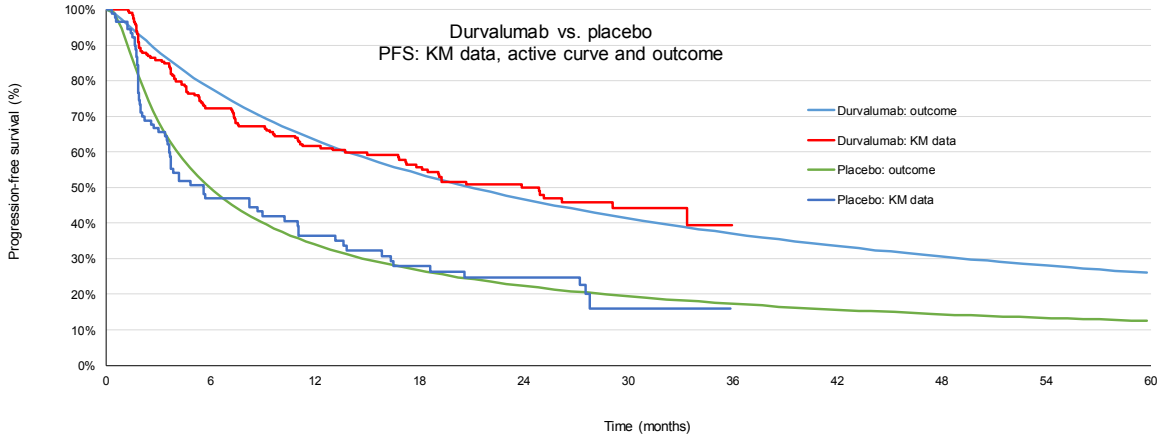
The ERG considers that alternative models with better external validity for extrapolating PFS should be considered in the analysis, particularly given the many censoring events at the end of the Kaplan-Meier curve that result in very small patient numbers at risk. The company claimed to have explored spline-based models, but these and the reasons for which they were discarded, were not reported. Especially given the apparent non-linearity in the log cumulative hazard plots shown in Figure 31 of the CS[1], the ERG considers that such spline-based analyses may potentially be informative.

Figure 5.2: PFS using generalised gamma for durvalumab and SoC (CS base-case)



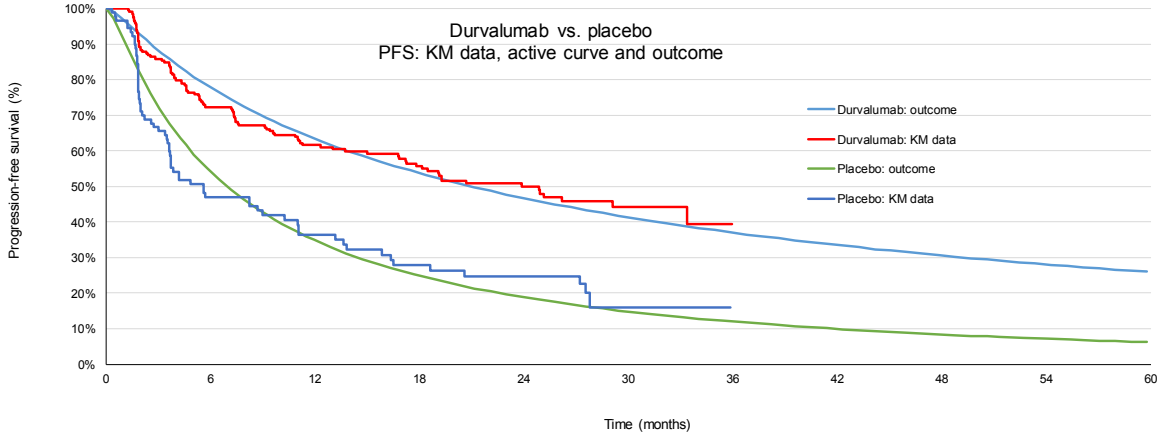
Source: Adapted from revised model[24], background mortality and treatment waning excluded

Figure 5.3: PFS using lognormal for durvalumab and generalised gamma for SoC (ERG base-case)



Source: Adapted from revised model[24], background mortality and treatment waning excluded

Figure 5.4: PFS using lognormal for durvalumab and SoC (ERG scenario)



Source: Adapted from revised model[24], background mortality and treatment waning excluded

Amongst the available fitted curves, the lognormal distribution made the second-best statistical fit based on AIC and BIC criteria for both the durvalumab and placebo arms (Table 31 of the CS), and predicted PFS below (and closer to, in case of durvalumab) that observed in PACIFIC at three years.[1] However, for SoC it would significantly under-estimate five-year PFS as observed in START and supported by expert opinion (6% in the model versus 15% in START). The ERG acknowledges that NICE DSU TSD 14 recommends the use of the same 'type' of model for individual treatment arms to avoid drastically different shapes of survival curves and recommends justification for using different model types per treatment arm by *"using clinical expert judgement, biological plausibility, and robust statistical analysis"* if different model types seem appropriate.[95] In this case, given the above arguments of external validity of modelled durvalumab survival with PACIFIC, and the match of SoC PFS extrapolations with START and clinical expectation, as well as the fact that durvalumab is a treatment with curative intent, the ERG considers there to be arguments for differential distributions per treatment. An additional argument against the choice of the generalised gamma for modelling durvalumab PFS is the potential lack of face validity of virtually no patients progressing or dying in the post-trial follow-up period when the generalised gamma was chosen (see Figure 5.2 durvalumab arm months 36 to 60). In the ERG base-case, the lognormal distribution was therefore used for durvalumab PFS, and the generalised gamma for SoC PFS (see Figure 5.3). ERG scenarios explore the use of a) the generalised gamma for both durvalumab and SoC (as per the company's base-case), and b) the lognormal distribution for both (see Figure 5.4). In each of these analyses, the distributions for modelling TTP are automatically selected based on the choice for PFS, as was done by the company. However, it is noteworthy that any of these choices for modelling PFS are associated with high levels of uncertainty, given the immaturity of the data.

c) The ERG was concerned that the small patient numbers at risk at the end of the KM curves for PFS and PPS potentially biased any extrapolation. In some studies, it has been recommended to truncate KM curves where patient numbers at risk are low.[96] As the company pointed out in response to clarification question B8[24], the NICE DSU TSD 14 only recommends such exclusion of data points when it can be clearly demonstrated that certain points are erroneous outliers.[95] In this case, the ERG considers that this condition is potentially fulfilled: upon examination of Figure 32 of the CS, it appeared that the KM curve after 28 months resulted in a PFS estimate of approximately 16% of patients in the placebo arm, which is based on one patient at risk (Table 32 of the CS).[1] The company, in response to clarification question B8, provided an analysis excluding data points where patient numbers at risk decrease below 5% for both PFS and PPS and showed that the impact on

the ICER was minimal. This satisfied the ERG's concern about small patient numbers at risk having an undue influence on the extrapolated survival curves.

d) The ERG considers the implementation and timing of the treatment waning effect assumed for PFS and TTP a major source of uncertainty. As the company acknowledge, future OS data from PACIFIC will become available that could help assess the long-term survival benefit of durvalumab. In the meantime, any economic modelling has to rely on assumptions that are not supported by data. It is therefore vital that a range of ICERs based on the different possible timings of a treatment waning effect be considered. Whilst the company have provided different scenarios, their choice for the base-case is the most optimistic of those tested (apart from no treatment waning), with a treatment waning effect only starting at 10 years after treatment initiation. In contrast to the company's statements, the OS estimates obtained using this cut-off could not be validated by expert opinion (OS only estimated for SoC at 10 years by clinical expert, see CS Table 35), or modelled OS from other appraisals in the metastatic setting (modelled OS with durvalumab 27% at 15 years compared with modelled OS with other IO treatments of 0-3%; based on CS Table 36).[1] It is the ERG's opinion (acknowledging the lack of evidence) that the five year cut-off would be more realistic than the 10 year cut-off, still resulting in durvalumab OS at 15 years of 20% (using the company's model settings). Although the ERG is unsure of its applicability to this setting, it should be noted that a five-year cut-off was accepted by NICE in TA520 (Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy).[50] The ERG base-case considers a five-year cut-off point. Seven- and three-year cut-offs are tested in scenarios.

   With regards to implementation of the treatment waning effect, setting the hazard ratio to one at the chosen cut-off can cause counter-intuitive results, if the per-period hazard in the comparator arm is below that of the hazard in the intervention arm. This can occur depending on the chosen cut-off and for example when patients in the comparator arm have high rates of progression or dying in the beginning periods, such that the few remaining patients alive and not progressed in later periods then have very low rates of progression or dying. This occurs in the ERG scenarios (3) and (4), where a shorter cut-off decreases the ICER and a longer cut-off increases it. Figure 5.3 illustrates that the hazards in the extrapolated PFS for SoC are below those of durvalumab in the ERG base-case. The ERG therefore considers the method for implementing treatment waning to be flawed, but acknowledges that there is a lack of guidance related to alternative modelling methods and that there is precedent for the company's method as was highlighted in response to clarification question B9b.[24] The ERG considered alternative methods for modelling treatment waning including setting the durvalumab PFS curve equal to that of SoC at the chosen cut-off, resulting in a sudden drop of patients not progressed or died (which the company had pointed out to lack realism in response to clarification question B9b[24]). In the absence of any supporting evidence for either approach, to explore the impact of different treatment waning cut-off points, the ERG kept the company's modelling method and added two scenarios where both alternative cut-off points were explored with the lognormal distribution used for modelling PFS in both the durvalumab and SoC arms. Furthermore, the impact of not modelling any treatment waning effect on the ERG base-case was explored in a scenario.

e) The company's way of ensuring that mortality in the model never falls below general background mortality may favour durvalumab, but is likely to have a minor impact. The company applied a fix in the transition to the progressed disease health state to avoid that the *"difference between the hazards derived from PFS and TTP survival functions [...] was smaller than the general population mortality"*.[24] In short, the company attempted to ensure that overall mortality from the PF state was never below that of the general population by artificially lowering the number of progressors (rather than lowering the number of people remaining in the PF state). Since this fix applies sooner for

durvalumab than for SoC, this was likely a non-conservative way of modelling transitions away from the PF state. However, this is unlikely to be influential and the ERG considers this to be acceptable.

f) Another small concern relates to crossing progression and survival curves in the company's model. In this case, this was an artefact of fitting survival models to relatively similar KM estimates. Parametric survival models with non-monotonic hazards may cause the progression curve (proportion of patients who have not progressed, with deaths censored) to drop quicker than the PFS curve (proportion of patients who have not progressed or died), resulting in a probability of progression that can exceed that of progressing or dying. The company claimed in their response to the clarification letter that this did not occur, but according to their own model check described in this response, this is not correct:[24] using the company's base-case generalised gamma distribution, this only occurred in cycle four in the durvalumab arm, and using the ERG's preferred lognormal distribution, this occurred only in cycle two in the durvalumab arm. The company's adjustment for background mortality meant that this did not result in negative patient numbers in any states, and since it only occurred in one cycle, the ERG considers this issue to be likely acceptable, with the caveat that more flexible models, such as spline models, should have been explored.

g) PPS data are immature and there is substantial uncertainty about post-progression survival. Additional bias in the extrapolation of PPS may be caused by inclusion of early progressors but not late progressors, and more progressors from the placebo arm than the durvalumab arm (see Section 5.2.2 ERG comment and NICE DSU TSD 19[90]). The company explored alternative ways of modelling PPS using data from other studies in a scenario. The generalisability of this analysis to this setting is unclear: for example, KEYNOTE-024 included metastatic patients. Apart from this, the ERG noted an error in the selection of the survival distribution applied in this scenario. The company claimed to have used the curve with the best statistical fit, but used the log-logistic distribution instead (third best statistical fit), which biased model outcomes in favour of durvalumab, compared with using the distribution with the best statistical fit in KEYNOTE-024 (lognormal). Furthermore, there was an inconsistency in the proportions of patients receiving IO treatment in the durvalumab arm, which did not appear to include those patients that were re-treated with durvalumab (7%, as used in the cost estimates of the model).

   To address some of the uncertainty in PPS, the ERG explored alternative assumptions around PPS: selecting an alternative model in the company's base-case modelling of PPS using PACIFIC (generalised gamma) with the second best statistical fit; and using the scenario to inform PPS based on the KEYNOTE-024 data, but with the distributions that exhibited the best statistical fit (lognormal instead of log-logistic) and a corrected estimate of patients receiving subsequent IO treatment in the durvalumab arm.

5.2.7 Adverse events

The main source of evidence on treatment adverse events used for durvalumab and SoC was the PACIFIC study. Adverse events (AEs) were included in the model in terms of their costs and not their impact on health-related quality of life (HRQoL). AEs were included if they had a frequency of ≥2% in either arm in the PACIFIC study (PD-L1 ≥1% group) and a severity of grade 3/4, or if they were judged to have a sizable impact on either costs or HRQoL (see CS Table 37 for a list of included AEs).[1] AEs were modelled as a per-cycle occurrence while patients were on treatment. No detail was provided on how the total treatment years per arm (183.6 and 66.2 years, for durvalumab and placebo, respectively) were derived from PACIFIC.

ERG comment: The main concerns of the ERG relate to: a) under-estimation of impact of AEs when treated with durvalumab; and b) the lack of justification for the total treatment years per arm to derive the incidence of AEs.

a) AEs were selected for inclusion in the model based on frequency (occurrence ≥2% in PACIFIC), severity (grade 3/4) and impact on costs (CS Table 37).[1] Incidence in the model for the selected AEs was comparable between treatment arms. However, in Table 18 (reproduced in Table 4.8) of the CS, percentages of 'Any AE of CTCAE grade 3 or 4, causally related to treatment', 'Any SAE (including events with outcome of death), causally related to treatment', and 'Any AE leading to discontinuation of study treatment, causally related to treatment' were mostly higher for durvalumab as compared to placebo in the PD-L1 ≥1% group.[1] The company did not provide an explanation for how this discrepancy between the AEs listed in Table 18 and the AEs used in the model occurred.[1, 24] The ERG was therefore concerned that the impact of AEs associated with durvalumab treatment in the model may be under-estimated and explored this in scenario analysis. This scenario used the numbers of events from 'Any AE of CTCAE grade 3 or 4, causally related to treatment' in Table 18 and total treatment years for durvalumab and placebo to calculate revised two-weekly (per cycle) incidences for all grade 3/4 AEs per treatment arm. Combined with the unweighted average utility decrements and costs for the AEs that were included in the company's base-case model, the ERG derived one-off costs and utility decrements per cycle that reflected the amended incidence. These were then used together with amended AE utility decrements as detailed in Section 5.2.8 of this report.
b) It was unclear how the total treatment years per arm were derived. The shorter duration in place for the placebo arm resulted in a higher incidence of AEs and may bias model outcomes in favour of durvalumab. However, the impact of assuming the same value for total treatment years on the ICER was only small.

5.2.8 Health-related quality of life

Utility values were estimated for the following health states: PF and PD. EQ-5D-5L data were collected in PACIFIC and, in alignment with the NICE position statement[97], the crosswalk mapping algorithm by van Hout et al.[98] was used to obtain EQ-5D-3L utility scores. These utility scores were subsequently used to model utility values for PF and PD health states. A variety of mixed effects models including different covariates were constructed and tested. The covariates included treatment, age, health state (pre- or post-progression), time to death, and treatment disposition (on or off treatment), but ultimately only progression was used as a covariate in the base-case analysis. As a consequence, utility values were equal across treatment arms and an age-related utility decrement was not incorporated.

Utility values resulting from the mixed effects model based on EQ-5D-3L data from the PACIFIC trial were 0.810 for PF and 0.776 for PD. These utility values were compared to the utility values in the studies identified in the SLR. Although the company stated in the CS that there was broad consistency, the utility values derived from PACIFIC data were higher than in these other studies. However, patients in PACIFIC had less metastatic disease than in the comparator studies. The PACIFIC utility values were also higher than in the general population.[99] A summary of all utility values used in the model is provided in Table 5.4.

Table 5.4: Health state utility values

State	Utility value	Reference	Justification
Progression free	0.810	PACIFIC data [100]	SLR did not identify suitable utility scores

State	Utility value	Reference	Justification
Progressed disease	0.776	PACIFIC data [100]	SLR did not identify suitable utility scores
Source: Based on Table 39 of the CS [1] CS = company submission; SLR = systematic literature review			

Health-related quality of life data identified in the review

According to the CS, the SLR identified three key studies reporting UK relevant utility values. Out of these, the company considered only one to be possibly suitable to provide an alternative value for utility after progression.[101] The other studies were deemed not suitable since they concerned a metastatic setting only, while the PD state in the CS is a combination of local and metastatic disease progression.

Adverse event related disutility values

In the base-case analysis, no adverse event related disutilities were taken into account. The company justified this claiming that the impact of adverse events on QoL was assumed to be reflected in the EQ-5D data as observed. In a scenario analysis, a disutility value was applied for grade 3/4 AEs. See Table 5.5 for details on the disutilities.

Table 5.5: Adverse event related disutility values

Adverse event	Disutility value (per 2-week cycle)	Reference	Justification
Pneumonia	-0.037	Nafees et al. 2008[57]	
Anaemia	-0.043	KEYNOTE-010 trial as per TA428[33]	
Hypertension	-0.110	Nafees et al. 2008[57]	
Pneumonitis	-0.037		Assumed equal to pneumonia
Endocrinopathy	0.000	Clinical opinion (no reference provided in CS)	
Hypokalaemia	-0.110	Nafees et al. 2008[57]	Assumed equal to fatigue
Haemoptysis	-0.037		Assumed equal to pneumonia
Radiation pneumonitis	-0.037		Assumed equal to pneumonia
Source: Based on Table 56 of the CS appendices[27] CS = company submission; TA = technology appraisal			

ERG comment: The main concerns of the ERG relate to: a) the high utility value of the PF health state which is also constant with age; b) the modest utility decrement for progressed disease; and c) utility scores for durvalumab and SoC being equal, without consideration for treatment or AEs.

a) The utility value for the PF health state was 0.810 which is comparable to the utility reported for the general population (0.80 for age category 55-64).[99] Utility scores equally high as in the general population seem quite unlikely in patients with locally advanced NSCLC. The company justified the use of the 0.810 for PF by stating that general population scores were based on EQ-5D-3L data (where PACIFIC used EQ-5D-5L) and population scores may also be outdated. In clarification question B16[24], the ERG argued that there are more recent population norms which

have not shown a significant increase (i.e. 0.81 and 0.802 for the relevant age category[102]). The difference between 3L and mapped 5L scores of the EQ-5D remains, but was recently shown to be only minor.[103] In addition, utility scores in the base-case model did not decrease with age, since age was not a significant factor in the mixed effects model. However, the mixed effects model only included two age categories (<65 and ≥65) and the ERG does not consider the absence of a significant effect in the short run of the trial to sufficiently support an assumption of utility values being constant over a lifetime time horizon. In summary, utility values for PF were remarkably high and remained high for the full-time horizon of the model. A high utility score for PF lowers the ICER, as in the model patients on durvalumab progressed later than patients receiving SoC. The ERG base-case incorporated an age-related decrement. The ERG also proposed a lower (start) utility score for PF, i.e. 0.73, taken from Ara and Brazier,[102]for people from the general population aged 65-70 with a history of cancer. Although this lower utility value may have better face validity, it does not fully apply to the population in the scope, and therefore it was only incorporated in a scenario.

b) The utility decrement for progressing to PD was -0.034, which could be considered quite modest given the information from the literature review performed by the company as provided in Table 38 of the CS[1], which shows the decrement for progressed disease to vary from -0.4[101] to -0.18[57]. The low decrement that resulted from the mixed effects model could partly be due to the fact that EQ-5D-5L data was only collected up to 30 days after progression. The company confirmed that HRQoL is likely to continue to decline further but also states that their approach was a conservative one since patients in SoC progressed earlier and a high utility value for PD would overestimate QALYs. The ERG agrees with this, but argued that a larger utility decrement would be more reflective of clinical reality. In line with findings by Chouaid et al.[101] in a Stage III/IV NSCLC population, the ERG explored a scenario (applied in addition to the lowered PF utility of 0.73 scenario mentioned above) considering a utility value of 0.67 for first-line progressed disease. Since this scenario was only performed in addition to the scenario with lowered PF utility of 0.73, it implied a decrement for progression of 0.06.

c) Although the mapped utility scores from PACIFIC were higher in the placebo as compared to the durvalumab arm at almost all measurement moments, treatment was found to be statistically insignificant in the mixed effects model and therefore, equal utilities were assumed for durvalumab and SoC. However, the company did not apply utility decrements for AEs in the base-case model as these were assumed to be incorporated in the utilities as observed. When applying utility decrements for AEs in a sensitivity analysis, the company only included these for a selected set of AEs (see also ERG comment in Section 5.2.7). In response to clarification question B18[24], the company provided results of alternative analyses using separate utility values for durvalumab and SoC, both as a factor in the mixed effects model and as the observed average EQ-5D-5L utility scores, which showed increased ICERs (£20,172 and £20,261, respectively). The ERG is concerned that by excluding treatment as a factor in the mixed effects model, and at the same time including disutilities of a limited set of AEs only in a sensitivity analysis, the true impact of adverse events was not appropriately captured in the base-case model or in the scenario. Given the fact that OS data are not fully mature (38% maturity at time of primary analysis), quality of life becomes all the more important, and therefore it is paramount to take AEs into account as accurately as possible. Also grade 1 and 2 AEs will have an impact on the patient's quality of life, but these less severe events were excluded from the analysis. For this reason, the ERG base-case included treatment as a factor in the mixed effects model.

5.2.9 Resources and costs

The cost categories included in the model were costs for PD-L1 testing, costs associated with treatment (drug acquisition costs including subsequent therapies, drug administration costs including subsequent therapies, costs associated with treatment-related AEs), costs associated with disease management and patient observation, and costs associated with end of life care.

Unit costs were based on the National Health Service (NHS) reference costs[104], Personal Social Services Research Unit (PSSRU)[105], Monthly Index of Medical Specialities (MIMS)[106], and the electronic Market Information Tool (eMIT)[107].

Resource use and costs data identified in the SLR

According to Appendix I of the CS[27], the SLR performed in October 2016 (with an update in March 2018) identified 115 publications of which five reported UK specific cost/resource data. The company stated that none of the eligible UK studies were precisely aligned with the population of interest for this appraisal and none reported cost or resource use information relevant for the economic model.

Treatment costs

The average cost per infusion of durvalumab was calculated by multiplying the cost per mg (£4.93) by the average body weight in the PD-L1 ≥1% group as observed in the PACIFIC study (71.1 kg) and dosage (10mg/kg). The base-case analysis assumed no wastage (perfect vial sharing), which was explored in a scenario analysis. Duration of treatment in the durvalumab arm was according to Kaplan-Meier (KM) data from the PACIFIC study. Total mean treatment costs using these numbers amounted to [redacted] (see Table 5.6). The model assumed zero acquisition costs for SoC as concomitant treatment use was similar in durvalumab and placebo arms of the PACIFIC study.

Treatment administration cost was, in the absence of a specific tariff for durvalumab administration, based on NHS reference cost code SB12Z (cost of administering simple chemotherapy)[104] at £241.07 per cycle. For SoC there were no administration costs.

PD-L1 testing costs were calculated as a cost per eligible patient. As per information in Table 41 of the CS[1], 1.89 patients would need to undergo a PD-L1 test in order to identify one patient eligible for treatment with durvalumab. That is, of the patients in PACIFIC for whom a PD-L1 test was performed (76.4% since PD-L1 testing was not mandated for inclusion), 56% was eligible for treatment with durvalumab. Corrected for 5% of patients who would have progressed in the meantime (based on clinical expert opinion[108]), final eligibility would be 53%. Therefore, the unit price of a PD-L1 test (£40.50 as reported in NICE TA531 [32]) was multiplied with 1.89 to obtain the cost for PD-L1 testing per eligible patient of £76.68.

Table 5.6: Treatment acquisition costs

Item	Durvalumab	Justification
Dosing per administration	10mg/kg	Draft SmPC [109]
Frequency of administration	Q2W	Draft SmPC [109]
Total dose per administration	711 mg	Mean patient weight in PACIFIC PD-L1≥1% group: 71.1 kg * 10 mg/kg
Treatment cost per 120 mg vial	£592	Anticipated list price
Treatment cost per 500 mg vial	£2,466	Anticipated list price
Treatment cost per cycle (Q2W)	£3,507	711*(£2,466/500)
Total mean treatment cost	[redacted]	£3,507*(30/14)*([redacted])
Administration cost per cycle (Q2W)	241,07	Total HRGs SB12Z[104] Same source as approved NICE TAs[110]

Source: Based on Table 40 of the CS[1]
CS = company submission; HRG = Healthcare Resource Group; Q2W = every two weeks; PD-L1 = programmed death-ligand 1; TA = technology appraisal; SmPC = Summary of Product Characteristics

Costs of subsequent treatments

Upon disease progression, be it local or metastatic, patients in the model could go on to receive further treatment. Immunotherapy was an option if patients met the required criteria. Subsequent therapies were included in the model if they were used in more than 3% of patients in either arm of the PACIFIC study. Once patients progressed in the model, a one-off cost for subsequent treatments was accrued. This cost was informed by the type of treatment, the required treatment dose, the dosing schedule, the unit drug cost at list prices, and the duration of treatment (see Table 5.7). The average cost of subsequent treatment was determined using the distribution of patients across the various treatments as observed in the PACIFIC study, resulting in a one-off total subsequent treatment cost of [redacted] for durvalumab and [redacted] for SoC. Duration of treatment could be manually adjusted in the economic model. The model also allowed for selecting the START trial[93] as a source for distribution of patients across subsequent treatments, thereby excluding immunotherapy.

Table 5.7: Costs of subsequent treatments

Subsequent treatment	% of progressed patients in durvalumab arm who received treatment*	% of progressed patients in placebo arm who received treatment*	Dose	Duration of treatment (weeks)	One off cost per patient applied in the model	Reference unit prices
Immunotherapy						
Nivolumab	15%	32%	240 mg	26.33	£37,832	MIMS (Opdivo)[106]
Pembrolizumab	5%	7%	200 mg	21.40	£39,241	MIMS[106]
Durvalumab	7%	0%	10 mg/kg	17.11	£32,056	AstraZeneca, anticipated list price
Other commonly-used subsequent therapies						
Radiotherapy	36%	35%	N/A	N/A	£2,802	NHS reference costs[104]
Docetaxel	22%	7%	75 mg/m^2	14.35	£1,274	eMIT 2018[107]
Erlotinib	6%	11%	150 mg	47.83	£18,209	MIMS (Tarceva)[106]
Carboplatin	34%	30%	AUC; 500 mg dose assumed	14.35	£1,253	eMIT 2018[107]
Pemetrexed	21%	12%	500 mg/m^2	14.35	£8,155	MIMS (Alimta)[106]
Gemcitabine	21%	18%	1000 mg/m^2	14.35	£2,449	eMIT 2018[107]
Cisplatin	9%	11%	75 mg/m^2	14.35	£1,212	eMIT 2018[107]
Paclitaxel	9%	14%	200 mg/m^2	14.35	£1,268	eMIT 2018[107]
Afatinib	6%	5%	40 mg	47.83	£16,935	MIMS (Giotrif)[106]

Source: Based on Tables 42-45 of the CS[1]

* Based on PACIFIC

Note: percentages can add up to more than 100% due to use of combination treatments and multiple lines of treatment

AUC = area under the curve; CS = company submission; eMIT = electronic Market Information Tool; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service

Health state costs

Resource use associated with patient observation and disease management in both PF and PD health states was applied to all patients based on their treatment arm, treatment status and disease progression status. For the PD health state, the model used resource use and costs identified and accepted in TA531.[32] It should be noted that TA531 concerned an all metastatic population, in contrast to the current

CS. For the PF health state, patients in SoC were assumed to receive care according to ESMO guidelines[111] and clinical expert opinion.[112] Patients on treatment in the durvalumab arm were assumed to receive a scan every two months as well as a blood test every visit. No costs of outpatient visits or clinical nurse specialist visits were included for patients on durvalumab, as these were expected to be captured in the cost of administering durvalumab. After discontinuation of durvalumab, SoC costs were applied to the durvalumab arm as well. For both treatment arms, observation and management costs were assumed to be reduced to £0 after five years (i.e. after four years off-treatment for durvalumab arm), which was confirmed by clinical expert opinion in response to clarification question B19.[24] See also Table 5.8.

Table 5.8: Health state related costs per month

Health state	Monthly costs durvalumab on-treatment	Monthly costs durvalumab off-treatment	Monthly costs SoC (off-treatment)	Reference resource use
PF				
Year 1	£62.28	£103.18	£103.18	Draft SmPC [109], Clinical expert opinion [112] and ESMO guidelines [111]
Year 2	NA	£68.37	£68.37	Clinical expert opinion [112] and ESMO guidelines [111]
Year 3	NA	£34.82	£34.82	Clinical expert opinion [112] and ESMO guidelines [111]
Year 4	NA	£34.82	£34.82	Clinical expert opinion [112] and ESMO guidelines [111]
Year 5	NA	0	£34.82	Clinical expert opinion [112] and ESMO guidelines [111]
Year 5+	NA	0	£0	Clinical expert opinion [112] and ESMO guidelines [111]
PD				
	NA	£304.94	£304.94	TA531 [32]and Big Lung trial [113]

Source: Based on Table 48 of the CS[1]
CS = company submission; ESMO = European Society for Medical Oncology; NA = not applicable; PD = progressed disease; PF = progression-free; SmPC = Summary of Product Characteristics; SoC = standard of care; TA = technology appraisal

Adverse event related costs and costs of terminal (end of life) care

The frequency of occurrence of grade 3/4 AEs was combined with a one-off cost per AE to obtain a total per-cycle cost for each arm: £6.88 for durvalumab and £9.20 for SoC. This total cost was applied to the duration that patients were on assigned treatment (see Table 5.9).

Furthermore, a one-off cost of £3,577 was applied in the model when a patient died, to reflect the costs of terminal care (see Table 5.9). This cost, according to the CS, was based on values accepted in a NICE multiple technology appraisal for erlotinib and gefitinib (TA374 [114]). Table 51 of the CS[1] also refers to TA531[32], the Marie Curie report[115] and NICE clinical guidance (CG) 81[116] for this.

Table 5.9: Adverse event related costs and costs of terminal care

Adverse event	Costs	Per cycle cost durvalumab	Per cycle cost SoC	Reference
Anaemia	£753.02	£0.96	£1.80	NHS reference costs 2016-2017[104]
Hypertension	£388.81	£0.00	£0.00	NHS reference costs 2016-2017[104]
Haemoptysis	£391.98	£0.00	£0.46	NHS reference costs 2016-2017[104]
Hypokalaemia	£151.69	£0.13	£0.46	NHS reference costs 2016-2017[104]
Pneumonia	£1,851.16	£4.79	£5.56	NHS reference costs 2016-2017[104]
Pneumonitis	£391.98	£0.50	£0.23	NHS reference costs 2016-2017[104]
Radiation pneumonitis	£391.98	£0.41	£0.70	Assumed equal to pneumonitis as no HRG available
Endocrinopathy	£443.46	£0.09	£0.00	NHS reference costs 2016-2017[104]
Total per cycle AE costs				
		£6.88	£9.20	
Total cost of terminal care				
One-off	£3,577.18			TA374 [114], TA351 [32], Marie Curie report [115], NICE CG81 [116]

Source: Based on Tables 49, 50, and 51of the CS [1]
CG = clinical guidance; CS = company submission; HRG = Healthcare Resource Group; NICE = National Institute for Health and Care Excellence; SoC = standard of care; TA = technology appraisal

ERG comment: The main concerns of the ERG relate to: a) the assumption of perfect vial sharing; b) resource use in the PD health state; and c) the criterion for inclusion of subsequent treatments in the model.

a) The assumption of perfect vial sharing that was maintained in the model is not realistic, also given the limited number of patients in England and Wales that would be eligible for treatment with durvalumab (367 annually). The company stated in their response to clarification question B22[24] that indeed, they did not expect perfect vial sharing to occur in clinical practice, but that their base-case was chosen based on recent policy initiatives put in place by NHS-E for IOs.[117] The ERG has looked into these policy initiatives documents and did not find information that, at this time, directly or indirectly supported the assumption of perfect vial sharing. When perfect vial sharing is so clearly not feasible in clinical practice, it should not be considered as base-case. The ERG base-case therefore assumed that there is no vial sharing, with the possibility of 30% vial-sharing in a scenario. The ERG noted an error in the implementation of vial wastage for nivolumab and pembrolizumab, which affected the company's vial sharing scenarios. The company had erroneously employed weight-based dosage calculations on a fixed dose. This was fixed in the revised ERG base-case.

b) The resource use in the PD health state was based on TA531[32], where these costs were estimated for patients with exclusively metastatic disease. However, only a minority (37%, as stated in section B.3.3 of the CS [1]) of the progression events in PACIFIC were metastatic, which is why the ERG considered that using TA531 resource use may have overestimated costs for PD in the economic model. In their response to clarification question B20, the company stated they believe that *"based on similar subsequent treatment use expected between local and metastatic progression, … TA531 is a reasonable source of costs for the PD state, in the absence of other data"*.[24] The ERG was not convinced by this argument. However, as the company has shown that incorporating a zero cost for local recurrence would only slightly increase the ICER, the ERG considers this issue likely to be acceptable.

c) Subsequent treatments were included in the model if they were used in more than 3% of patients in either treatment arm in the PACIFIC study. The company did not justify what this cut-off of 3% was based on. Moreover, this 3% criterion was apparently (looking at Table 42 of the CS[1]) applied to the total study population (including progression-free patients), not only to the progressed patients. That is, any subsequent therapy that would be used in 3% of progressed patients would not be included in the model since the percentage would be lower in the complete group. As the proportion of progressed patients was higher in the placebo arm, the effect of this difference would not be equal between the arms. That is, treatments that were given to 6% of the *progressed* durvalumab patients would *not* be included (since it would translate into just below 3% of all durvalumab patients), while treatments that were given to 6% of the *progressed* SoC population *would* be included (since it would translate into just over 3% of all SoC patients). Although the magnitude of the bias caused might be limited, the cost of subsequent treatment was an influential factor in the model. The ERG's predominant concern is that the selection criterion was not transparent, nor justified. No adjustments were made in the ERG base-case with regards to this issue.

5.2.10 Cost effectiveness results

In the deterministic base-case analysis, total LYs and QALYs gained were larger in the durvalumab arm compared to the SoC arm. Incremental QALYs (2.93) were mainly driven by QALY gains in the PF health state. Total costs were also higher for durvalumab than for SoC. The incremental costs ([redacted]) mainly resulted from higher treatment costs. The deterministic incremental cost effectiveness ratio (ICER) amounted to £19,366 per QALY gained (Table 5.10).

Table 5.10. Company's revised base-case results

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	--	--	--	--
SoC	[redacted]	[redacted]	[redacted]	[redacted]	3.60	2.93	£19,366

Source: Based on the revised base-case results in the economic model
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year; SoC = standard of care

ERG comment: In response to the clarification letter, and as requested by the ERG, the company corrected an error that was present in the age calculations for the SoC treatment arm. The base-case

results were slightly changed by this correction (ICER increased from £19,320 to £19,366 per QALY gained), and Table 5.10 above presents the revised base-case results after correction by the company.

5.2.11 Sensitivity analyses

The company performed and presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) in order to show the uncertainty surrounding the base-case results.

Compared with the deterministic results, the PSA with 1,000 iterations showed lower incremental QALYs and higher incremental costs, which resulted in an increased ICER (£21,601) (Table 5.11). The cost effectiveness acceptability curve in the revised model showed that durvalumab approximately had a 87% and 98% probability of being cost effective at willingness to pay (WTP) thresholds of £30,000 and £50,000 respectively.

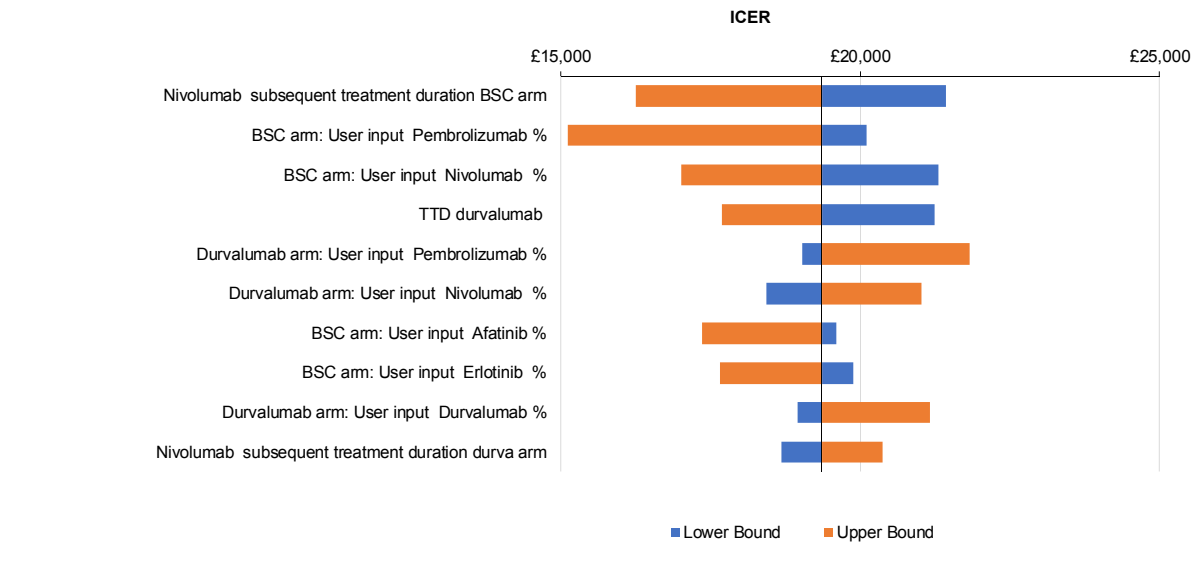
The company conducted DSAs by varying key model parameters between the upper and lower 95% CIs of the expected value used in the deterministic base-case. The ICER was most sensitive to the duration of post-progression immunotherapy use, the percentage of patients receiving subsequent immunotherapy use and the time to discontinuation of durvalumab. In none of the DSAs the ICER exceeded the WTP thresholds of either £30,000 or £50,000 (Figure 5.5).

Table 5.11: Company's revised base-case results (probabilistic, 1,000 iterations)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Durvalumab	[redacted]	[redacted]	--	--	--
SoC	[redacted]	[redacted]	[redacted]	2.67	£21,601

Source: Based on the revised PSA results in the economic model.
ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SoC =standard of care

Figure 5.5: Tornado diagram presenting the results of the deterministic sensitivity analysis (revised)



Source: Based on the revised tornado diagram presented in the model.

Scenario analyses

The company conducted several scenario analyses, which are shown in Table 5.12 below. The results showed ICERs ranging between £11,368 and £30,629 per QALY gained, excluding the scenario analyses with a 10, 20, and 30 years' time horizon. Apart from different scenarios for the time horizon, the three most influential scenarios that increased the ICER were a shorter treatment waning cut-off (three years: £30,629 and five years: £24,391), increased cost for PF health state (£24,069), and an alternative PFS distribution (independent models; Gompertz: £23,237). The three most influential scenarios that decreased the ICER were different subsequent immunotherapy durations (two years for pembrolizumab and nivolumab: £11,369) and alternative EQ-5D-5L utility values (PACIFIC, EQ-5D-5L ITT: £17,960, PACIFIC, EQ-5D-5L PD-L1 ≥ 1%: £18,162). Scenarios with shorter time horizons of 10, 20 and 30 years increased the ICER to respectively £39,161, £23,099 and £20,001.

Table 5.12: Results of the scenario analyses conducted by the company (revised)

Scenario	Values	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base-case	-	[redacted]	2.93	£19,366
Time horizon	10 years	[redacted]	1.43	£39,161
	20 years	[redacted]	2.45	£23,099
	30 years	[redacted]	2.84	£20,001
Alternative PFS distributions	Independent models; Gompertz	[redacted]	2.48	£23,350
	Proportional hazards; Gompertz	[redacted]	2.86	£20,078
Alternative PPS distributions	Weibull	[redacted]	2.96	£19,220
	PPS fitted by treatment arm (exponential for both arms)	[redacted]	3.14	£18,375
Parametric analyses excluding numbers of risk < 5	-	[redacted]	2.96	£19,204
Treatment waning cut-off	3 years	[redacted]	1.94	£30,629
	5 years		2.39	£24,391
	Lifetime		3.06	£18,415
Subsequent treatment	Alternative PPS curve (KEYNOTE-024), 39% subsequent immunotherapy use in SoC arm and 20% in durvalumab arm	[redacted]	2.58	£21,297
	Alternative PPS curve (KEYNOTE-024), 0% subsequent immunotherapy use in both arms	[redacted]	2.80	£22,792
	Alternative PPS curve (KEYNOTE-024), 20% subsequent immunotherapy use in both arms	[redacted]	2.75	£22,404
	Alternative PPS curve (KEYNOTE-024), + 30% subsequent immunotherapy use in SoC arm and 2% in durvalumab arm	[redacted]	2.56	£20,985

Scenario	Values	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Alternative PPS curve (KEYNOTE-024), + 60% subsequent immunotherapy use in SoC arm, 2% in durvalumab arm	[redacted]	2.27	£19,011
Utility approach	Time to death and progression	[redacted]	2.95	£19,280
	Inclusion of age parameter	[redacted]	2.81	£20,237
	PF utilities capped at general population levels (PF = 0.79, PD = 0.756)	[redacted]	2.86	£19,853
	Include AE dis-utilities	[redacted]	2.93	£19,365
	20% decrease in HRQoL upon progression (PF = 0.81, PD = 0.65)	[redacted]	3.00	£18,961
	PACIFIC PF EQ-5D-5L data ITT (PF = 0.874, 0.842)	[redacted]	3.16	£17,960
	PACIFIC PF EQ-5D-5L data PD-L1 ≥ 1% (PF = 0.865, 0.840)	[redacted]	3.13	£18,162
	Progression and treatment arm included (mixed model)	[redacted]	2.82	£20,172
	Mean utility scores by treatment arm (EQ-5D-3L)	[redacted]	2.80	£20,261
Vial sharing	No vial sharing	[redacted]	2.93	£23,020
	50% vial sharing	[redacted]	2.93	£21,193
Subsequent treatment costs	50% discount for all subsequent treatments, where applicable (pembrolizumab nivolumab, erlotinib, afatinib)	[redacted]	2.93	£20,744
Subsequent immunotherapy duration	Pembrolizumab and nivolumab: two years duration	[redacted]	2.93	£11,368
Increased cost for progression-free health state	Extreme scenario: cost of metastatic disease applied to stage III	[redacted]	2.93	£24,069
Lower costs for progressed disease health state	Extreme scenario: Reduction in costs of 64%	[redacted]	2.93	£19,457

Source: Based on Table 32 of the company's response to the clarification letter[24]
AE =adverse events; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; ITT = intention to treat; PD = progressed disease; PF = progression-free; PFS = progression-free survival; PPS = post-progression survival QALY = quality adjusted life year; SoC = standard of care

ERG comment: The ERG had minor concerns regarding a) the difference in incremental QALYs in the PSA results compared to the deterministic analysis as well as stability of PSA results, b) the inclusion of patient characteristics in the PSA, and c) errors in the company's scenario analyses.

a) Compared with the company's deterministic base-case results, probabilistic incremental QALYs were lower. The ERG agrees with the company's explanation in the response to clarification letter that

that this was likely driven by the skewedness of the generalised gamma PFS curve. Furthermore, the 1,000 iterations used in the PSA did not achieve stability of results and the ERG used 5,000 iterations.

b) The company included patient characteristics in their PSA, despite intending to exclude them (the model setting designed to exclude them did not work). Given that these parameters reflected first order uncertainty, these should not be incorporated in the PSA. This was corrected in the ERG base-case.

c) The ERG identified several errors in the company's scenario analyses, including several settings in the controls sheet that were not functioning, and incorrect results of scenario analyses in Table 55 of the CS. In response to the clarification letter, the company corrected all of these errors. However, the ERG was unable to reproduce the company's scenario in which the costs for progressed disease reduced by 64% and noted additional errors in the subsequent treatment scenarios. The ERG only presented the revised results of the scenario analyses that were corrected by the company.

5.2.12 Model validation and face validity check

Face validity and internal validity
The model was reviewed by health economists within the company who performed face validity and internal validity checks. A third-party vendor also checked the model for basic validity of model outcomes, application and sources of costs and utilities, clinical inputs, sensitivity analyses and macros. In addition, model structure and approach (partitioned survival vs. semi-Markov) was reviewed by an expert in the field who advised on most appropriate methodology.

Cross validity
No cross validity checking of the model was reported by the company.

External validity
OS predictions from the model for durvalumab and SoC were validated against other sources. OS for SoC was compared to relevant clinical trials, UK real-world data, and clinical expert opinion. OS for durvalumab was compared to OS as observed in PACIFIC (see Table 35 of CS[1]). The company concluded that modelled OS for SoC broadly matched survival from all available sources of evidence, although none of these sources provided any estimates beyond a five year time horizon (except one 10 year estimate from expert opinion by four clinical experts[118]). The company did not state anything about the comparability of modelled OS for durvalumab with PACIFIC data. From Table 35 of the CS it can be seen that from the first to the third year, modelled OS for durvalumab goes from 1% underestimation (86% predicted vs 87% observed) to 3% overestimation (63% predicted vs 60% observed).[1]

In addition, OS for both durvalumab and SoC was compared to values accepted by NICE for immunotherapies in the advanced metastatic NSCLC setting (see Table 36 of CS[1]). Modelled OS was substantially higher (in both durvalumab and SoC) than these comparator values. The company stressed that these studies concerned distinct populations and disease stages, and therefore the predicted effect could be considered in line with that seen for other immunotherapies, when accounting for the greater potential for long-term survival when treating with curative intent.

Predictive validity
No predictive validity checking was reported by the company.

ERG comment: The main concern of the ERG relates to the fact that no firm conclusion could be drawn from the external validation exercised by the company. The company stated that modelled OS broadly matched survival of the available sources, but this was a subjective observation. In addition,

there was a marked difference between model survival and survival in previous TAs, but there is no way of telling whether the differences between model predictions and other immunotherapy values in Table 35 of CS were caused by the differences in population (metastatic vs. curative intent) or whether these were partly (or largely) caused by poor external validity of the current model.[1] The ERG appreciates the fact that durvalumab is first in class and so all comparison is difficult, but the ERG also considers the company's claims that any model outcome can be considered 'in line' with previous findings not to be substantiated.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Table 5.13 summarises the main issues highlighted by the ERG in Section 5.2, indicates the expected direction of bias introduced by these issues and whether these are examined in any analyses/incorporated in the ERG base-case.

Table 5.13: Main ERG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Model structure (Section 5.2.2)			
State transition model instead of partitioned survival analysis	+/-	No	Requested but not provided
Population, interventions and comparators, perspective and time horizon (Sections 5.2.3-5.2.5)			
The PD-L1 ≥ 1% population is a post-hoc subgroup of the population in the scope and the ITT population in PACIFIC	+/-	No	No
Half-cycle correction applied, but not to treatment and administration costs	+	Base-case (FV)	No
Treatment effectiveness and extrapolation (Section 5.2.6)			
Treatment effectiveness based on post-hoc subgroup (PD-L1 ≥ 1% patients), and not pre-specified TTP and PPS analysis	+/-	No	No
Evidence based on patients with mostly ≥2 overlapping cycles of platinum-based CRT, but UK practice is mostly sequential cycles	+/-	No	No
Survival evidence from PACIFIC is immature	+/-	No	No
Durvalumab PFS (extrapolated with generalised gamma) likely over-estimated compared to evidence from PACIFIC	+	Base-case (MJ), and scenarios	Scenario, but second-best fitting with better external validity unexplored
Treatment waning effect after 10-year cut-off	+	Base-case (MJ), and scenarios	Scenarios, where alternative cut-offs are explored
Age calculations performed incorrectly	+	Base-case (FE)	Addressed in response to request for clarification letter, in revised model
Uncertainty about PPS (driven by data source, modelling method and subsequent treatments)	+/-	Scenarios	Scenarios, explored using alternative data sources
Adverse events (Section 5.2.7)			
Treatment-related AEs potentially under-estimated	+	Scenario	No

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Health-related quality of life (Section 5.2.8)			
Utility scores for the PF state is likely high (0.810)	+	Scenario	No
No age-related utility decrement	+	Base-case (MJ)	Scenario uses age decrement
Utility decrement for PD state is likely small (-0.034)	-	Scenario	Yes
Utility estimates treatment-independent	+	Base-case (MJ)	Scenario in response to request for clarification[24]
Impact of AEs on HRQoL not reflected	+/-	Scenario	Scenario
Resources and costs (Section 5.2.9)			
Perfect vial-sharing assumption not appropriately justified and likely unrealistic	+	Base-case (FV), scenarios	Yes, scenarios allow for imperfect vial sharing
Resource use for PD health state based on metastatic disease	+	No	Scenario in response to request for clarification[24]
Inclusion criterion for subsequent treatments (>3% in all patients) may lead to biased inclusion per treatment arm	+/-	No	No
Cost effectiveness analyses (Sections 5.2.10 and 5.2.11)			
Patient characteristics included in PSA	+/-	Base-case (FV)	No

Footnotes: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator.
ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; ICER = incremental cost effectiveness ratio; MJ = matters of judgement; PD = progressed disease; PSA = probabilistic sensitivity analysis

Based on all considerations in Section 5.2 (summarised in Table 5.13), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[119]):

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Fixing errors

1. Incorrect age calculations (Section 5.2.11).
   The ERG used the company's revised model in response to request for clarification[24], in which the error was corrected, as requested.
2. Incorrect vial wastage calculations for nivolumab and pembrolizumab
   The ERG corrected the error by assuming perfect vial sharing throughout for nivolumab and pembrolizumab (given that these are now offered at fixed dosages)
3. Incorrect implementation in PSA of utility decrements for progression and treatment. IN probabilistic mode the minus sign was lost, turning the decrements into increments. The ERG corrected the error.

Fixing violations

4. Half-cycle correction not applied to treatment and administration costs (Section 5.2.5).
   The ERG corrected this.
5. Perfect vial sharing assumption lacks plausibility.
   The ERG assumed no vial sharing.
6. Patient characteristics included in the PSA (Section 5.2.11).
   The ERG corrected this.

Matters of judgment

7. Durvalumab PFS likely over-estimated using the generalised gamma (Section 5.2.6).
   The ERG used the lognormal instead for durvalumab PFS (and also TTP, by company's default setting).
8. Treatment waning effect after 10-year cut-off (Section 5.2.6).
   The ERG used a five-year cut-off instead.
9. No age-related utility decrement used (Section 5.2.8).
   The ERG applied an age-related utility decrement.
10. Treatment was excluded from utility mixed effects model (Section 5.2.8).
    The ERG included treatment as a covariate in the utility mixed effects model.

Table 6.1 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the (deterministic) ERG base-case. The FV and MJ ERG analyses were performed also incorporating the 'fixing error' adjustments given that the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

5.3.1 ERG base-case results

The results of the deterministic ERG base-case showed that incremental costs were [redacted] and incremental QALYs were 1.32 (Table 5.14). This resulted in an ICER of £50,238, which was mainly

driven by using the lognormal distribution for extrapolation of durvalumab PFS, using a five-year cut-off for treatment waning effect, and assuming no vial sharing (see Table 6.1).

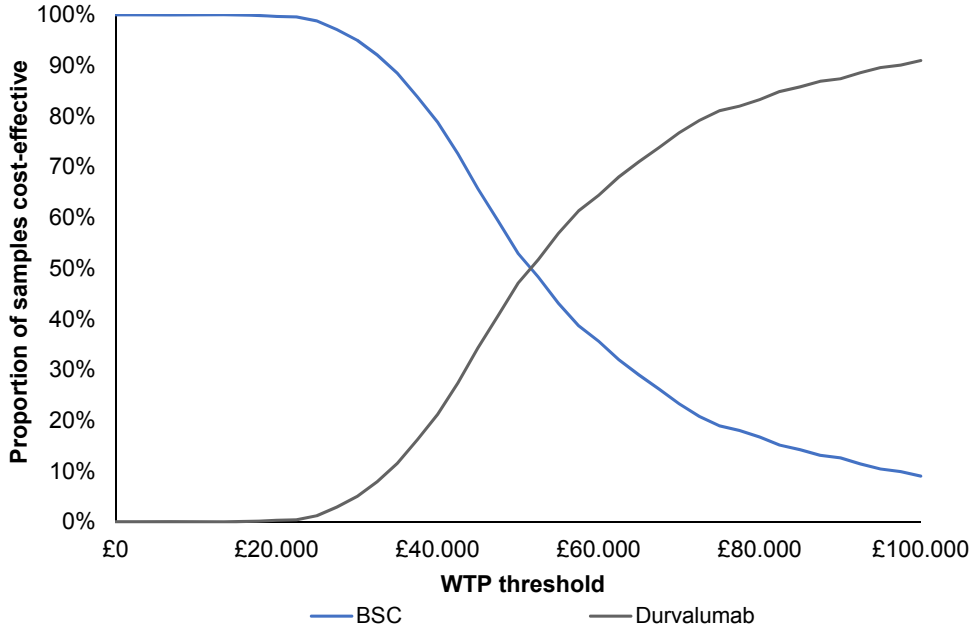
Compared with the deterministic ERG base-case results, the ERG PSA with 5,000 iterations resulted in lower incremental QALYs and slightly lower incremental costs, which resulted in an increased ICER (£52,353). The company's base-case also showed a marked difference between the deterministic and probabilistic ICERs. In their response to clarification question B24d[24] the company argued that this difference was due to the skewedness of the generalized gamma PFS curve, which caused skewed QALY results, but slightly differently so for durvalumab and SoC. At a later stage, the ERG noted an error in the model in the implementation of the utility decrements for progression and treatment, turning these into increments when running the PSA. The ERG fixed this for the ERG analyses. The company's probabilistic ICER results still contain the error but as no treatment decrement was applied in the company base-case, only the effect of the progression decrement remains. The cost effectiveness acceptability curve showed that durvalumab approximately had a 5.0% and 47.1% probability of being cost effective at willingness to pay (WTP) thresholds of £30,000 and £50,000 respectively (Figure 5.6).

Table 5.14: ERG base-case results

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			
Probabilistic ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.25	£52,353
SoC	[redacted]	[redacted]			

ERG = Evidence Review Group = ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care

Figure 5.6: ERG base-case cost effectiveness acceptability curve



5.3.2 Additional exploratory analyses performed based on the ERG base-case

Additional sensitivity analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. These were all performed using the ERG base-case. Results are presented in Table 6.2 in Section 6.

Exploratory analyses using the ERG base-case:

0. ERG base-case with no treatment waning effect
1. Alternative PFS distributions: generalised gamma for both durvalumab and SoC
2. Alternative PFS distributions: lognormal for both durvalumab and SoC
3. Treatment waning effect at three years with a) durvalumab and SoC PFS modelled using lognormal and generalised gamma and b) durvalumab and SoC PFS modelled using lognormal
4. Treatment waning effect seven years with a) durvalumab and SoC PFS modelled using lognormal and generalised gamma and b) durvalumab and SoC PFS modelled using lognormal
5. Use PPS based on PACIFIC, but using generalised gamma
6. Use PPS based on KEYNOTE-024, but correcting the following errors:
    - corrected the choice of survival distribution to the one with the best statistical fit (lognormal instead of log-logistic)
    - corrected estimate of patients receiving subsequent IO treatment in the durvalumab arm (27%)
7. Adverse events incorporated with amended incidence and including impact on HRQoL
8. Alternative utility score for PF state from literature (0.73)
9. Alternative utility scores for PF state (0.73) and PD state (0.67) from literature
10. Vial sharing possible (30%)

5.3.3 Subgroup analyses performed based on the ERG base-case

No subgroup analyses were performed.

5.4 Conclusions of the cost effectiveness section

- The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches and the 2018 update searches. A good range of databases and additional resources were searched.

- The company submission was largely in line with the NICE reference case. The modelled population, however, was narrower than that in the scope, but in line with the anticipated marketing authorisation (focussing on the subgroup with PD-L1 tumour expression ≥1%).

- Given the immaturity of the survival data in the PACIFIC subpopulation, the ERG had concerns about the appropriateness of the semi-Markov approach and its superiority over a partitioned survival model approach and would have liked to see both approaches appropriately explored.

- The ERG had concerns about the model being based on treatment effectiveness estimates derived from a post-hoc subgroup analysis and post-hoc TTP and PPS analyses, as well as in a population with mostly prior overlapping CRT instead of sequential CRT, although any bias introduced by this remained unclear.

- The main concern of the ERG was that it considered modelled long-term durvalumab PFS as highly uncertain and likely over-estimated, due to a model choice (generalised gamma) that resulted in PFS estimates above those observed in PACIFIC at three years, with the PACIFIC estimate notably being derived from small numbers of patients at risk and immature data. This model choice caused

ICERs of durvalumab versus SoC to be lower than other model choices. This issue was exacerbated by the choice of time-point at which treatment waning was modelled (10 years), which was deemed by the ERG as highly uncertain, not appropriately validated, and potentially late, additionally lowering ICERs of durvalumab versus SoC in the CS. Alternative modelling methods, such as spline-based models, remained unexplored in the CS.

- There was a discrepancy between AEs causally related to treatment in PACIFIC, which were mostly higher for the durvalumab arm than in the placebo arm, and AE incidence in the model, which was comparable between treatments, that remained unexplained, likely lowering ICERs of durvalumab versus SoC.

- The ERG considered utility values for both (progression-free and progressed disease) health states to be potentially over-estimated, being comparable to those in the general population and not adjusted by general population age utility estimates. Excluding treatment as a factor in utility estimation and excluding the HRQoL impact of AEs contributes to QALY gains being likely over-estimated. These assumptions on balance likely lowered ICERs of durvalumab versus SoC.

- The ERG considered the assumption of perfect vial sharing to be unrealistic in this setting, given the limited number of patients in England and Wales that would be eligible for treatment with durvalumab. This assumption caused the ICER of durvalumab against SoC to be lower than alternative assumptions.

- The ERG made various adjustments to the company base-case. The probabilistic ERG base-case ICER of durvalumab versus SoC was £52,353 per QALY gained (based on 5,000 iterations). The difference was likely caused by the skewedness of distributions used for modelling PFS.

- Deterministic scenario analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. Alternative assumptions regarding PFS and treatment waning effects had the most significant impact. The scenario in which PFS distributions were changed into generalised gamma for both arms (as per the company's base-case) resulted in an ICER of £29,302 per QALY gained, whereas applying lognormal distributions for PFS in both arms drove up the ICER to £52,300 per QALY gained. Applying the company's KEYNOTE-024 PPS scenario, but with errors corrected, resulted in an ICER of £59,131 per QALY gained. The scenario exploring a treatment waning effect with three-year cut-off and using the lognormal distribution for both durvalumab and SoC PFS increased the ICER the most (to £64,531 per QALY gained). All other scenarios had a relatively modest impact (<£5,000) on the ERG base-case ICER.

- In conclusion, given that the ERG base-case ICER was estimated to be substantially above £40,000 per QALY gained, and only one scenario resulting in ICERs slightly below £30,000 per QALY gained, and the large uncertainty induced by mainly the immature survival data, uncertainty around the cost effectiveness of durvalumab is substantial.

6. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Analyses undertaken by the ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.2. These are all conditional on the ERG base-case. The analyses numbers in Tables 6.1 and 6.2 correspond to the analyses numbers reported in Section 5.3. The submitted model file contains technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.1: Deterministic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	2.94	£19,320
SoC	[redacted]	[redacted]			
Fixing error (1, age calculations)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.93	£19,366
SoC	[redacted]	[redacted]			
Fixing violations (3, half-cycle correction for treatment costs)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.93	£20,001
SoC	[redacted]	[redacted]			
Fixing violations (4, no vial sharing) and error 2 (vial wastage)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.93	£20,647
SoC	[redacted]	[redacted]			
Matter of judgement (6, lognormal for durvalumab PFS)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£45,878
SoC	[redacted]	[redacted]			
Matter of judgement (7, treatment waning at 5 years)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.39	£24,391
SoC	[redacted]	[redacted]			
Matter of judgement (8, age-related utility decrement applied)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.81	£20,237
SoC	[redacted]	[redacted]			
Matter of judgement (9, treatment included in utility model)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.82	£20,172
SoC	[redacted]	[redacted]			
ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			

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

Table 6.2: Deterministic scenario analyses conditional on ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			
ERG base-case, no treatment waning effect (0)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.10	£60,928
SoC	[redacted]	[redacted]			
Alternative PFS distributions both arms, generalised gamma (1)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.19	£29,302
SoC	[redacted]	[redacted]			
Alternative PFS distributions both arms, lognormal (2)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.27	£52,300
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as ERG base-case (3a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.35	£48,766
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as scenario 2 (3b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.04	£64,531
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as ERG base-case (4a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.25	£52,833
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as scenario 2 (4b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.41	£47,000
SoC	[redacted]	[redacted]			
PACIFIC PPS, but generalised gamma (5)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.33	£49,868
SoC	[redacted]	[redacted]			
Company's KEYNOTE-024 PPS scenario, with errors corrected (6)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.10	£59,131
SoC	[redacted]	[redacted]			
Adverse events with amended incidence and including impact on HRQoL (7)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,288
SoC	[redacted]	[redacted]			
Alternative PF utility score (8)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.42	£51,805
SoC	[redacted]	[redacted]			
Alternative PF and PD utility scores (9)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.28	£51,587

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]			
Vial sharing possible at 30% (10)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£49,350
SoC	[redacted]	[redacted]			

ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; PD = progressed disease; PF = progression-free; PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year; SoC = standard of care

7. End of life

NICE end of life considerations apply when two criteria are satisfied:

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months; and
2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current NHS treatment.

Table 27 of the CS summarises available data which might support the applicability of end-of-life criteria.[1] The data are summarised below.

Criterion 1: According to the CS, "in the PACIFIC study, median OS in the placebo arm was 28.7 months in the ITT population, and 29.1 months in the PD-L1 ≥1% group of patients".[1] However, the company highlighted that *"data may not reflect real-world survival outcomes in the UK cohort of locally-advanced, unresectable, Stage III NSCLC patients …*(as)*…intensive management of patients and other factors that are unique to a clinical trial setting can improve patient outcomes relative to what is known / expected in real-world settings"*.[1]

In support of this statement, the CS presented some UK-specific data:

- National Lung Cancer Audit (2016 audit period){Royal College of Physicians, 2018 [accessed 13.2.18] #399}: Average 1-year survival rate from diagnosis of stage III patients = 42.5%
- Moller et al. 2017{Moller, 2018 #56}: Patients treated with radical radiotherapy with 2-year survival probability from diagnosis <25%
- Royal College of Radiologists audit{Royal College of Radiologists (RCR), 2016 #432}: Median OS following radical radiotherapy = 22 months, 2-year survival rate = 44%; 2-year survival rate (overlapping CRT) = 46%
- Public Health England{AstraZeneca, 2018 #435}: Median OS for patients with unresected stage III who had received overlapping CRT = 20.7 months
- SOCCAR RCT{Maguire, 2014 #51}: Median OS from start of overlapping / sequential CRT = 24.3 / 18.4 months
- Expert opinion (mean of 10 responses){AstraZeneca, 2018 #402} = 22.3 months (median OS)

ERG comment: While this claim is plausible, it should be noted that for NICE committees mean values are preferable to median values when measuring OS time.{National Institute for Health and Care Excellence, 2017 [accessed 4.12.18] #436} Therefore, the extent of the possible effect is unclear, i.e. whether the reported data (including median OS) could indicate that patients would have a life expectancy of less than 24 months (mean OS). There is additional uncertainty due to the immaturity of the OS data reported in PACIFIC.

Criterion 2: The company highlights that PACIFIC found *"significantly extended OS relative to placebo in the PD-L1 ≥1% group"*, presenting two different estimates: HR 0.54, 95% CI 0.35 to 0.81, section B.2.6; and HR 0.53, 95% 0.36 to 0.77, Table 27.[1]

ERG comment: There is insufficient evidence whether the treatment offers an extension to life as no OS estimate is reported for the durvalumab arm in the relevant PD-L1 ≥1% subgroup (Table 4.6). However, it should be noted that in the whole trial population, a difference of median survival time of 12 months can be seen when comparing the lower 95% CIs (Table 4.6). However, this again is based on median survival time (when normally mean is preferable) and is unlikely to be *"sufficiently robust"*.{National Institute for Health and Care Excellence, 2013 [accessed 4.12.18] #19} Furthermore,

there is additional uncertainty due to the immaturity of the OS data reported in PACIFIC; results in the relevant subgroup might become available in future analyses.

8. Overall conclusions

8.1 Statement of principal findings

The CS comprised of a systematic review of the evidence for durvalumab for the treatment of locally advanced unresectable, Stage III NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based CRT.

The main database searches in the CS were on the whole transparent and reproducible, and a good range of resources were used. Better use of synonyms could have been applied in some database searches to aid the retrieval of relevant references. The presented evidence included one RCT, PACIFIC.

The PACIFIC trial included patients with confirmed PD-L1 expression on ≥1% of TCs. After randomisation procedures, this resulted in 476 patients in the durvalumab group and 237 patients in the placebo group. However, when focusing on only the patients with confirmed PD-L1 expression on ≥1% of TCs, there were 212 patients in the durvalumab group and 91 patients in the placebo group. While the PACIFIC trial met a multi-centre, international design, only eight patients were seeking treatment in the UK.

Based on the PACIFIC data there appears to be a benefit in both PFS and OS for durvalumab patients compared with placebo patients, however, the data are immature and there remains substantial uncertainty about the comparative effectiveness.

Common adverse events were reported in both the durvalumab and placebo groups. The common AEs in the durvalumab patients included cough, fatigue, and radiation pneumonitis, whereas patients in the placebo group also included dyspnoea. Overall, more serious adverse events were reported for durvalumab compared to placebo (64/213 (30%) vs. 18/90 (20%)).

Due to the PACIFIC trial being ongoing, final results will be confirmed at a later date.

Economic evaluation

The ERG made various adjustments to the company's base-case. The probabilistic ERG base-case ICER of durvalumab versus SoC was ££52,353 per QALY gained (based on 5,000 iterations). This was higher than the deterministic ERG base-case ICER of £50,238 per QALY gained. The difference was likely caused by the skewedness of distributions used for modelling PFS.

Deterministic scenario analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. Alternative assumptions regarding PFS and treatment waning effects had the most significant impact. The scenario in which PFS distributions were changed into generalised gamma for both arms (as per the company's base-case) resulted in an ICER of £29,302 per QALY gained, whereas applying lognormal distributions for PFS in both arms drove up the ICER to £52,300 per QALY gained. Applying the company's KEYNOTE-024 PPS scenario, but with errors corrected, resulted in an ICER of £59,131 per QALY gained. The scenario exploring a treatment waning effect with three-year cut-off and using the lognormal distribution for both durvalumab and SoC PFS increased the ICER the most (to £64,531 per QALY gained). All other scenarios had a relatively modest impact (<£5,000) on the ERG base-case ICER.

In conclusion, given that the ERG base-case ICER was estimated to be substantially above £40,000 per QALY gained, and only one scenario resulting in ICERs slightly below £30,000 per QALY gained, and the large uncertainty induced by mainly the immature survival data, uncertainty around the cost effectiveness of durvalumab is substantial.

8.2 Strengths and limitations of the assessment

Overall, the CS reported searches were clearly reported and reproducible. The selection of databases searched was adequate and a good range of additional resources were included. Study design limits to identify economic evaluations, utility data, and costs and resource use data were applied. A good range of intervention terms for durvalumab and comparators were used in the cost effectiveness strategy.

A substantial source of uncertainty lies in the generalisability of PACIFIC data to the UK setting, as PACIFIC pertains predominantly to prior overlapping CRT, whereas in clinical practice in the UK, mostly sequential CRT is applied. In addition, the PD-L1≥1% subgroup and TTP and PPS analyses were performed post-hoc. Furthermore, main results come from interim analysis, e.g. according to the response to the request for clarification the company *"will conduct a final analysis of OS once a maturity of 70% has been reached. OS is an event-driven endpoint; therefore, the timing of this analysis is uncertain"* which will be reached *"when 491 OS events have occurred"*.[1, 24] The current maturity in the relevant subgroup is 33.0% for durvalumab and 49.5% for placebo.[27]

The company submission was largely in line with the NICE reference case. Utility scores were estimated using a mixed effects model based on observed EQ-5D data in the PACIFIC study.

The model was, in general, well-built and transparent. Apart from their base-case, the company provided opportunities for exploratory analyses using alternative data derived from clinical trials in similar populations.

A main limitation was the immaturity of survival data in the PACIFIC subpopulation, and the inherent uncertainty in PFS and PPS extrapolations. The ERG considers particularly durvalumab PFS to be overestimated, even more so because the company chose to incorporate treatment waning only at 10 years. Given the immaturity of survival data, the ERG also has concerns on the appropriateness of the semi-Markov model structure, but the company did not provide an opportunity to explore a partitioned survival approach. Alternative modelling methods, such as spline-based models, remained unexplored in the CS.

Lastly, the utility scores used in the model do not seem representative of the patient population. The ERG considers the utilities for both (progression-free and progressed disease) health states to be an overestimate.

8.3 Suggested research priorities

PACIFIC is an ongoing trial so more information will be available to reduce the uncertainties in progression-free and overall survival, and other outcomes.

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Appendix 1: ERG search strategies

Additional limitations of the CS searches not covered in the main body of the report:

Clinical effectiveness

- Greater use could have been made of indexing terms and free-text terms in the population facet. Recall could have been increased by truncating 'cancer*', including terms such as 'pulmonary' and 'bronchial' to the lung cancer facet, searching for specific CRT interventions and broader CRT terms, and including 'stage three' as a disease stage term.

Cost effectiveness

- Bronchial has been misspelled as "brochial" in the 2016 MEDLINE In Process and Econlit searches and the 2018 MEDLINE, MEDLINE In Process, HTA and NHSEED searches.
- There is an error in the cost effectiveness studies 2016 MEDLINE In Process strategy (line #72 should read '#9 AND #35 AND #71' not '#9 AND #35 AND #70'). This is likely to have affected the search results.
- Some of the 2016 cost effectiveness strategies (HTA, NHS EED, MEDLINE In Process, EconLit) do not include search terms for chemoradiotherapy. These terms are included in the 2016 MEDLINE and Embase database searches and all 2018 update searches

Search line numbers were omitted in some 2016 strategies. This did not affect the search results, but made it difficult to check the strategies.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID1175]

You are asked to check the ERG report from Kleijnen Systematic Reviews Ltd to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Thursday 29 November** using the below proforma comments table. All factual errors 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.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Covering letter:

Dear NICE Technical Team and Kleijnen Systematic Reviews Ltd. Evidence Review Group,

Thank you for the opportunity to provide this Factual Accuracy Check pro-forma in response to the ERG's report. In our pro-forma response, we have classified "Issues" into three categories, as follows:

1. **Correction:** instances where we believe the information stated by the ERG is factually incorrect.
2. **Clarity:** instances where the ERG's statement can be misleading, omit relevant context or information provided by the company, or could be misinterpreted by the Committee.

   We have suggested alternative wording for both correction- and clarity-points – all proposed edits are in **bold**.
3. **Comment:** instances where no actions are required. These include notes about availability of materials (e.g. EPAR) or acknowledgement of the ERG's comment. We have avoided commenting on matters of judgement.

We hope this structure will be helpful when reviewing / considering the pro-forma and would like to thank the ERG for their detailed review and consideration of our submission.

We look forward to the next steps of the appraisal process and are happy to answer any questions on the pro-forma in the meantime.

Kind regards,
AstraZeneca UK

Section 1: Summary

Issue 1 Clarity: rationale for population considered in the company submission being narrower than the NICE scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1, page 10: Compared to the National Institute for Health and Care Excellence (NICE) scope, the population is narrower, i.e. only includes patients in the relevant population whose tumours expressed PD-L1.	Compared to the National Institute for Health and Care Excellence (NICE) scope, the population is narrower, **but in line with the European Commission (EC) marketing authorisation** (i.e. only **those** patients whose tumours express PD-**L1 on ≥1% of tumour cells**).	Restricting our reimbursement submission to the PD-L1 ≥1% population was not AstraZeneca's choice, rather, it was done to align our submission with the EC marketing authorisation for durvalumab in this indication. We feel this clarity is important and is also aligned to wording used elsewhere in the ERG report (e.g. page 11, section 1.3).	This is not a factual error. NB: Further details are given in section 3 of the ERG report.
Section 1.6.2, p17: The population included in the PACIFIC trial is narrower than in the NICE scope and the ERG identified additional issues which might potentially limit the applicability of study results, see Section 1.1.	The population included in the PACIFIC trial is narrower than in the NICE scope, **but in line with the marketing authorisation for durvalumab in this indication**. The ERG identified additional issues which might potentially limit the applicability of study results, see Section 1.1.		This is not a factual error. NB: Further details are given in section 3 of the ERG report.

Issue 2 Correction: proportion of patients in PACIFIC who received durvalumab treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, p10 (second paragraph): The population of participants receiving durvalumab represents	The population of participants receiving durvalumab represents approx. **67%** of the overall population included in PACIFIC	We believe this is a typo and should have said 67%, i.e. 476 of 713 patients in the ITT population.	Corrected as suggested.

approx. 6% of the overall population included in PACIFIC			

Issue 3 Correction: source of data on sequential versus overlapping (concurrent) CRT use in the UK

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, p10 (third paragraph)*: However, the clinical expert highlighted that *"most UK patients receive sequential rather than overlapping treatment"* while *"the efficacy and safety of durvalumab in the PACIFIC study was evaluated after overlapping, rather than sequential, CRT".*	**Data from the National Lung Cancer Audit** highlighted that "*most patients received sequential rather than overlapping treatment*" **in the 2016 audit period**, while "*the efficacy and safety of durvalumab in the PACIFIC study was evaluated after overlapping, rather than sequential, CRT*".	The data communicated prior to publication by [redacted] is based on the 2016 NLCA. It does not reflect her opinion, but rather a national snap-shot of CRT use in England and Wales. This distinction is important, as the use of sequential versus overlapping CRT varies widely across UK centres, with some centres treating the majority of patients concurrently if they have good PS and no contradictions to chemotherapy regimens. Clinical experts consulted to provide advice on this submission emphasised that overlapping / concurrent CRT is "**gold standard**" treatment for locally-advanced, unresectable, Stage III NSCLC patients with good performance status, and that there is a "**desire within the clinical community to drive its use in UK patients** [who are suitable to receive this treatment]".	This is not a factual error. The ERG refers here to the quote provided by the clinical expert.
*Please also see the following for related comments: Issue 8, Issue 17, Issue 21 and Issue 26			

Issue 4 Clarity: generalisability of the PACIFIC population to UK patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, p10 (third paragraph): These issues impact on the certainty regarding these findings and might limit the applicability of any findings to UK clinical practice.	These issues impact on the certainty regarding these findings **in sequential CRT patients** and might limit their applicability **to these patients** in UK clinical practice.	As noted, we acknowledge that clinical trial evidence on the effectiveness of durvalumab in patients who have received sequential CRT is lacking. However, we feel it is important to distinguish this from the concurrent (i.e. overlapping) CRT patient population, where we have robust clinical trial data from PACIFIC and significant evidence confirming generalisability to UK (from bespoke analysis of Public Health England data and clinical expert opinion, provided in the CS and response to ERG clarification questions).	This is not a factual error. NB: Making the suggested change would change the meaning of this sentence which summarises the whole previous paragraph, including the statement on UK patients.

Issue 5 Correction: use of "interim" versus "primary" to describe analyses of PFS and OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, p11*: However, it should be noted that these results come from an interim cut-off, i.e. not from the final analysis	We suggest deleting this sentence, as used of "interim" is incorrect.	As explained in the CS, since durvalumab achieved statistical significance for PFS in the first pre-specified interim analysis of this endpoint (13 February 2017), this is considered the **primary analysis** of PFS. Similarly, since durvalumab achieved statistical significance for OS at first pre-specified interim analysis of this endpoint (22 March 2018), this is considered the	This is not a factual error. NB: The response to request for clarification stated that "The 22 March 2018 data cut is the most recent. No additional analyses from the PACIFIC study have been performed at this time." thus indicating that this was indeed an interim analysis at the time the ERG
Section 1.6.2, p17*: Furthermore, main results come from interim analysis […]	Please remove "interim", as data from the **primary** analysis of PFS and OS are provided (see justification provided). No further analysis of PFS		

	is planned at this time.	**primary analysis** of OS. Since both primary endpoints for PACIFIC were met, AstraZeneca are not required to conduct any further analyses, and **no further updates to PFS or secondary endpoints are planned**. Therefore, the use of "interim" is incorrect. There are plans to update the OS data; however, given that durvalumab has already demonstrated a significant OS benefit versus placebo, and met the study endpoint, referring to these data as "primary" rather than "interim" analyses is statistically more appropriate.	report was prepared.
*Please also see the following for related comments: Issue 20 and Issue 37			

Issue 6 Clarity: maturity of survival data from PACIFIC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, p11: Based on the PACIFIC data there appears to be a benefit in both PFS and OS for durvalumab patients compared with placebo patients, however, the data are immature and there remains substantial uncertainty about the comparative effectiveness.	We suggest adding maturity for both PFS and OS to this sentence: Based on the PACIFIC data there appears to be a benefit in both PFS and OS for durvalumab patients compared with placebo patients, however, the data are immature **(54.5% and 38% mature for PFS and OS, respectively)** and there remains substantial uncertainty about the comparative effectiveness.	We feel this clarity is important since the PFS data are more mature than OS data.	This is not a factual error. Details on maturity are reported in the ERG comment on Section 4.2.3 of the ERG report.

Issue 7 Clarity: semi-Markov approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, p11 (third paragraph): The company claimed that the semi-Markov approach largely avoided crossing of PFS and OS curves. However, relying on PPS to estimate survival instead of using OS drew on even fewer patients for extrapolation and potentially introduced additional bias (selection bias by relying on early progressors, with more progressions in the placebo arm than in the durvalumab arm). The magnitude and direction of any bias are unclear."	The company claimed that the semi-Markov approach avoided crossing of PFS and OS curves**, and that the state transition approach predicted observed OS with reasonable accuracy within the trial period.** However, **the ERG considers that** relying on PPS to estimate survival instead of using OS drew on even fewer patients for extrapolation and potentially introduced additional bias (selection bias by relying on early progressors, with more progressions in the placebo arm than in the durvalumab arm). The magnitude and direction of any bias are unclear."	Slight misrepresentation of CS / response content. The ERG's statement also omitted useful information about the internal validity of the PFS + PPS approach, which should be considered against any potential biases.	This is not a factual error.

Issue 8 Correction: reference to sequential CRT as "standard practice"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, p11 (last paragraph)*:	However, the generalisability of PACIFIC to the United Kingdom setting was questioned, because	Concurrent / overlapping CRT is the **standard of care** in locally-advanced, unresectable, Stage III patients and	This is not a factual error. The ERG refers here to the quote provided by the clinical expert

However, the generalisability of PACIFIC to the United Kingdom setting was questioned, because patients in PACIFIC largely received overlapping CRT, whilst sequential CRT is standard practice in the United Kingdom.	patients in PACIFIC largely received overlapping CRT, whilst sequential CRT **was more commonly-used in the last National Lung Cancer Audit (2016 audit period)**.	recommended in clinical practice guidelines. While sequential CRT was more commonly-used in the analysis of 2016 NLCA data, it is **not** considered "standard practice in the United Kingdom".	(please refer to Issue 3). The company did not refer to the NLCA audit in this context.
*Please also see the following for related comments: Issue 3, Issue 17, Issue 21, and Issue 26			

Issue 9 Comment: half-cycle correction of treatment and treatment administration costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, p12 (third paragraph): […]in the absence of any justification for not applying the half-cycle correction to treatment and treatment administration costs, the ERG considered this inconsistent with the calculation of resource use and other model calculations, which lowered the ICER.	No amendment. We note the ERG's amendment. Note that other appraisals have advocated not applying half cycle correction to costs. However, this amendment makes minimal difference to ICER and is unlikely to influence decision making.	--	This is not a factual error. No amendment required.

Issue 10 Clarity / correction: number of patients at risk

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, p12 (third paragraph): The main concern of the ERG was that it considered durvalumab PFS to be probably over-estimated in the model, due to a model choice (generalised gamma) that resulted in PFS estimates above those observed in PACIFIC at three years, with the PACIFIC estimate notably being derived from small numbers of patients at risk	The main concern of the ERG was that it considered durvalumab PFS to be probably over-estimated in the model, due to a model choice (generalised gamma) that resulted in PFS estimates above those observed in PACIFIC at three years, with the PACIFIC estimate notably being derived **from a single patient at risk (n=1)**	We believe it is important to state the sample size, since "small numbers of patients at risk" implies more than one patient.	This is not a factual error. The PFS overestimate does not only apply to the 3-year timepoint, it is already present before that, when number of patients at risk was >1 (but still small). Furthermore, a single patient would qualify as "small numbers", and this was marked as CiC.

Issue 11 Clarity: application of adverse event rates in the economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, p13 (third paragraph): Whilst AEs causally related to treatment were mostly higher for the durvalumab arm than in the placebo arm in PACIFIC, incidence of AEs in the model between treatments was	The incidence/ number of AEs in the model between treatments was comparable, **although more patients in the durvalumab arm experienced AEs causally related to treatment than in the placebo arm.** Exploratory analyses however showed that any bias caused by this would be limited.	The adverse event tables presented in the clinical section of the CS show the **observed number of patients** with adverse events. For the economic modelling, the **number of adverse events** was used instead. This information was provided in the CS p149, which states "*AE rates in the economic analysis were based on number of events (rather than number*	This is not a factual error. The ERG did take note of the difference between patients and events, but considered the difference between particularly table 18 and table 36 of the CS to be substantial and not transparently explained.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
comparable. It was unclear how this discrepancy occurred, likely lowering ICERs of durvalumab versus SoC. Exploratory analyses however showed that any bias caused by this would be limited.		*of patients, as is the case for data presented in Section B.2.10)*."	
Section 1.3, p13 (fourth paragraph): No adverse event related disutilities were taken into account	No adverse event related disutilities were taken into account **in the company base case analysis, although they were explored in sensitivity analyses**.	Misrepresentation of company submission	This is not a factual error. This is a description of the company's base-case. The ERG presented all sensitivity analyses performed by the company in table 5.6 of the ERG report.

Issue 12 Correction: source of resource use associated with the PF health state

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, p14 (first paragraph): Resource use for the PF state was modelled in accordance with European Society for Medical Oncology guidelines,	Resource use for the PF state was modelled in accordance with European Society for Medical Oncology guidelines **and clinical expert opinion**	Misrepresentation of company submission	This is not a factual error. The main text also refers to expert opinion.

Issue 13 Clarity: impact of vial sharing assumption on the ICER

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, p14 (first paragraph): This assumption caused the ICER of durvalumab against SoC to be lowered.	**Assuming perfect vial sharing** caused the ICER of durvalumab against SoC to be lowered **by approximately £5k.**	We suggest stating the impact on ICER for transparency.	This is not a factual error.

Issue 14 Correction: validation of modelled survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, p14 (fourth paragraph): OS predictions from the model were validated against PACIFIC, other sources and expert opinion. No firm conclusion could be drawn from the external validation exercise performed by the company using alternative data sources, due to differences in population.	We suggest deleting / amending the following sentence: No firm conclusion could be drawn from the external validation exercise performed by the company using alternative data sources, due to differences in population.	This sentence is misleading, since several alternative data sources presented in the CS focus on PACIFIC-like patient populations (for example: clinical trials such as START, UK clinical expert opinion, Public Health England real-world data). Without specifying this, readers may interpret the ERG's sentence as meaning there are no alternative survival data sources for locally-advanced, unresectable, Stage III NSCLC patients who have completed curative intent CRT.	This is not a factual error. The CS states on p. 147 that the values compared to are from 'distinct populations and disease stages' (i.e. advanced metastatic NSCLC setting) and that it concerns an illustrative comparison. The ERG considers this to be a less than ideal situation for external validation.

Issue 15 Correction: partitioned survival approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.6.2, p17: Given the immaturity of survival data, the ERG also has concerns over the appropriateness of the semi-Markov model structure, but the company did not provide an opportunity to explore a partitioned survival approach.	Given the immaturity of survival data, the ERG also has concerns over the appropriateness of the semi-Markov model structure**. The company provided PFS and OS extrapolations but did not provide a model with partitioned survival approach**.	We provided the survival extrapolations for PFS and OS from the PACIFIC trial PD-L1 ≥1% group in Appendix M.3. and M.6.	This is not a factual error. On p. 122 and in table 55 of the CS, the partSA modelling approach was said to be used in a sensitivity analysis. The ERG does not consider the provision of PFS and OS curves an opportunity to explore and verify this approach.

Section 2: Background

Issue 16 Clarity: use of subsequent therapies upon disease progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2, p18: If patients remain disease-free for a period of >12 months, they are treated with first-line (1-L) systemic drug therapies, otherwise second-line (2-L) drug therapies are utilised.	If patients remain disease-free for a period of >12 months, they are treated with first-line (1-L) systemic drug therapies **approved for advanced metastatic (Stage IV) NSCLC upon disease progression**. Otherwise second-line (2-L) drug therapies **approved in the advanced metastatic setting** are utilised **upon progression**.	We have added further detail for clarity on what is meant by "1-L" and "2-L" therapies, and that these apply only once the patient has experienced disease progression	This is not a factual error.

Section 3: Critique of company's definition of decision problem

Issue 17 Clarity: quote on sequential CRT use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.1, p24 (third bullet)*: Clinical expert Dr Susan Harden stated that "*most UK patients receive sequential rather than overlapping treatment*" while "*the efficacy and safety of durvalumab in the PACIFIC study was evaluated after overlapping, rather than sequential, CRT*".	No edits needed if the quote was directly obtained from Dr. Harden by the ERG. If this refers to the personal communication described on page 24 of the CS, then we suggest clarifying that this relates to National Lung Cancer Audit data from the 2016 audit period (please see edit proposed in Issue 3.	Please see justification provided for Issue 3.	This is not a factual error.
*Please also see the following for related comments: Issue 3, Issue 8, Issue 21, and Issue 26			

Issue 18 Comment: final SmPC and EPAR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2, p24: The final summary of product characteristics (SmPC) and European public assessment report (EPAR) are not available at the present time (October 2018).	No amendment. The final versions of these documents are now available at: https://www.ema.europa.eu/documents/overview/imfizi-epar-medicine-overview_en.pdf https://www.ema.europa.eu/documents/product-information/imfizi-epar-product-information_en.pdf	N/A	Thanks for providing these links. No amendment needed.

Section 4: Clinical effectiveness

Issue 19 Comment: quality assessment of the PACIFIC study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.4, page 34: In the quality assessment of the PACIFIC trial, presented in Table 7 of the CS appendices, the company identifies the PACIFIC trial as having a low risk of bias for concealment of treatment allocation. The response does not describe how concealment of allocation was concealed, i.e. this question should be rated as unclear. However, describing the randomisation, the company describes that IVRS/IWRS were used which are acceptable methods of concealment of allocation.	No amendments needed. We note the ERG's comment and apologise for not reiterating the use of IVRS / IWRS in relation to "concealment of treatment allocation" – as stated by the ERG, these are appropriate methods of concealment, therefore, we maintain that the risk of bias is **low**.	N/A	Thanks for the clarification which confirms the assumption made in the ERG report. No amendment needed.

Issue 20 Correction: number of data-cuts used to inform the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.5, page 34*:	**Two data-cuts** were utilised, namely, **13 February 2017 (primary analysis**	There have been only **two** data-cuts to date:	This is not a factual error. See response to issue 5 for further

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Three interim analyses were utilised.	**of PFS) and 22 March 2018 (primary analysis of OS)**	- First pre-specified interim analysis of PFS: since the study met statistical significance for this endpoint at this time, this data-cut (13 February 2017) is considered the primary analysis of PFS - First pre-specified interim analysis of OS: since the study met statistical significance for this endpoint at this time, this data-cut (22 March 2018) is considered the primary analysis of OS	details.
*Please also see the following for related comments: Issue 5 and Issue 37			

Issue 21 Correction: reference to National Lung Cancer Audit data and sequential CRT being "standard of care"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.1, p33*: However, according to the clinical expert cited in the CS, sequential CRT is the method of treatment most often received for patients in the UK and is identified as the standard of care.	However, according to **National Lung Cancer Audit data from England and Wales (2016 audit period)** cited in the CS, sequential CRT **was more commonly-used in the UK**. While the company acknowledges this difference, they state the PACIFIC patient population is broadly general to UK patients with locally-advanced, unresectable, stage III NSCLC patients who receive curative-intent CRT treatment.	As stated previously, the communication from [redacted] relates to analyses of NLCA data from the 2016 audit period – we believe this distinction is important, so as to not misrepresent information. Furthermore, while sequential CRT was more commonly-used in the NLCA dataset, it is incorrect to refer to it as "standard of care". Of the treatment options available at present, concurrent (i.e. overlapping) CRT achieves the best	This is not a factual error.

		outcomes in locally-advanced, unresectable, Stage III NSCLC patients is recommended in several guidelines as "treatment of choice". This is also consistent with the opinion of clinical experts, who consider overlapping CRT as "**gold standard**" treatment in this setting. Finally, as stated previously (Issue 3), the use of sequential versus overlapping CRT varies significantly across centres – overlapping CRT may be just as frequently or more commonly-used in some centres.	
Section 4.2.2., p34*: Therefore, most participants in the PACIFIC trial received two or more concurrent cycles of CRT. However, most UK patients, according to a clinical expert, receive sequential cycles of CRT which was not included in the evaluation of durvalumab.	**In the 2016 National Lung Cancer Audit, majority of** UK patients received sequential cycles of CRT, which was not included in the evaluation of durvalumab. **The PACIFIC trial enrolled patients who had** received ≥2 concurrent cycles of CRT, **since it is recommended in clinical practice guidelines as "treatment of choice" in this setting.**		This is not a factual error.
*Please also see the following for related comments: Issue 3, Issue 8, Issue 17, and Issue 26			

Issue 22 Correction: safety evaluation in PACIFIC-5 and PACIFIC-6 studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.5, p43: A safety evaluation is set to start in mid-2019, focusing on any new safety signals particular to a population of sequential CRT patients.	**Both PACIFIC-5 and PACIFIC-6 studies will provide an indication of** any new safety signals particular to the population of sequential CRT patients.	The timing of the safety evaluation is not confirmed. We have amended related narrative in Document B and provided a revised version to NICE on 9 November 2018.	Not a factual error. NB: The statement was based on the response to the request for clarification, i.e. reflects the information at the time the ERG report was prepared.

Issue 23 Correction: further analysis of PACIFIC data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.6, p44: Due to the trial being identified as ongoing, some results are not yet available	Due to the trial being identified as ongoing, **final OS** results are not yet available	For transparency and accuracy, we suggest specifying OS, as there are no plans to update other endpoints at present. There are also no plans to publish the final OS data at present.	This is not a factual error.
Section 4.6, p44: Final results for PACIFIC will be published at a later date.	Final **OS** results for PACIFIC will be **available** at a later date		This is not a factual error.

Section 5: Cost effectiveness

Issue 24 Correction / clarity: ERG comment on the company model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.2, p50:			
However, in their current approach using a semi-Markov model, the ERG also observed early crossing of OS and PFS curves as a result of extrapolating the data using the generalised gamma distribution.	This sentence should be deleted or "OS" and "PFS" replaced with "TTP" and "PFS".	This is explained more clearly by the ERG in subsequent sections and relates to the TTP and PFS curves (not OS and PFS).	This has been amended.
[…] whilst the company is correct in pointing out that this issue persists regardless of model choice (OS or PPS), modelling PPS instead of OS is necessarily based on smaller sample sizes used for long-term extrapolation, thereby exacerbating uncertainty	We suggest the removing or revising this sentence, since it is not quite correct and may be misleading to the committee.	The method of extrapolating PFS (the primary driver of long-term OS) is the same between the partitioned survival and the Markov model. In both models, long-term PFS is informed by PFS extrapolations, so there is no difference in sample size. Any difference is driven by the number of patients in the progressed disease state over time.	This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
More specifically, this analysis used data from early progressors, who may have different survival to patients with later progression. Moreover, the PPS data included more patients treated with placebo (who progress earlier), introducing additional bias. The ERG therefore considers that using PPS data instead of OS data may exacerbate the issue of the immaturity of the survival data.	More specifically, this analysis used data from early progressors, who may have different survival to patients with later progression. Moreover, the PPS data included more patients treated with placebo (who progress earlier), introducing additional bias. **The company provided analyses showing that observable patient characteristics for those included in the PPS analyses were not different between durvalumab and placebo. Nevertheless,** the ERG considers that using PPS data instead of OS data may exacerbate the issue of the immaturity of the survival data.	Paragraph did not reflect full evidence provided in response to clarification question B6 (part 'c').	This is not a factual error.
The ERG requested results of a partitioned survival analysis to assess any potential differences in results in both approaches, but this was not provided (as the company did not provide survival curves estimated using PFS and OS data from PACIFIC).	The ERG requested results of a partitioned survival analysis to assess any potential differences in results in both approaches, but this was not provided. **However, the company did provide the PFS and OS survival curves estimated by PACIFIC in their original submission document.**	We did provide survival extrapolations for PFS and OS from the PACIFIC PD-L1 ≥1% group in Appendix M.3. and M.6.	This is not a factual error.

Issue 25 Clarity: reference to timing of CRT

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.3., p51: ERG comment: The main concerns of the ERG relate to: a) modelling a subgroup of the population that was in the final scope issued by NICE, and b) the timing at which the modelled population received CRT.	ERG comment: The main concerns of the ERG relate to: a) modelling a subgroup of the population that was in the final scope issued by NICE, and b) **the type of CRT (sequential vs concurrent) received by the modelled population.**	Clarification on wording, to ensure sentence is not misinterpreted.	This is not a factual error. More clarity is provided right afterwards.

Issue 26 Correction: reference to sequential CRT as "standard practice"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.3. (bullet 'b'), page 51: Although sequential CRT is standard practice in the UK[1], the population in PACIFIC and therefore in the model largely received ≥2 overlapping cycles of platinum-based CRT.	Although sequential CRT was **more-commonly used in the UK in the latest (2016) NLCA**, the population in PACIFIC and therefore in the model largely received ≥2 overlapping cycles of platinum-based CRT.	As stated previously (Issue 8), concurrent / overlapping CRT is the **standard of care** in locally-advanced, unresectable, Stage III patients and recommended in clinical practice guidelines. While sequential CRT was more commonly-used in the analysis of 2016 NLCA data, it is **not** considered "standard practice in the United Kingdom".	This is not a factual error. The ERG refers here to the quote provided by the clinical expert (please refer to Issue 3). The company did not refer to the NLCA audit in this context
*Please also see the following for related comments: Issue 3, Issue 8, Issue 17, and Issue 21			

Issue 27 Correction: PFS extrapolations in CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6 (Progression-free survival), p52−53: The company stated that their PFS extrapolation for SoC was in line with all these data sources, although it did over-estimate PFS for durvalumab and SoC as observed in PACIFIC (CS Tables 32 and 33).	The company stated that their PFS extrapolation for SoC was in line with all these data sources **and "generally performed well"** compared to PACIFIC study data, although it did over-estimate PFS for durvalumab and SoC as observed in PACIFIC (CS Tables 32 and 33) **at three years"**	Mis-representation of the CS	This is not a factual error. Phrasing this as 'in line with' is not mis-representing 'generally performed well'. Also, from figure 33 of the CS it is very clear that the generalized gamma curve does not over-estimate only at three years, it starts at two years already.

Issue 28 Correction: scenario analysis provided in CS for PFS survival distributions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6 (General population mortality), p55: The ERG was surprised that given this uncertainty, the only other tested model was the Gompertz model, which provided very similarly high PFS estimates at the end of the trial period, whilst the second-best fitting and potentially more realistic lognormal distribution was omitted.	The ERG was surprised that given this uncertainty, the only other tested model was the Gompertz model, which provided very similarly high PFS estimates at the end of the trial period, whilst the second-best fitting and potentially more realistic lognormal distribution was omitted **from the main document. The company included scenario analysis exploring the lognormal distribution in an appendix and stated that it was not clinically plausible**	Scenario analysis using all fitted distributions including the log-normal distribution was provided in appendix J.3.	This is not a factual error. The company chose not to present this information in their scenario analyses.

Issue 29 Correction: exploration of spline models in the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6 (General population mortality), p55: The company claimed to have explored spline-based models, but these and the reasons for which they were discarded, were not reported.	The company **did not explore** spline-based models **due to the fit of the standard distributions and the linear shape of the hazard function**	As stated in CS p. 131, "Spline models and more-flexible piecewise modelling approaches were explored, if required, based on the fit of the standard distributions listed above and the shape of the hazard function."	This is not a factual error. The company's proposed amendment would lead to misrepresentation.

Issue 30 Correction: OS benefit of durvalumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.8 (Adverse event related disutility values; part 'c'), p61: Given the fact that a clear benefit of durvalumab on OS has not been demonstrated yet, quality of life becomes all the more important, and therefore it is paramount to take AEs into account as accurately as possible.	Given the fact that **OS data are not fully mature (38% maturity at time of primary analysis)**, quality of life becomes all the more important, and therefore it is paramount to take AEs into account as accurately as possible.	PACIFIC met it's primary endpoint for OS, demonstrating a statistically significant benefit and clinically meaningful benefit for durvalumab versus placebo. Therefore, it is inaccurate to state that "clear benefit of durvalumab on OS has not been demonstrated yet". We have suggested alternative wording to hopefully convey the same point.	This has been amended.

Issue 31 Correction / comment: cost of subsequent treatments in the ERG base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.9 (Cost of subsequent treatments), p63:	We propose adding a sentence to the ERG report stating that discounts associated with subsequent treatments were not accounted for in their base case.	This clarification is important since ICERs will be used for decision-making.	This is not a factual error. The ERG analyses were performed using the same list prices as used in the company submission. Discounts were accounted for in the confidential appendix.
	We identified two errors in the model in the no vial sharing scenario, which affected the ERG base case and all scenario analyses. These were: 1). Weight-based vial use calculations were implemented on fixed dosages for nivolumab and pembrolizumab – the ERG subsequently corrected this in their erratum so no action is required 2). Discounts for pembrolizumab and nivolumab were not applied to the no vial sharing calculations	N/A	This is not a factual error. 1) This was based on a company's modelling error which already has been corrected by the ERG. 2) Discounts are accounted for in the confidential appendix.

Issue 32 Clarity: numbers at risk (OS extrapolation)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.12, p71:			
External validity:	From Table 35 of the CS it can be seen that from the first to the third	We propose adding numbers at risk, as otherwise the sentence is missing	This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
From Table 35 of the CS it can be seen that from the first to the third year, modelled OS for durvalumab goes from 1% underestimation (86% predicted vs 87% observed) to 3% overestimation (63% predicted vs 60% observed).	year, modelled OS for durvalumab goes from 1% underestimation (86% predicted vs 87% observed [n=178 at risk]) to 3% overestimation (63% predicted vs 60% observed [**n=12 at risk**]).	important contextual information.	
Predictive validity: The main concern of the ERG relates to the fact that no firm conclusion could be drawn from the external validation exercised by the company. The company stated that modelled OS broadly matched survival of the available sources, but this was a subjective observation. […] The ERG appreciates the fact that durvalumab is first in class and so all comparison is difficult, but the ERG also considers the company's claims that any model outcome can be considered 'in line' with previous findings not to be substantiated.	We request that Table 35 and Table 36 of the CS are added to the ERG report for completeness.	So as to not omit important contextual information.	This is not a factual error.

Issue 33 Correction: presentation of company scenarios in Table 5.13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3 (Table 5.13), p73−74			
Issue: State transition model instead of partitioned survival analysis Addressed in company analysis: Requested but not provided	Issue: State transition model instead of partitioned survival analysis Addressed in company analysis: PFS and OS curves provided but model not provided	Mis-representation of the company submission / response.	This is not a factual error.
Issue: Utility scores for the PF state is likely high (0.810) Addressed in company analysis: no	Issue: Utility scores for the PF state is likely high (0.810) Addressed in company analysis: yes; the company supplied scenario analysis capping the PF utility score at general population values		This is not a factual error. The company, with their analysis, did not address the high utility value. The ERG does not consider capping to 0.79 which was then kept constant over all ages a sufficient way to address the high utility value.
Issue: Utility decrement for PD state is likely small (-0.034) Addressed in company analysis: no	Issue: Utility decrement for PD state is likely small (-0.034) Addressed in company analysis: yes; the company supplied scenario analysis using 20% decrease in PD utility score compared to PF		This has been amended.

Issue 34 Correction: ERG scenarios

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.1 (Table 6.1), p79:			
Scenario 7 of the ERG analysis	Rename or clarify scenario	We believe the ERG have based this on adverse event tables in the clinical section of the dossier, which reflect the number of **patients** who experience adverse events, not the number of **events**.	This is not a factual error. See also response at issue 11.
Scenario 8 of the ERG analysis	Delete or amend scenario	As far as we can tell, this scenario assumes a utility score of 0.73 for the PF health state and 0 for the PD health state, which does not make sense. It also includes an age decrement, so QALYs become negative in the PD state.	This is indeed an error. This was amended in the model file and results tables.

Section 7: End of life

Issue 35 Correction: applicability of end-of-life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There was no indication in the CS or related documents, of the company claiming that the intervention meets the end of life criteria published by NICE	**The company have indicated that the intervention meets the end of life criteria published by NICE**	We have clearly indicated this in both Document A and Document B. Please see the following extracts as example: Document A, p33: Based on available data on the life expectancy of Stage III NSCLC patients in the UK, and OS data from PACIFIC, which shows a remarkable survival benefit in this population of high unmet need and no alternative treatment options, AstraZeneca believe that end-of-life criteria should apply to this appraisal. Document B, p108: Collectively, the data described above and the statistically-significant OS benefit achieved with durvalumab treatment versus placebo in the PACIFIC ITT population support the applicability of end-of-life criteria for this appraisal.	The text in Section 7 of the ERG report has been amended accordingly.
Life expectancy on current SoC			
While this claim is plausible, the extent of the effect is unclear, i.e. whether this could indicate that patients would have a life expectancy of less than 24	We suggest adding a sentence describing OS on current SoC (i.e. overlapping CRT followed by active follow-up) in the UK cohort of patients. As described in the CS, multiple	Without the broader context of UK data (presented in Document B, Section B.2.13), this sentence is misleading, and does not give the reader a full appreciation of the evidence available.	The text in Section 7 of the ERG report has been amended accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
months.	sources of UK data, including national/multicentre audits, bespoke analysis of Public Health England data, UK RCTs, and clinical expert opinion, suggests that average life expectancy in these patients is less than <24 months.		
Extension to life compared to current SoC			
There is insufficient evidence whether the treatment offers an extension to life as no OS estimate is reported for the durvalumab arm in the relevant PD-L1 ≥1% subgroup	Durvalumab showed a statistically significant OS benefit versus placebo in the PD-L1 ≥1% group (HR 0.54; *P*-value=0.0003). Median OS was not reached in the durvalumab arm in either the ITT population or the PD-L1 ≥1% group; however, the lower bound of the 95% CI (of 34.7 months) for durvalumab indicates a benefit of at least six months versus the median OS for placebo (22.9 months) in the ITT population.	Durvalumab met the primary endpoint in the PACIFIC study, demonstrating a significant survival benefit versus placebo in both the ITT population and the PD-L1 ≥1% group. Therefore, the ERG's statement is factually incorrect. Evidence on the OS benefit of durvalumab is presented in the Section B.2.6 of the CS and also summarised below (information taken from Document A, Table 11): **PACIFIC RCT OS data (durvalumab versus active follow-up)** • ITT – HR (95% CI), *P*-value = 0.68 (0.53, 0.87); 0.003 – Median OS ▪ Durvalumab: NR (95% CI 34.7, NR); lower bound indicates OS benefit of 6 months versus median OS for placebo (below). ▪ Placebo: 28.7 (22.9, NR) • PD-L1 ≥ 1% group – HR (95% CI), *P*-value = 0.54 (0.35,	The text in Section 7 of the ERG report has been amended accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		0.81), *P*=0.003 – Median OS ▪ Durvalumab: NR (95% CI NR, NR); lower bound not reached in durvalumab arm, verses 17.7 months for placebo ▪ Placebo: 29.1 (95% CI 17.7, NR) – OS24 ▪ Durvalumab: 72.8% (95% CI 66.2, 78.4) ▪ Placebo: 53.6% (95% CI 42.5, 63.4)	
However, it should be noted that in the whole trial population, a difference of median survival time of 12 months can be seen (Table 4.6).	We suggest deleting this, as the statement is incorrect	As stated above, median OS was not reached in the in the durvalumab arm in either the ITT population or the PD-L1 ≥1% group. However, the lower bound of the 95% CI (of 34.7 months) for durvalumab indicates a benefit of at least **six** months versus the median OS for placebo (22.9 months) in the ITT population.	The text in Section 7 of the ERG report has been amended accordingly.

Section 8: Overall conclusions

Issue 36 Correction: PACIFIC patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 8.1, page 83: The PACIFIC trial was conducted on patients with confirmed PD-L1 expression on ≥1% of TCs.	The PACIFIC trial was conducted on **locally-advanced, unresectable Stage III NSCLC patients whose disease has not progressed following CRT**	The PACIFIC trial enrolled patients regardless of PD-L1 expression on tumour cells.	Corrected. Sentence now reads: "The PACIFIC trial included patients with confirmed PD-L1 expression on ≥1% of TCs."

Issue 37 Correction: "interim" versus "primary" analysis of OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 8.1, page 83: Furthermore, main results come from interim analysis, e.g. according to the response to the request for clarification the company *"will conduct a final analysis of OS once a maturity of 70% has been reached. OS is an event-driven endpoint; therefore, the timing of this analysis is uncertain"* which will be reached *"when 491 OS events have occurred"*.[1, 24] The current maturity in the relevant	The main results come **from the primary analysis of OS; however**, the company *"will conduct a final analysis of OS once a maturity of 70% has been reached. OS is an event-driven endpoint; therefore, the timing of this analysis is uncertain"* which will be reached *"when 491 OS events have occurred"*.[1, 24] The current maturity in the relevant subgroup is 33.0% for durvalumab and 49.5% for placebo.[27]	As stated previously, PACIFIC met the primary endpoint of OS at the 22 March 2018 DCO – this is the primary analysis of OS.	This is not a factual error. See response to issue 5 for further details.

subgroup is 33.0% for durvalumab and 49.5% for placebo.[27]			
*Please also see the following for related comments: Issue 5 and Issue 20			

Issue 38 Correction: provision of PFS and OS extrapolations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 8.1, page 83: Given the immaturity of survival data, the ERG also has concerns on the appropriateness of the semi-Markov model structure, but the company did not provide an opportunity to explore a partitioned survival approach. Alternative modelling methods, such as spline-based models, remained unexplored in the CS.	Given the immaturity of survival data, the ERG also has concerns over the appropriateness of the semi-Markov model structure**. The company provided PFS and OS extrapolations but did not provide a model with partitioned survival approach**.	We provided the survival extrapolations for PFS and OS from the PACIFIC trial PD-L1 ≥1% group in Appendix M.3. and M.6.	This is not a factual error.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

ERRATUM

This document contains errata with respect to the ERG report following errors that were identified in the model and following the FAC. These matters and the associated changes are described separately below.

The ERG noted an error in the company's implementation of the subsequent treatment (nivolumab and pembrolizumab) vial wastage calculations, which affect the company's no vial sharing scenarios, the ERG base-case and all ERG scenarios. The company had erroneously implemented weight-based vial use calculations on fixed dosages for nivolumab and pembrolizumab. The ERG fixed this error and provides here the corrected results in tables as well as in the text of the report. The ERG also added critique points to the report to reflect this error.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
14-16	Corrected analysis results in text and table overviews
66	Description of error in cost & resource use section
71	Mention of error in scenario analysis critique
75-76	Description of ERG amendments and corrected ERG base-case results
78-81	Amendment of conclusions and ERG base-case and scenario results tables
83-84	Amendment of conclusions

Following the check for factual inaccuracies, a number of changes were made to the ERG report. The table below lists the page to be replaced in the original document and the nature of the change:

Page number:	**Change:**	**Related to FAC issue number**
10	Corrected typo	2
44	Sentence changed to read "The PACIFIC trial included patients with confirmed PD-L1 expression on ≥1% of TCs."	36
50	Replaced OS by TTP	24
61	Amended sentence in section 5.2.8 on adverse event related disutility values	30
74	In table 5.13, changed into 'yes' on issue whether company had addressed small utility decrement for PD state.	33
80	Amended ICER for ERG scenario 8 in Table 6.2 NB: The company incorrectly referred to Table 6.1, however, the results of ERG scenario 8 were actually reported in Table 6.2	34
82	Text amended to reflect that the company indicated that the intervention meets the end of life criteria published by NICE	35
83	Sentence changed to read "The PACIFIC trial included patients with confirmed PD-L1 expression on ≥1% of TCs."	36
94	New references included	35

The ERG noted an additional error in how the utility decrements for treatment and progression were implemented in the probabilistic sensitivity analysis. Specifically, in the probabilistic estimates for these parameters the minus sign was lost, and so the decrements would turn into increments when running the probabilistic analysis. This affected probabilistic ICER estimates. As the company base-case only used a utility decrement for progression which would affect both arms, the ICER was less affected than in the ERG base-case, which also applied a utility decrement for treatment. The ERG fixed this error and provides here the corrected results (for ERG base-case) in tables as well as in the text of the report.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
14-15	Corrected analysis results in text and table overviews
75-76	Description of error, corrected ERG base-case probabilistic results and adjusted CEAC
78	Amendment of conclusions
83	Amendment of conclusions

1. Summary

1.1 Critique of the decision problem in the company's submission

The population defined in the company submission (CS) is adults with locally-advanced, unresectable, stage III non-small cell lung cancer (NSCLC) whose tumours express programmed death-ligand 1 (PD-L1) on ≥1% of tumour cells (TCs) and whose disease has not progressed following platinum-based chemoradiation therapy (CRT). Compared to the National Institute for Health and Care Excellence (NICE) scope, the population is narrower, i.e. only includes patients in the relevant population whose tumours expressed PD-L1.

The intervention (durvalumab 10mg/kg every two weeks intravenously), comparator (standard of care) and outcomes are defined in line with the NICE scope.

1.2 Summary of the key issues in the clinical effectiveness evidence

The CS comprised of a systematic review of the evidence for durvalumab for the treatment of locally advanced unresectable, stage III NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based CRT. The CS and response to clarification provided sufficient details for the Evidence Review Group (ERG) to appraise the literature searches. A good range of databases and conference proceedings were searched. Of concern to the ERG was the restrictive population search, which combined NSCLC terms with disease stage and chemoradiation therapy search terms, and did not include intervention terms as an additional facet. However, this is unlikely to have greatly affected the recall of results.

The CS presented direct evidence from one randomised controlled trial (RCT), PACIFIC, which compared durvalumab to standard of care in adults with locally-advanced, unresectable, stage III NSCLC whose tumours express PD-L1 on ≥1% of TCs and whose disease has not progressed following platinum-based CRT. The population of participants receiving durvalumab represents approx. 67% of the overall population included in PACIFIC. It should be noted that randomisation was not stratified based on PD-L1 status. While reported baseline characteristics, such as age, histology, or smoking status, were balanced between the durvalumab and placebo groups, there are potential problems linked to overinterpretation of subgroup analyses which might impact on the findings.

The PACIFIC trial included only eight patients from the United Kingdom (UK). Another concern to the ERG was the applicability of durvalumab to a population receiving different types of CRT cycles. The CS notes that in the PACIFIC trial concurrent CRT was received prior to beginning treatment with durvalumab. However, the clinical expert highlighted that *"most UK patients receive sequential rather than overlapping treatment"* while *"the efficacy and safety of durvalumab in the PACIFIC study was evaluated after overlapping, rather than sequential, CRT"*. The response to request for clarification suggested the cohort in the PACIFIC trial is generalisable to UK patients with locally-advanced, unresectable, stage III, NSCLC. It also suggested that survival rates might be lower amongst patients treated with sequential CRT approaches than overlapping. However, more pertinently, as the company admitted in the response to clarification, the effectiveness of durvalumab in following sequential therapy remains unknown, i.e. *"…clinicians would expect to see some benefit of durvalumab treatment after sequential CRT, although the magnitude of this remains uncertain in the absence of robust clinical evidence"*. These issues impact on the certainty regarding these findings and might limit the applicability of any findings to UK clinical practice.

treatments was accrued. This cost was informed by the type of treatment, the required treatment dose, the dosing schedule, the unit drug cost at list prices, and the duration of treatment. Resource use for the PF state was modelled in accordance with European Society for Medical Oncology guidelines, and resource use for the PD health state was derived from NICE Technology Appraisal 531 in the metastatic setting. The frequency of occurrence of included AEs was combined with a one-off cost per AE to obtain a total per-cycle cost for each arm. The ERG considered the assumption of perfect vial sharing to be unrealistic in this setting, given the limited number of patients in England and Wales that would be eligible for treatment with durvalumab. This assumption caused the ICER of durvalumab against SoC to be lowered.

Total deterministic life years (LYs) and quality-adjusted life years (QALYs) gained were larger in the durvalumab arm compared to the SoC arm. Incremental QALYs (2.93) were mainly driven by QALY gains in the PF health state. The revised (in response to clarification letter an error was corrected) deterministic incremental cost effectiveness ratio (ICER) amounted to £19,366 per QALY gained. Compared with the deterministic results, the probabilistic sensitivity analysis (PSA) with 1,000 iterations showed lower incremental QALYs and higher incremental costs, which resulted in an increased ICER (£21,601 per QALY gained). Some deterministic sensitivity analyses (DSA) and scenario analyses significantly affected the ICER.

At the clarification stage, the ERG identified several errors in the company's base-case and scenario analyses, including several settings in the controls sheet that were not functioning, and incorrect results of scenario analyses, which were corrected by the company. The ERG was still unable to reproduce one of the company's scenarios added in response to the clarification letter and found an error in another.

Face and internal validity checks were performed by the company and a third-party provider, as well as an expert in the field. Cross validity checks were not performed. OS predictions from the model were validated against PACIFIC, other sources and expert opinion. No firm conclusion could be drawn from the external validation exercise performed by the company using alternative data sources, due to differences in population.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG made various adjustments to the company's base-case, including the fixing of errors, violations and amending the model according to its preferred assumptions (matters of judgement).

1.4.1 Fixing errors

1. Correction of age calculations
2. Correction of nivolumab and pembrolizumab vial sharing calculations
3. Correction of probabilistic utility decrements for progression and treatment

1.4.2 Fixing violations

4. Applying the half-cycle correction also to treatment and administration costs
5. Assumption of no vial sharing
6. Excluding patient characteristics from the PSA

1.4.3 Matters of judgment

7. Use of the lognormal instead of the generalised gamma distribution for modelling durvalumab PFS (and also TTP, as per company's default setting)
8. Treatment waning effect after five-year cut-off instead of 10-year cut-off
9. Applying an age-related utility decrement

10. Including treatment as a covariate in the utility mixed effects model

The probabilistic ERG base-case ICER of durvalumab versus SoC was £52,353 per QALY gained (based on 5,000 iterations). This was higher than the deterministic ERG base-case ICER of £50,238 per QALY gained. This difference was also observed in the company base-case results, and was likely caused by the skewedness of distributions used for modelling PFS.

Table Error! No text of specified style in document.**.1: ICER resulting from ERG's preferred assumption**

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			
Probabilistic ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.25	£52,353
SoC	[redacted]	[redacted]			
ERG = Evidence Review Group = ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care					

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Deterministic scenario analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. Alternative assumptions regarding PFS and treatment waning effects had the most significant impact. The scenario in which PFS distributions were changed into generalised gamma for both arms (as per the company's base-case) resulted in an ICER of £29,302 per QALY gained, whereas applying lognormal distributions for PFS in both arms drove up the ICER to £52,300 per QALY gained. Applying the company's KEYNOTE-024 PPS scenario, but with errors corrected, resulted in an ICER of £59,131 per QALY gained. The scenario exploring a treatment waning effect with three-year cut-off and using the lognormal distribution for both durvalumab and SoC PFS increased the ICER the most (to £64,531 per QALY gained). All other scenarios had a relatively modest impact (<£5,000) on the ERG base-case ICER.

In conclusion, given that the ERG base-case ICER was estimated to be substantially above £40,000 per QALY gained, and only one scenario resulting in ICERs slightly below £30,000 per QALY gained, and the large uncertainty induced by mainly the immature survival data, uncertainty around the cost effectiveness of durvalumab is substantial.

Table Error! No text of specified style in document.**.2: Exploratory analyses undertaken by the ERG**

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			
ERG base-case, no treatment waning effect (0)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.10	£60,928
SoC	[redacted]	[redacted]			
Alternative PFS distributions both arms, generalised gamma (1)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.19	£29,302
SoC	[redacted]	[redacted]			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Alternative PFS distributions both arms, lognormal (2)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.27	£52,300
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as ERG base-case (3a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.35	£48,766
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as scenario 2 (3b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.04	£64,531
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as ERG base-case (4a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.25	£52,833
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as scenario 2 (4b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.41	£47,000
SoC	[redacted]	[redacted]			
PACIFIC PPS, but generalised gamma (5)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.33	£49,868
SoC	[redacted]	[redacted]			
Company's KEYNOTE-024 PPS scenario, with errors corrected (6)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.10	£59,131
SoC	[redacted]	[redacted]			
Adverse events with amended incidence and including impact on HRQoL (7)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,288
SoC	[redacted]	[redacted]			
Alternative PF utility score (8)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.42	£46,539
SoC	[redacted]	[redacted]			
Alternative PF and PD utility scores (9)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.28	£51,587
SoC	[redacted]	[redacted]			
Vial sharing possible at 30% (10)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£49,350
SoC	[redacted]	[redacted]			

ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; PD = progressed disease; PF = progression-free; PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year; SoC = standard of care

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company's submission provided sufficient details for the ERG to appraise the database searches, which were generally transparent and reproducible. An adequate number of databases were searched and a good range of additional searches were conducted for grey literature.

Study design limits to identify economic evaluations, utility data, and costs and resource use data were applied. A good range of intervention terms for durvalumab and comparators were used in the cost effectiveness strategy.

4.6 Conclusions of the clinical effectiveness section

The CS comprised of a systematic review of the evidence for durvalumab for the treatment of locally advanced unresectable, Stage III NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based CRT. The presented evidence included one RCT, the PACIFIC trial.[1]

The PACIFIC trial included patients with confirmed PD-L1 expression on ≥1% of TCs. After randomisation procedures, this resulted in 476 patients in the durvalumab group and 237 patients in the placebo group. However, when focusing on only the patients with confirmed PD-L1 expression on ≥1% of TCs, there were 212 patients in the durvalumab group and 91 patients in the placebo group. While the PACIFIC trial met a multicentre, international design, only eight patients were seeking treatment in the UK. Due to the trial being identified as ongoing, some results are not yet available.

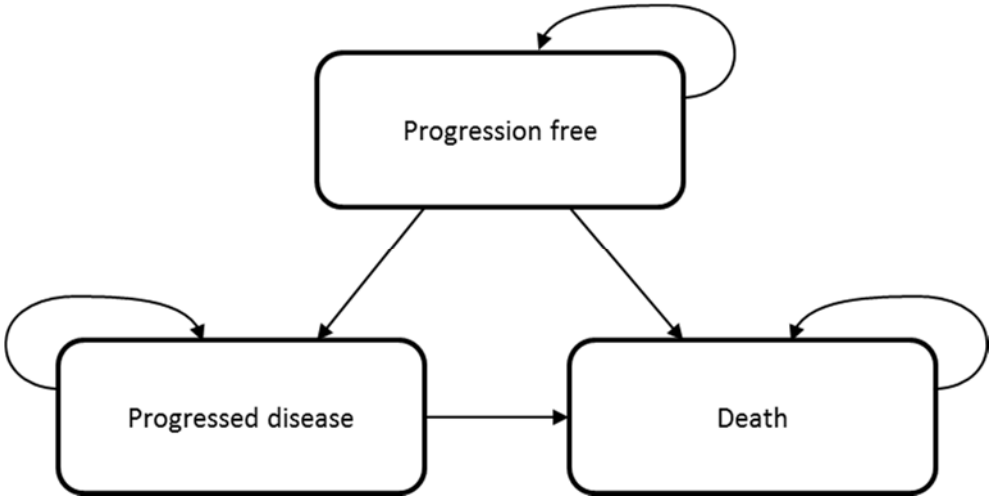
Based on the PACIFIC data there appears to be a benefit in both PFS and OS for durvalumab patients compared with placebo patients, however, the data are immature and there remains substantial uncertainty about the comparative effectiveness.

Common adverse events were reported in both the durvalumab and placebo groups. The common AEs in the durvalumab patients included cough, fatigue, and radiation pneumonitis, whereas patients in the placebo group also included dyspnoea. Overall, more serious adverse events were reported for durvalumab compared to placebo (64/213 (30%) vs. 18/90 (20%)).

Final results for PACIFIC will be published at a later date.

metastatic disease in the same health state. Patients could remain in the progressed disease state, or transition to death (modelled using PPS data for both arms pooled).

Figure Error! No text of specified style in document.**.1: Model structure**



1. Source: Based on Figure 25 of the CS[1]

ERG comment: The main concern of the ERG relates to the chosen modelling approach. The company's argument to use a semi-Markov approach over a partitioned survival analysis approach was based on the fact that the OS curve could fall below the PFS curve in partitioned survival analysis, therefore being prone to logical inconsistencies. However, in their current approach using a semi-Markov model, the ERG also observed early crossing of TTP and PFS curves as a result of extrapolating the data using the generalised gamma distribution. Furthermore, the ERG considers that the approach may be introducing bias. Survival data in PACIFIC are immature, and whilst the company is correct in pointing out that this issue persists regardless of model choice (OS or PPS), modelling PPS instead of OS is necessarily based on smaller sample sizes used for long-term extrapolation, thereby exacerbating uncertainty. Furthermore, the ERG was concerned that the PPS analysis was potentially biased because groups were no longer balanced. In Technical Support Document (TSD) 19 it is stated: *"Only those patients who have experienced a progression event within the trial follow-up will inform estimation of PPS. This could introduce bias in the extrapolation period if patients who progress within the trial are not representative of those who progress later"*.[90] More specifically, this analysis used data from early progressors, who may have different survival to patients with later progression. Moreover, the PPS data included more patients treated with placebo (who progress earlier), introducing additional bias. The ERG therefore considers that using PPS data instead of OS data may exacerbate the issue of the immaturity of the survival data. The ERG requested results of a partitioned survival analysis to assess any potential differences in results in both approaches, but this was not provided (as the company did not provide survival curves estimated using PFS and OS data from PACIFIC). The magnitude and direction of any bias are unclear.

5.2.3 Population

In line with its anticipated marketing authorisation, durvalumab was considered in the cost effectiveness model for the treatment of 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 platinum-based CRT. This was a subgroup from the final scope issued by NICE, which considered the same population regardless of their PD-L1 status.

have not shown a significant increase (i.e. 0.81 and 0.802 for the relevant age category[102, #358]). The difference between 3L and mapped 5L scores of the EQ-5D remains, but was recently shown to be only minor.[103] In addition, utility scores in the base-case model did not decrease with age, since age was not a significant factor in the mixed effects model. However, the mixed effects model only included two age categories (<65 and ≥65) and the ERG does not consider the absence of a significant effect in the short run of the trial to sufficiently support an assumption of utility values being constant over a lifetime time horizon. In summary, utility values for PF were remarkably high and remained high for the full-time horizon of the model. A high utility score for PF lowers the ICER, as in the model patients on durvalumab progressed later than patients receiving SoC. The ERG base-case incorporated an age-related decrement. The ERG also proposed a lower (start) utility score for PF, i.e. 0.73, taken from Ara and Brazier,[102]for people from the general population aged 65-70 with a history of cancer. Although this lower utility value may have better face validity, it does not fully apply to the population in the scope, and therefore it was only incorporated in a scenario.

b) The utility decrement for progressing to PD was -0.034, which could be considered quite modest given the information from the literature review performed by the company as provided in Table 38 of the CS[1], which shows the decrement for progressed disease to vary from -0.4[101] to -0.18[57]. The low decrement that resulted from the mixed effects model could partly be due to the fact that EQ-5D-5L data was only collected up to 30 days after progression. The company confirmed that HRQoL is likely to continue to decline further but also states that their approach was a conservative one since patients in SoC progressed earlier and a high utility value for PD would overestimate QALYs. The ERG agrees with this, but argued that a larger utility decrement would be more reflective of clinical reality. In line with findings by Chouaid et al.[101] in a Stage III/IV NSCLC population, the ERG explored a scenario (applied in addition to the lowered PF utility of 0.73 scenario mentioned above) considering a utility value of 0.67 for first-line progressed disease. Since this scenario was only performed in addition to the scenario with lowered PF utility of 0.73, it implied a decrement for progression of 0.06.
c) Although the mapped utility scores from PACIFIC were higher in the placebo as compared to the durvalumab arm at almost all measurement moments, treatment was found to be statistically insignificant in the mixed effects model and therefore, equal utilities were assumed for durvalumab and SoC. However, the company did not apply utility decrements for AEs in the base-case model as these were assumed to be incorporated in the utilities as observed. When applying utility decrements for AEs in a sensitivity analysis, the company only included these for a selected set of AEs (see also ERG comment in Section 5.2.7). In response to clarification question B18[24], the company provided results of alternative analyses using separate utility values for durvalumab and SoC, both as a factor in the mixed effects model and as the observed average EQ-5D-5L utility scores, which showed increased ICERs (£20,172 and £20,261, respectively). The ERG is concerned that by excluding treatment as a factor in the mixed effects model, and at the same time including disutilities of a limited set of AEs only in a sensitivity analysis, the true impact of adverse events was not appropriately captured in the base-case model or in the scenario. Given the fact that OS data are not fully mature (38% maturity at time of primary analysis), quality of life becomes all the more important, and therefore it is paramount to take AEs into account as accurately as possible. Also grade 1 and 2 AEs will have an impact on the patient's quality of life, but these less severe events were excluded from the analysis. For this reason, the ERG base-case included treatment as a factor in the mixed effects model.

Table Error! No text of specified style in document.**.3: Adverse event related costs and costs of terminal care**

Adverse event	Costs	Per cycle cost durvalumab	Per cycle cost SoC	Reference
Anaemia	£753.02	£0.96	£1.80	NHS reference costs 2016-2017[104]
Hypertension	£388.81	£0.00	£0.00	NHS reference costs 2016-2017[104]
Haemoptysis	£391.98	£0.00	£0.46	NHS reference costs 2016-2017[104]
Hypokalaemia	£151.69	£0.13	£0.46	NHS reference costs 2016-2017[104]
Pneumonia	£1,851.16	£4.79	£5.56	NHS reference costs 2016-2017[104]
Pneumonitis	£391.98	£0.50	£0.23	NHS reference costs 2016-2017[104]
Radiation pneumonitis	£391.98	£0.41	£0.70	Assumed equal to pneumonitis as no HRG available
Endocrinopathy	£443.46	£0.09	£0.00	NHS reference costs 2016-2017[104]
Total per cycle AE costs				
		£6.88	**£9.20**	
Total cost of terminal care				
One-off	**£3,577.18**			TA374 [114], TA351 [32], Marie Curie report [115], NICE CG81 [116]
Source: Based on Tables 49, 50, and 51of the CS [1] CG = clinical guidance; CS = company submission; HRG = Healthcare Resource Group; NICE = National Institute for Health and Care Excellence; SoC = standard of care; TA = technology appraisal				

ERG comment: The main concerns of the ERG relate to: a) the assumption of perfect vial sharing; b) resource use in the PD health state; and c) the criterion for inclusion of subsequent treatments in the model.

a) The assumption of perfect vial sharing that was maintained in the model is not realistic, also given the limited number of patients in England and Wales that would be eligible for treatment with durvalumab (367 annually). The company stated in their response to clarification question B22[24] that indeed, they did not expect perfect vial sharing to occur in clinical practice, but that their base-case was chosen based on recent policy initiatives put in place by NHS-E for IOs.[117] The ERG has looked into these policy initiatives documents and did not find information that, at this time, directly or indirectly supported the assumption of perfect vial sharing. When perfect vial sharing is so clearly not feasible in clinical practice, it should not be considered as base-case. The ERG base-case therefore assumed that there is no vial sharing, with the possibility of 30% vial-sharing in a scenario. The ERG noted an error in the implementation of vial wastage for nivolumab and pembrolizumab, which affected the company's vial sharing scenarios. The company had erroneously employed weight-based dosage calculations on a fixed dose. This was fixed in the revised ERG base-case.

that this was likely driven by the skewedness of the generalised gamma PFS curve. Furthermore, the 1,000 iterations used in the PSA did not achieve stability of results and the ERG used 5,000 iterations.

b) The company included patient characteristics in their PSA, despite intending to exclude them (the model setting designed to exclude them did not work). Given that these parameters reflected first order uncertainty, these should not be incorporated in the PSA. This was corrected in the ERG base-case.

c) The ERG identified several errors in the company's scenario analyses, including several settings in the controls sheet that were not functioning, and incorrect results of scenario analyses in Table 55 of the CS. In response to the clarification letter, the company corrected all of these errors. However, the ERG was unable to reproduce the company's scenario in which the costs for progressed disease reduced by 64% and noted additional errors in the subsequent treatment scenarios. The ERG only presented the revised results of the scenario analyses that were corrected by the company.

5.2.12 Model validation and face validity check

Face validity and internal validity
The model was reviewed by health economists within the company who performed face validity and internal validity checks. A third-party vendor also checked the model for basic validity of model outcomes, application and sources of costs and utilities, clinical inputs, sensitivity analyses and macros. In addition, model structure and approach (partitioned survival vs. semi-Markov) was reviewed by an expert in the field who advised on most appropriate methodology.

Cross validity
No cross validity checking of the model was reported by the company.

External validity
OS predictions from the model for durvalumab and SoC were validated against other sources. OS for SoC was compared to relevant clinical trials, UK real-world data, and clinical expert opinion. OS for durvalumab was compared to OS as observed in PACIFIC (see Table 35 of CS[1]). The company concluded that modelled OS for SoC broadly matched survival from all available sources of evidence, although none of these sources provided any estimates beyond a five year time horizon (except one 10 year estimate from expert opinion by four clinical experts[118]). The company did not state anything about the comparability of modelled OS for durvalumab with PACIFIC data. From Table 35 of the CS it can be seen that from the first to the third year, modelled OS for durvalumab goes from 1% underestimation (86% predicted vs 87% observed) to 3% overestimation (63% predicted vs 60% observed).[1]

In addition, OS for both durvalumab and SoC was compared to values accepted by NICE for immunotherapies in the advanced metastatic NSCLC setting (see Table 36 of CS[1]). Modelled OS was substantially higher (in both durvalumab and SoC) than these comparator values. The company stressed that these studies concerned distinct populations and disease stages, and therefore the predicted effect could be considered in line with that seen for other immunotherapies, when accounting for the greater potential for long-term survival when treating with curative intent.

Predictive validity
No predictive validity checking was reported by the company.

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Health-related quality of life (Section 5.2.8)			
Utility scores for the PF state is likely high (0.810)	+	Scenario	No
No age-related utility decrement	+	Base-case (MJ)	Scenario uses age decrement
Utility decrement for PD state is likely small (-0.034)	-	Scenario	Yes
Utility estimates treatment-independent	+	Base-case (MJ)	Scenario in response to request for clarification[24]
Impact of AEs on HRQoL not reflected	+/-	Scenario	Scenario
Resources and costs (Section 5.2.9)			
Perfect vial-sharing assumption not appropriately justified and likely unrealistic	+	Base-case (FV), scenarios	Yes, scenarios allow for imperfect vial sharing
Resource use for PD health state based on metastatic disease	+	No	Scenario in response to request for clarification[24]
Inclusion criterion for subsequent treatments (>3% in all patients) may lead to biased inclusion per treatment arm	+/-	No	No
Cost effectiveness analyses (Sections 5.2.10 and 5.2.11)			
Patient characteristics included in PSA	+/-	Base-case (FV)	No

2. Footnotes: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator.

3. ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; ICER = incremental cost effectiveness ratio; MJ = matters of judgement; PD = progressed disease; PSA = probabilistic sensitivity analysis

Based on all considerations in Section 5.2 (summarised in Table 5.13), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[119]):

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Fixing errors

1. Incorrect age calculations (Section 5.2.11).
   The ERG used the company's revised model in response to request for clarification[24], in which the error was corrected, as requested.
2. Incorrect vial wastage calculations for nivolumab and pembrolizumab
   The ERG corrected the error by assuming perfect vial sharing throughout for nivolumab and pembrolizumab (given that these are now offered at fixed dosages)
3. Incorrect implementation in PSA of utility decrements for progression and treatment. IN probabilistic mode the minus sign was lost, turning the decrements into increments. The ERG corrected the error.

Fixing violations

4. Half-cycle correction not applied to treatment and administration costs (Section 5.2.5).
   The ERG corrected this.
5. Perfect vial sharing assumption lacks plausibility.
   The ERG assumed no vial sharing.
6. Patient characteristics included in the PSA (Section 5.2.11).
   The ERG corrected this.

Matters of judgment

7. Durvalumab PFS likely over-estimated using the generalised gamma (Section 5.2.6).
   The ERG used the lognormal instead for durvalumab PFS (and also TTP, by company's default setting).
8. Treatment waning effect after 10-year cut-off (Section 5.2.6).
   The ERG used a five-year cut-off instead.
9. No age-related utility decrement used (Section 5.2.8).
   The ERG applied an age-related utility decrement.
10. Treatment was excluded from utility mixed effects model (Section 5.2.8).
    The ERG included treatment as a covariate in the utility mixed effects model.

Table 6.1 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the (deterministic) ERG base-case. The FV and MJ ERG analyses were performed also incorporating the 'fixing error' adjustments given that the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

5.3.1 ERG base-case results

The results of the deterministic ERG base-case showed that incremental costs were [redacted] and incremental QALYs were 1.32 (Table 5.14). This resulted in an ICER of £50,238, which was mainly driven by using the lognormal distribution for extrapolation of durvalumab PFS, using a five-year cut-off for treatment waning effect, and assuming no vial sharing (see Table 6.1).

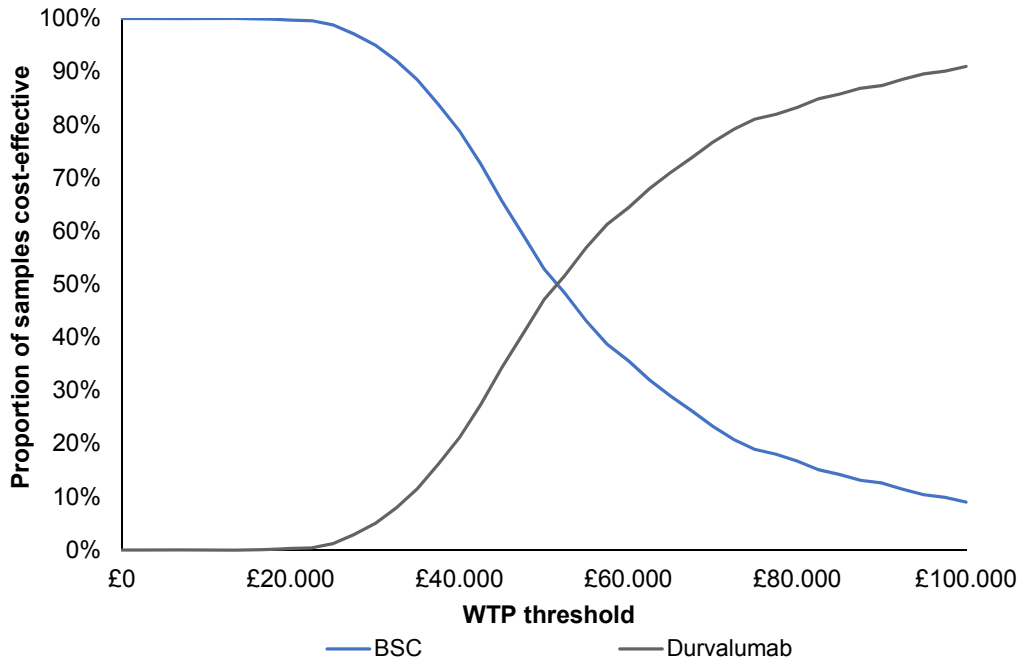
Compared with the deterministic ERG base-case results, the ERG PSA with 5,000 iterations resulted in lower incremental QALYs and slightly lower incremental costs, which resulted in an increased ICER (£52,353). The company's base-case also showed a marked difference between the deterministic and probabilistic ICERs. In their response to clarification question B24d[24] the company argued that this difference was due to the skewedness of the generalized gamma PFS curve, which caused skewed QALY results, but slightly differently so for durvalumab and SoC. At a later stage, the ERG noted an error in the model in the implementation of the utility decrements for progression and treatment, turning these into increments when running the PSA. The ERG fixed this for the ERG analyses. The company's probabilistic ICER results still contain the error but as no treatment decrement was applied in the company base-case, only the effect of the progression decrement remains. The cost effectiveness acceptability curve showed that durvalumab approximately had a 5.0% and 47.1% probability of being cost effective at willingness to pay (WTP) thresholds of £30,000 and £50,000 respectively (Figure 5.6).

Table Error! No text of specified style in document.**.4: ERG base-case results**

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			
Probabilistic ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.25	£52,353
SoC	[redacted]	[redacted]			

ERG = Evidence Review Group = ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care

Figure Error! No text of specified style in document.**.2: ERG base-case cost effectiveness acceptability curve**



- resulted in PFS estimates above those observed in PACIFIC at three years, with the PACIFIC estimate notably being derived from small numbers of patients at risk and immature data. This model choice caused ICERs of durvalumab versus SoC to be lower than other model choices. This issue was exacerbated by the choice of time-point at which treatment waning was modelled (10 years), which was deemed by the ERG as highly uncertain, not appropriately validated, and potentially late, additionally lowering ICERs of durvalumab versus SoC in the CS. Alternative modelling methods, such as spline-based models, remained unexplored in the CS.

- There was a discrepancy between AEs causally related to treatment in PACIFIC, which were mostly higher for the durvalumab arm than in the placebo arm, and AE incidence in the model, which was comparable between treatments, that remained unexplained, likely lowering ICERs of durvalumab versus SoC.

- The ERG considered utility values for both (progression-free and progressed disease) health states to be potentially over-estimated, being comparable to those in the general population and not adjusted by general population age utility estimates. Excluding treatment as a factor in utility estimation and excluding the HRQoL impact of AEs contributes to QALY gains being likely over-estimated. These assumptions on balance likely lowered ICERs of durvalumab versus SoC.

- The ERG considered the assumption of perfect vial sharing to be unrealistic in this setting, given the limited number of patients in England and Wales that would be eligible for treatment with durvalumab. This assumption caused the ICER of durvalumab against SoC to be lower than alternative assumptions.

- The ERG made various adjustments to the company base-case. The probabilistic ERG base-case ICER of durvalumab versus SoC was £52,353 per QALY gained (based on 5,000 iterations). The difference was likely caused by the skewedness of distributions used for modelling PFS.

- Deterministic scenario analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. Alternative assumptions regarding PFS and treatment waning effects had the most significant impact. The scenario in which PFS distributions were changed into generalised gamma for both arms (as per the company's base-case) resulted in an ICER of £29,302 per QALY gained, whereas applying lognormal distributions for PFS in both arms drove up the ICER to £52,300 per QALY gained. Applying the company's KEYNOTE-024 PPS scenario, but with errors corrected, resulted in an ICER of £59,131 per QALY gained. The scenario exploring a treatment waning effect with three-year cut-off and using the lognormal distribution for both durvalumab and SoC PFS increased the ICER the most (to £64,531 per QALY gained). All other scenarios had a relatively modest impact (<£5,000) on the ERG base-case ICER.

- In conclusion, given that the ERG base-case ICER was estimated to be substantially above £40,000 per QALY gained, and only one scenario resulting in ICERs slightly below £30,000 per QALY gained, and the large uncertainty induced by mainly the immature survival data, uncertainty around the cost effectiveness of durvalumab is substantial.

6. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Analyses undertaken by the ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.2. These are all conditional on the ERG base-case. The analyses numbers in Tables 6.1 and 6.2 correspond to the analyses numbers reported in Section 5.3. The submitted model file contains technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table Error! No text of specified style in document.**.5: Deterministic ERG base-case**

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	2.94	£19,320
SoC	[redacted]	[redacted]			
Fixing error (1, age calculations)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.93	£19,366
SoC	[redacted]	[redacted]			
Fixing violations (3, half-cycle correction for treatment costs)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.93	£20,001
SoC	[redacted]	[redacted]			
Fixing violations (4, no vial sharing) and error 2 (vial wastage)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.93	£20,647
SoC	[redacted]	[redacted]			
Matter of judgement (6, lognormal for durvalumab PFS)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£45,878
SoC	[redacted]	[redacted]			
Matter of judgement (7, treatment waning at 5 years)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.39	£24,391
SoC	[redacted]	[redacted]			
Matter of judgement (8, age-related utility decrement applied)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.81	£20,237
SoC	[redacted]	[redacted]			
Matter of judgement (9, treatment included in utility model)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.82	£20,172
SoC	[redacted]	[redacted]			
ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			

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

Table Error! No text of specified style in document.**.6: Deterministic scenario analyses conditional on ERG base-case**

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,238
SoC	[redacted]	[redacted]			
ERG base-case, no treatment waning effect (0)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.10	£60,928
SoC	[redacted]	[redacted]			
Alternative PFS distributions both arms, generalised gamma (1)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.19	£29,302
SoC	[redacted]	[redacted]			
Alternative PFS distributions both arms, lognormal (2)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.27	£52,300
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as ERG base-case (3a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.35	£48,766
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as scenario 2 (3b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.04	£64,531
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as ERG base-case (4a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.25	£52,833
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as scenario 2 (4b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.41	£47,000
SoC	[redacted]	[redacted]			
PACIFIC PPS, but generalised gamma (5)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.33	£49,868
SoC	[redacted]	[redacted]			
Company's KEYNOTE-024 PPS scenario, with errors corrected (6)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.10	£59,131
SoC	[redacted]	[redacted]			
Adverse events with amended incidence and including impact on HRQoL (7)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,288
SoC	[redacted]	[redacted]			
Alternative PF utility score (8)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.42	£46,539
SoC	[redacted]	[redacted]			
Alternative PF and PD utility scores (9)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.28	£51,587
SoC	[redacted]	[redacted]			
Vial sharing possible at 30% (10)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£49,350
SoC	[redacted]	[redacted]			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; PD = progressed disease; PF = progression-free; PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year; SoC = standard of care					

7. End of life

NICE end of life considerations apply when two criteria are satisfied:

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months; and
2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current NHS treatment.

Table 27 of the CS summarises available data which might support the applicability of end-of-life criteria.[1] The data are summarised below.

Criterion 1: According to the CS, "in the PACIFIC study, median OS in the placebo arm was 28.7 months in the ITT population, and 29.1 months in the PD-L1 ≥1% group of patients".[1] However, the company highlighted that *"data may not reflect real-world survival outcomes in the UK cohort of locally-advanced, unresectable, Stage III NSCLC patients …*(as)*…intensive management of patients and other factors that are unique to a clinical trial setting can improve patient outcomes relative to what is known / expected in real-world settings"*.[1]

In support of this statement, the CS presented some UK-specific data:

- National Lung Cancer Audit (2016 audit period)[7]: Average 1-year survival rate from diagnosis of stage III patients = 42.5%
- Moller et al. 2017[120]: Patients treated with radical radiotherapy with 2-year survival probability from diagnosis <25%
- Royal College of Radiologists audit[13]: Median OS following radical radiotherapy = 22 months, 2-year survival rate = 44%; 2-year survival rate (overlapping CRT) = 46%
- Public Health England[121]: Median OS for patients with unresected stage III who had received overlapping CRT = 20.7 months
- SOCCAR RCT[122]: Median OS from start of overlapping / sequential CRT = 24.3 / 18.4 months
- Expert opinion (mean of 10 responses)[20] = 22.3 months (median OS)

ERG comment: While this claim is plausible, it should be noted that for NICE committees mean values are preferable to median values when measuring OS time.[123] Therefore, the extent of the possible effect is unclear, i.e. whether the reported data (including median OS) could indicate that patients would have a life expectancy of less than 24 months (mean OS). There is additional uncertainty due to the immaturity of the OS data reported in PACIFIC.

Criterion 2: The company highlights that PACIFIC found *"significantly extended OS relative to placebo in the PD-L1 ≥1% group"*, presenting two different estimates: HR 0.54, 95% CI 0.35 to 0.81, section B.2.6; and HR 0.53, 95% 0.36 to 0.77, Table 27.[1]

ERG comment: There is insufficient evidence whether the treatment offers an extension to life as no OS estimate is reported for the durvalumab arm in the relevant PD-L1 ≥1% subgroup (Table 4.6). However, it should be noted that in the whole trial population, a difference of median survival time of 12 months can be seen when comparing the lower 95% CIs (Table 4.6). However, this again is based on median survival time (when normally mean is preferable) and is unlikely to be *"sufficiently robust"*.[124] Furthermore, there is additional uncertainty due to the immaturity of the OS data reported in PACIFIC; results in the relevant subgroup might become available in future analyses.

8. Overall conclusions

8.1 Statement of principal findings

The CS comprised of a systematic review of the evidence for durvalumab for the treatment of locally advanced unresectable, Stage III NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed after platinum-based CRT.

The main database searches in the CS were on the whole transparent and reproducible, and a good range of resources were used. Better use of synonyms could have been applied in some database searches to aid the retrieval of relevant references. The presented evidence included one RCT, PACIFIC.

The PACIFIC trial included patients with confirmed PD-L1 expression on ≥1% of TCs. After randomisation procedures, this resulted in 476 patients in the durvalumab group and 237 patients in the placebo group. However, when focusing on only the patients with confirmed PD-L1 expression on ≥1% of TCs, there were 212 patients in the durvalumab group and 91 patients in the placebo group. While the PACIFIC trial met a multi-centre, international design, only eight patients were seeking treatment in the UK.

Based on the PACIFIC data there appears to be a benefit in both PFS and OS for durvalumab patients compared with placebo patients, however, the data are immature and there remains substantial uncertainty about the comparative effectiveness.

Common adverse events were reported in both the durvalumab and placebo groups. The common AEs in the durvalumab patients included cough, fatigue, and radiation pneumonitis, whereas patients in the placebo group also included dyspnoea. Overall, more serious adverse events were reported for durvalumab compared to placebo (64/213 (30%) vs. 18/90 (20%)).

Due to the PACIFIC trial being ongoing, final results will be confirmed at a later date.

Economic evaluation

The ERG made various adjustments to the company's base-case. The probabilistic ERG base-case ICER of durvalumab versus SoC was £52,353 per QALY gained (based on 5,000 iterations). This was higher than the deterministic ERG base-case ICER of £50,238 per QALY gained. The difference was likely caused by the skewedness of distributions used for modelling PFS.

Deterministic scenario analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. Alternative assumptions regarding PFS and treatment waning effects had the most significant impact. The scenario in which PFS distributions were changed into generalised gamma for both arms (as per the company's base-case) resulted in an ICER of £29,302 per QALY gained, whereas applying lognormal distributions for PFS in both arms drove up the ICER to £52,300 per QALY gained. Applying the company's KEYNOTE-024 PPS scenario, but with errors corrected, resulted in an ICER of £59,131 per QALY gained. The scenario exploring a treatment waning effect with three-year cut-off and using the lognormal distribution for both durvalumab and SoC PFS increased the ICER the most (to £64,531 per QALY gained). All other scenarios had a relatively modest impact (<£5,000) on the ERG base-case ICER.

In conclusion, given that the ERG base-case ICER was estimated to be substantially above £40,000 per QALY gained, and only one scenario resulting in ICERs slightly below £30,000 per QALY gained, and the large uncertainty induced by mainly the immature survival data, uncertainty around the cost effectiveness of durvalumab is substantial.

8.2 Strengths and limitations of the assessment

Overall, the CS reported searches were clearly reported and reproducible. The selection of databases searched was adequate and a good range of additional resources were included. Study design limits to identify economic evaluations, utility data, and costs and resource use data were applied. A good range of intervention terms for durvalumab and comparators were used in the cost effectiveness strategy.

A substantial source of uncertainty lies in the generalisability of PACIFIC data to the UK setting, as PACIFIC pertains predominantly to prior overlapping CRT, whereas in clinical practice in the UK, mostly sequential CRT is applied. In addition, the PD-L1≥1% subgroup and TTP and PPS analyses were performed post-hoc. Furthermore, main results come from interim analysis, e.g. according to the response to the request for clarification the company *"will conduct a final analysis of OS once a maturity of 70% has been reached. OS is an event-driven endpoint; therefore, the timing of this analysis is uncertain"* which will be reached *"when 491 OS events have occurred"*.[1, 24] The current maturity in the relevant subgroup is 33.0% for durvalumab and 49.5% for placebo.[27]

The company submission was largely in line with the NICE reference case. Utility scores were estimated using a mixed effects model based on observed EQ-5D data in the PACIFIC study.

The model was, in general, well-built and transparent. Apart from their base-case, the company provided opportunities for exploratory analyses using alternative data derived from clinical trials in similar populations.

A main limitation was the immaturity of survival data in the PACIFIC subpopulation, and the inherent uncertainty in PFS and PPS extrapolations. The ERG considers particularly durvalumab PFS to be overestimated, even more so because the company chose to incorporate treatment waning only at 10 years. Given the immaturity of survival data, the ERG also has concerns on the appropriateness of the semi-Markov model structure, but the company did not provide an opportunity to explore a partitioned survival approach. Alternative modelling methods, such as spline-based models, remained unexplored in the CS.

Lastly, the utility scores used in the model do not seem representative of the patient population. The ERG considers the utilities for both (progression-free and progressed disease) health states to be an overestimate.

8.3 Suggested research priorities

PACIFIC is an ongoing trial so more information will be available to reduce the uncertainties in progression-free and overall survival, and other outcomes

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Correspondence with clinical expert (Prof. Matthew Hatton – TC 26/11/2018)

Prior CRT

Questions to expert	The durvalumab PACIFIC trial only recruited people after two or more overlapping cycles of platinum-based prior chemoradiation therapy (CRT). It has been suggested by both the company and the Evidence Review Group (ERG) that in UK clinical practice the majority of patients receive sequential CRT not overlapping. • In clinical practice, what proportion of people with unresectable stage III NSCLC receive overlapping CRT? • Do clinical outcomes (such as overall survival) differ based on type of CRT received? If so, how? • If the clinical outcomes do differ between the different types of CRT, are these differences likely to persist after a subsequent treatment is given (for example, treatment with other immunotherapy post-progression)? • In clinical practice, how many cycles of platinum-based CRT are patients likely to receive before durvalumab? • Overall do you think the results of the PACIFIC trial are generalisable to UK clinical practice?
Summary of clinical expert input	• In the UK, around 10-20% of patients would be suitable for overlapping CRT; the majority of patients receive sequential CRT • You would expect to see only a small difference (around 4-5%) in overall survival outcomes between overlapping and sequential CRT • The majority of patients with Stage 3 NSCLC receiving CRT would have more than 1 cycle • The PACIFIC trial is generalisable to UK clinical practice

Subsequent treatments

Questions to expert	• In clinical practice, what proportion of patients are likely to go on to receive treatments after durvalumab/standard of care? • Which treatments are patients likely to receive after durvalumab, or after standard of care? • What is the likely duration of these treatments?
Summary of clinical expert input	• Subsequent treatment would be offered on relapse, so the proportion of patients expected to receive subsequent treatment after durvalumab depends on its effectiveness • Patients would be likely to receive the same type of subsequent treatment after both durvalumab and chemotherapy • The majority of patients who receive subsequent treatment (around 75%)are likely to have chemotherapy 2nd line (likely to be 3 or 4 cycles) • If there is a short interval between initial CRT and subsequent treatment, this chemotherapy is likely to be a taxane; if it is a longer interval, patients may have a rechallenge with platinum based chemotherapy • The effectiveness of subsequent immunotherapies after initial immunotherapy (with durvalumab) is unknown • A small proportion of people may receive erlotinib or afatinib as subsequent treatments if they had the appropriate mutations

Treatment effect duration

Questions to expert	In its base case, the company assumed that the effects of treatment with durvalumab would continue up to 10 years. It explored 3 years, 5 years and lifetime treatment effect durations as scenario analyses

	• What would you expect the duration of treatment effect with durvalumab to be?
Summary of clinical expert input	• Treatment effect duration of durvalumab is unlikely to be more than 5 years

Progression-free survival

Questions to expert	The company and ERG have used different statistical analyses for predicting progression free survival over time. In your opinion what is a realistic proportion of patients remaining progression free with durvalumab and standard care at 3, 5 and 10 years?

	Company's estimates		**ERG's estimates**	
Years	**Durvalumab**	**SoC**	**Durvalumab**	**SoC**
3	46%	17%	37%	17%
5	40%	12%	26%	12%
10	34%	8%	14%	8%

Summary of clinical expert input	• The ERG's extrapolation of the durvalumab progression-free survival data is realistic (predicting 37%, 26% and 14% of patients alive at 3, 5 and 10 years respectively)

Post-progression survival

Questions to expert	The company pooled the post-progression survival estimates for durvalumab and standard of care, assuming that treatment only affects progression-free survival (this was accepted by the ERG in its base-case). • Is it realistic to assume equal treatment effect of durvalumab and standard of care post-progression?

<table>
<tr><td></td><td>
In your opinion, what is a realistic proportion of patients remaining alive post-progression with durvalumab and standard of care at 1, 3 and 5 years?
<table>
<tr><th></th><th>Company's estimates</th></tr>
<tr><th>Years</th><th>Durvalumab & SoC</th></tr>
<tr><td>1</td><td>62%</td></tr>
<tr><td>3</td><td>24%</td></tr>
<tr><td>5</td><td>9%</td></tr>
</table>
</td></tr>
<tr><td>Summary of clinical expert input</td><td>
It is realistic to assume equal treatment effect of durvalumab and standard of care post-progression
The company's extrapolation of post-progression survival is realistic (predicting 62%, 24% and 9% of patients alive post-progression at 1, 3 and 5 years respectively)
</td></tr>
</table>

Utilities

Questions to expert	The company used a utility value of 0.810 for the people who remain progression-free, and a value of 0.776 for people with progressed disease. The ERG suggested that these might be too high (because the progression-free utility is higher than the value for the same age group in the general population). It explored scenarios with a utility value of 0.73 for people who remain progression-free state and 0.67 for people with progressed disease. • What is the appropriate utility value for the progression-free state in this setting? • What is the appropriate utility value for the progressed disease state in this setting?
Summary of clinical expert input	• It is unlikely that patients in the progression-free state have the same utility value as members of the general population in the same age cohort • You would expect to see a substantial difference in utility between the progression-free and progressed disease states

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

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

1. Summary of technical report

1.1 This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements of the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the key evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

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

1.2 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale. Scientific judgments that have been updated after engagement are highlighted in **bold** below.

1.3 In summary, the technical team considered the following:

- Issues with the generalisability of the trial to clinical practice increases the uncertainty in cost-effectiveness estimates, **particularly in relation to the comparability of overlapping and sequential chemo-radiation therapy** (see Issue 1). However, the PACIFIC trial remains the best available source of evidence for this appraisal.
- In the absence of evidence for the treatment effect duration, it is preferable to model a duration of 3 to 5 years (see Issue 2).
- A log-normal extrapolation for the durvalumab arm provides more plausible estimates of progression-free survival than the generalised-gamma extrapolation (see Issue 3).
- **Where appropriate, it is reasonable to 'cap' hazard functions of progression-free survival extrapolations so that the risk in durvalumab arm is always less than or equal to the risk in the standard of care arm to prevent clinically implausible results when changing treatment effect duration (see Issue 2 and 3).**
- An exponential extrapolation of post-progression survival is acceptable (see Table 2).
- Age-related utility decrements should be captured in the model (see Issue 4).
- **It is preferable to use health state utility values from the PACIFIC trial (with treatment-related decrement applied) for both progression-free and progressed disease health states** (see Issue 4).
- It is preferable to model health state utility values as being treatment specific (see Table 3).
- A vial sharing assumption for durvalumab is not realistic (see Table 3).

1.4 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The company's marketing authorisation is based on a subgroup of the company's pivotal trial which has the potential for bias because it was determined post-randomisation.
- The generalisability of the trial due to patient demographics could mean that the results might not reflect patients in the UK (also related to Issue 1). However, the technical team consider that PACIFIC remains the best available source of evidence for this appraisal.
- Overall survival is captured implicitly through the modelling of post-progression survival, rather than being modelled explicitly. This increases uncertainty (as the extrapolation is based on a smaller sample size), and also has a risk of bias. However, this cannot be resolved without restructuring the model (see Table 2).

1.5 The analyses included in this report do not include the commercial arrangements for some of the relevant subsequent treatments (nivolumab, pembrolizumab, afatinib, erlotinib) because these are confidential and cannot be reported here. Using the technical team's preferred assumptions and including these commercial arrangements is likely to increase the ICERs.

1.6 Taking these aspects into account, the technical team's preferred assumptions result in incremental cost-effectiveness ratios (ICERs) ranging between **£48,649 to £48,631per QALY** gained.

1.7 Durvalumab is unlikely to meet the end of life criteria specified in NICE's guide to the methods of technology appraisal (see Issue 7).

1.8 Durvalumab is unlikely to meet the criteria for inclusion in the Cancer Drugs Fund because there is no plausible potential for it to be cost-effective. However, if there was a plausible potential for it to be cost-effective, data collection (more mature data from the PACIFIC trial and

data from future trial exploring the sequential CRT population) would resolve uncertainty. (see Issue 8).

1.9 All relevant benefits associated with durvalumab are adequately captured in the model (see Table 3)

1.10 No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts (Table 3).

2. Key issues for consideration

Issue 1 – Overlapping vs sequential prior chemoradiation therapy (CRT) and generalisability of PACIFIC trial

Questions for engagement	1. Are the results of the PACIFIC trial generalisable to clinical practice in the NHS? 2. Are clinical outcomes likely to differ between overlapping and sequential chemoradiation therapy? Does this affect the generalisability of the trial?
Background/description of issue	Durvalumab's marketing authorisation does not specify the number of cycles of prior chemoradiation (CRT) therapy, or whether cycles had to be overlapping (concurrent) or sequential (i.e. whether chemotherapy could be given at the same time as radiotherapy, or before radiotherapy). The PACIFIC trial only recruited people after two or more overlapping cycles of platinum-based CRT. The company submission highlights that overlapping cycles of CRT may improve overall survival (OS) compared to sequential cycles. However, it cites evidence that the majority of patients receive sequential CRT in UK clinical practice (66%). The company have acknowledged the challenges of generalising PACIFIC to the UK population, and are conducting future studies (PACIFIC 6) to explore the effectiveness of durvalumab in people with prior CRT given in sequential cycles. The Evidence Review Group (ERG) is concerned that the results of the PACIFIC trial may not be generalisable to UK clinical practice because of the difference in administration of

	prior CRT (i.e. overlapping rather than sequential CRT), and the potential effect of this on survival outcomes and therefore quality-adjusted life years (QALYs). However, clinical expert advice indicates that the differences in survival outcomes for overlapping compared to sequential CRT is likely to be small.
Why this issue is important	The difference between types of prior CRT could affect the generalisability of trial results to clinical practice in the NHS because: • patients who are selected for overlapping CRT may be fitter, and so have better survival outcomes than patients who are not suitable for overlapping CRT • overlapping CRT may improve survival over sequential CRT • if the relevant population has a worse prognosis than the trial population, any relative survival gain is likely to be lower (therefore reducing the number of incremental life years gained by durvalumab). Issues with generalisability increase the uncertainty in the model and resulting estimates.
Technical team judgement before engagement	Problems with the generalisability of the trial to clinical practice increases the uncertainty in cost-effectiveness estimates. However, PACIFIC remains the best available source of evidence for this appraisal. Based on clinical expert advice, the difference in outcomes between overlapping and sequential CRT is likely to be small. Uncertainty about the initial fitness of patients who are suitable for overlapping CRT compared to the initial fitness of patients who receive sequential CRT could be explored using national audit data.
Summary of comments	Comments received from company: • Clinical experts consulted by the company agree that difference in outcomes between overlapping and sequential CRT is likely to be small

	• Data from the durvalumab early access programme show that the majority of patients receive durvalumab after overlapping CRT • Effectiveness of durvalumab after sequential CRT will be explored in PACIFIC-6 RCT and PACIFIC-R follow up of early access programme [redacted] • Company present a scenario in which a risk derived from the Auperin et al. (2010)[1] meta-analysts and the START study (2014)[2] is applied to PACIFIC data to reflect any difference in effectiveness of sequential CRT Comments received from Roy Castle Lung Cancer foundation: • Majority of people in the UK receive sequential CRT, but practice would change if durvalumab was recommended in people with prior overlapping CRT • Agree that difference in outcomes between types of CRT are likely to be small Comments received from BTOG-NCRI-ACP-RCP-RCR: • PACIFIC is generalisable to patients fit for overlapping CRT • However, the 'sequential' cohort are likely to be older and have more co-morbidities than the PACIFIC cohort, leading to a worse performance status • Toxicity of durvalumab in the sequential cohort is unknown and should not be extrapolated from PACIFIC • Studies such as PACIFIC-6 are needed to provide robust data for the sequential cohort

[1] Meta-analysis of randomised trials directly comparing overlapping and sequential CRT, published by the NSCLC Collaborative Group. The study showed a significant PFS benefit associated with overlapping versus sequential CRT (HR, 0.90; 95% CI, 0.79 to 1.01).
[2] Randomised controlled trial of tecemotide (L-BLP25) versus placebo after CRT for stage III non-small-cell lung cancer

	ERG considerations on new evidence received during technical engagement: • ERG emphasises the uncertainty about the generalisability of PACIFIC (due to the comparability of sequential and overlapping CRT) • Comparisons between sequential and overlapping CRT are largely based on expert opinion rather than robust clinical trial data • Consider that the company's approach for exploring cost-effectiveness of durvalumab in the sequential CRT population is reasonable
Technical team scientific judgement after engagement	The results of PACIFIC are considered to be generalisable to patients who have had prior overlapping CRT. However, there remains uncertainty about the comparability of overlapping and sequential prior CRT. People who have sequential CRT might be older and have worse performance than people who have overlapping CRT. There is limited robust trial evidence to show that durvalumab has equivalent effectiveness in the sequential CRT population, although some of the clinical expert opinion supports this. This issue could be addressed with data from future trials. This may be relevant when considering eligibility for the Cancer Drugs Fund (see Section 8).

Issue 2 – Treatment effect duration

Questions for engagement	3. Is a 3 to 5 year treatment effect duration for durvalumab appropriate?
Background/description of issue	4. In its original base-case, the company assumed a duration of treatment effect of 10 years after the start of treatment (that is, treatment is continued for a maximum of 12 months in line with the stopping rule in the marketing authorisation but the effects of treatment last an additional 9 years). It explored 3 years, 5 years and lifetime treatment effect durations as scenario analyses.

	The ERG considered that the durvalumab treatment effect duration was uncertain because the overall survival (OS) data from PACIFIC were immature (26.9 and 21.1 months median follow-up for durvalumab and placebo respectively). It considered that 10 years was one of the most optimistic scenarios explored by the company; the 10 year assumption was not validated by the expert opinion presented in the company's submission or by the OS modelled in other appraisals in the metastatic setting. The ERG considered that a 5 year duration was more realistic, in line with the committee's preferred assumptions in other NSCLC appraisals (for example, NICE technology appraisal guidance on atezolizumab for NSCLC after chemotherapy [TA520] in which committee's preferred assumption was a 3 to 5 year treatment effect duration). The ERG modelled a 5 year duration using different distributions to extrapolate progression-free survival in each arm (see Issue 3). However, this gave counter-intuitive results in some instances (with the ICER decreasing when the treatment effect duration decreases). This is because the hazard of an event in the standard care arm could be lower than the hazard in the durvalumab arm (so an earlier treatment effect cut-off lowers the hazard of progression in the durvalumab arm). The ERG acknowledges that this is not ideal, but accepts the company's method of modelling of treatment effect duration, as the alternative options are clinically implausible (e.g. a sudden drop in the number of patients not progressed or dead). Clinical expert advice indicated that assuming a treatment effect duration of up to 5 years was realistic. The technical team is aware that in previous lung cancer appraisals (such as TA520), the committee have preferred to assume a 3 to 5 year treatment effect duration, commencing after treatment discontinuation. However, these appraisals have typically featured a 2 year stopping rule (rather than 1 year). The technical team consider that it is possible that the treatment effect duration for durvalumab may be lower than that assumed in previous

	appraisals. However, taking into account the clinical expert opinion, the technical team considers that a 3 to 5 treatment effect duration is acceptable.
Why this issue is important	Decreasing the assumed treatment effect duration from 10 years to 5 and 3 years increased the company's original base-case ICER by around £5,000 and £10,000 respectively (based on the company's modelled progression-free survival extrapolations).
Technical team judgement before engagement	Lack of mature OS data means there is substantial uncertainty about durvalumab's treatment effect duration. The technical team would like to see more evidence to support the 10 year duration assumption. Lacking this, it is preferable to model a more conservative duration of 3 to 5 years (in line with clinical expert advice and previous appraisals in this disease area). The effect of different assumed treatment effect durations depends on the choice of survival extrapolations used in the model; due to uncertainty about the extrapolation of progression-free survival (see Issue 3), the technical team were unable to conclude the likely effect of the 3 to 5 year treatment effect duration assumption on the ICER.
Summary of comments	Comments received from company: • Treatment effect waning was not seen in the PACIFIC follow up period (~41 months) which implies that a treatment effect duration of 3 years is not realistic • Updated base-case model assumes 5 year treatment effect duration (with 3 and 10 year treatment durations explored as scenario analyses) • In relevant scenarios, hazard functions are 'capped' so that risk in durvalumab arm is always less than or equal to the risk in the SoC arm to prevent spurious results when varying treatment effect duration (see Issue 3)

	• Although the stopping rule differs from other NSCLC appraisals, a prolonged treatment effect is still plausible because durvalumab is used at an earlier stage and combines the treatment effect from CRT • Uncertainty can be addressed with PACIFIC follow-up data ([redacted]) if durvalumab was recommended via the Cancer Drugs Fund Comments received from Roy Castle Lung Cancer foundation: • A treatment effect duration of up to 5 years seems reasonable
Technical team scientific judgement after engagement	It is reasonable to assume a treatment effect duration of at least 3 years (based on the PACIFIC trial data). It is plausible that the actual treatment effect duration could be up to 5 years. This uncertainty could be resolved with more PACIFIC follow-up data (and with additional data collection if durvalumab was recommended via the Cancer Drugs Fund).

Issue 3 – Progression-free survival (PFS) extrapolation

Questions for engagement	5. Is it reasonable to use a model that predicts that 38%, 27% and 17% of the durvalumab arm would be progression free at 3, 5 and 10 years respectively? (This is the log-normal distribution used to extrapolate PFS in the durvalumab arm)[3] 6. Is it reasonable to use a model that predicts that 17%, 13% and 8% of the standard care arm would be progression free at 3, 5 and 10 years respectively? (This is the generalised gamma distribution used to extrapolate PFS in the standard care arm)[4].

[3] Updated post-committee meeting to correct factual inaccuracy. Proportions in original report were 37%, 26% and 14%.
[4] Updated post-committee meeting to correct factual inaccuracy. Proportions in original report were 17%, 12% and 8%.

	7. The Decision Support Unit (DSU) advise that fitting separate distributions to treatment arms should be justified using clinical expert judgement, biological plausibility and robust statistical analysis (DSU Technical Support Document 14). Have the DSU criteria been sufficiently met to justify fitting different model types per treatment arm? 8. Would a mixture cure rate model be appropriate for this topic?
Background/description of issue	The company used a generalised gamma extrapolation for both treatment arms in its base case, and explored Gompertz and log-normal (standard care (SoC) only) in scenario analyses. The company's preferred generalised gamma extrapolation of the durvalumab data predicts 46%, 40% and 26%[5] PFS at 3, 5 and 10 years respectively. The ERG highlighted that different extrapolations led to very different PFS predictions and considered that there was uncertainty in all extrapolations. It considered that the company's base-case was likely to overestimate PFS for people receiving durvalumab. Based on statistical assessment of fit and external validity, the ERG's preferred a log-normal extrapolation for the durvalumab arm. The ERG's preferred log-normal extrapolation of the durvalumab data predicts 38%, 27% and 17% PFS at 3, 5 and 10 years respectively[6]. Clinical expert advice indicated that the proportions of patients in the progression-free state predicted by the ERG's model (log-normal extrapolation of durvalumab; generalised gamma extrapolation of SoC) were reasonable. The technical team is aware of the advice in DSU TSD 14 that the same type of model should be fitted to both arms (so that the comparison focuses on difference in treatment effect rather than differences in the scale and shape parameters). However, the ERG considered that using different distributions for the treatment arms was justified in this

[5] Updated post-committee meeting to correct factual inaccuracy. Proportions in original report were 46%, 40% and 34%.
[6] Updated post-committee meeting to correct factual inaccuracy. Proportions in original report were 37%, 26% and 14%.

	instance because durvalumab is a treatment with curative intent, and because using the same curves has poor external validity. The technical team is aware that the ERG's approach to modelling progression-free survival leads to counter-intuitive results in the modelling of treatment-effect duration (see Issue 2), and consider that these results are not clinically plausible. The technical team is also mindful of the proportion of people remaining progression-free at 10 years predicted by both the company and the ERG models, and suggest that these patients may be considered cured. It recalled that cure rate models have been used in some previous appraisals of immunotherapies (for example, NICE technology appraisal guidance on dinutuximab beta for treating neuroblastoma [TA538]), on the rationale that immunotherapies may change the natural history of the disease. The technical team consider that this might be a relevant model structure for the company to explore.
Why this issue is important	Using the ERG's preferred PFS extrapolations increased the company's original base-case ICER from £19,320 to £45,878.
Technical team judgement before engagement	The generalised gamma extrapolation appears to have acceptable visual and statistical fit for the standard care arm. However, the tail of the generalised gamma extrapolation in the durvalumab arm predicts a higher proportion of patients remaining alive than expected in clinical practice (based on clinical expert advice and exploration of external validity provided by the company). Based on the clinical expert advice, the technical team consider that the predictions from the lognormal extrapolation of durvalumab are more clinically plausible than the predictions from the generalised gamma extrapolation. The technical team is aware that the ERG's approach to modelling progression-free survival leads to counter-intuitive results in the modelling of treatment-effect duration (see Issue 2). It would prefer to see an extrapolation that estimates progression-free survival in line with clinical expert advice that captures treatment effect duration more realistically. The technical team would also like the company to explore the possibility of a cure rate model to capture

	the possibility that the proportion of patients remaining progression-free at 10 years could be considered cured.
Summary of comments	Comments received from company: • Updated base-case uses generalised gamma extrapolation in both treatment arms (with a 5 year treatment effect duration) • Company explores different PFS extrapolations in scenario analyses: o Log-normal extrapolation for durvalumab and generalised gamma for SoC o Log-normal extrapolation in both arms o Scenario with durvalumab arm extrapolated using a distribution that is a 50:50 average of generalised gamma and log-normal in both arms o Cure rate model where people who have not progressed after 5 years are considered cured, with no risk of progression (scenario uses generalised gamma extrapolation in both arms) o Cure rate model where people who have not progressed after 10 years are considered cured, with no risk of progression (scenario uses generalised gamma extrapolation in both arms) o Mixture cure rate model where a proportion of people are assumed to have a reduced risk of event (scenario uses log-normal extrapolation in both arms) • Company introduced an option in the updated model whereby the progression hazard for the durvalumab arm was not allowed to exceed that of the SoC arm (hence assuming equal risk of progression or death for durvalumab and SoC arms from the point at which the hazard curves cross)

	• Clinical experts consulted by the company consider there is no clinical rationale for the risk of progression in the durvalumab arm to be higher than the risk of progression in the SoC arm • Clinical experts consulted by the company considered that longer-term PFS predictions for generalised gamma extrapolations in both treatment arms (assuming 5 year treatment effect duration) were reasonable • Clinical experts consulted by the company predicted 10-25% point progression-free survival benefit for the durvalumab arm compared with the SoC arm at 10 and 15 years • Company considers that there is not sufficient rationale to fit separate distributions to the treatment arms (as separate distributions lead to the hazard curves crossing, which violates the internal validity of the model) ERG considerations on new evidence received during technical engagement:: • Generalised gamma extrapolation is likely overestimates PFS • There are very few patients at the end of the Kaplan-Meier curve for PFS which makes the extrapolations highly uncertain • The scenario which averages the log-normal and generalised gamma curves reflects a middle ground approach, but the ERG does not consider that there is any scientific or clinical rational to support it • Cure rate models that assume that people who have not progressed after a given time point are cured are overly optimistic and lack clinical rationale • PACIFIC data are not mature enough to establish the proportion of people who are cured, meaning a mixture cure rate model is of limited use

	• The ERG considers that it has not seen any relevant new evidence for PFS, and continues to support a log-normal extrapolation of durvalumab with generalised gamma extrapolation of SoC • The ERG considers that company's amendment to 'cap' the PFS hazard curves is useful; this has been incorporated into ERG updated base-case Extrapolations of the durvalumab Kaplan-Meier data from the updated company model: Figure 1: PFS extrapolations (no assumption about cure rate)

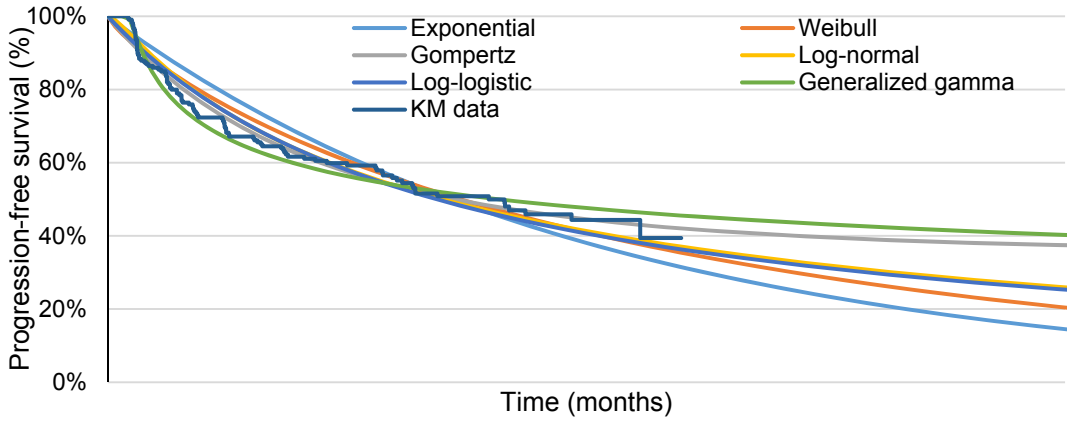

Figure 2: PFS extrapolations from mixture cure model

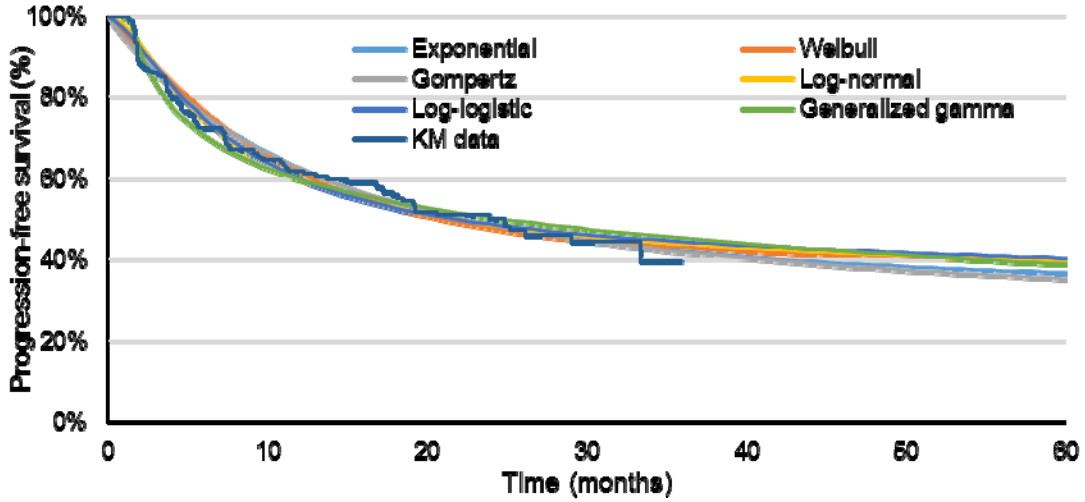

Table A: Predicted PFS in durvalumab arm for different extrapolations

	3 year	5 year	10 year
Generalised gamma for both arms	46%	40%	26%[7]
Log-normal durvalumab & generalised gamma SoC	38%	27%	17%[8]
Log-normal for both arms	37%	26%	9%
Average of generalised gamma & log-normal for durvalumab & generalised gamma for SoC	41%	33%	24%
Generalised gamma for both arms, patients progression-free at 5 years assumed 'cured'	46%	40%	36%
Generalised gamma for both arms, patients progression-free at 10 years assumed 'cured'	46%	40%	26%
Mixture cure rate model with log-normal for both arms (implies [redacted] durvalumab & [redacted] SoC 'cured')	44%	39%	33%[9]

Technical team scientific judgement after engagement	The generalised gamma extrapolation appears to have acceptable visual and statistical fit for the standard care arm. However, the company's preferred generalised gamma extrapolation is not plausible because its predictions are more optimistic that the expected

[7] Updated post-committee meeting to correct factual inaccuracy. Proportions in original report were 46%, 40% and 34%.
[8] Updated post-committee meeting to correct factual inaccuracy. Proportions in original report were 37%, 26% and 14%.
[9] Updated post-committee meeting to correct factual inaccuracy. Proportions in original report were 44%, 39% and 35%.

	survival predicted by the clinical experts. Predictions from the cure rate models are also more optimistic than the clinical expert predictions, and there is substantial uncertainty around the 'cure'-related parameters (i.e. the proportion of patients cured at a given time-point, or the time after which a patient is considered cured). This uncertainty could be reduced with more mature data. In choosing its preferred extrapolation of progression-free survival in the durvalumab arm, the technical team considered the remaining parametric distributions. Of these, the log-normal had the best statistical fit. Based on the clinical expert advice, the technical team consider that the predictions from the log-normal extrapolation of durvalumab are more clinically plausible than the predictions from other PFS extrapolations explored by the company. Capping the distribution hazard functions so that risk of progression in the durvalumab arm is always less than or equal to the risk of progression in the SoC arm is an acceptable approach to avoid spurious results when varying treatment effect duration.

Issue 4 – Utility values

Questions for engagement	9. Should utility values incorporate an age-related disultility? 10. Is the utility value for the progression-free state taken from the literature appropriate (0.73)? 11. Is the utility value for the progressed disease state taken from the literature appropriate (0.67)?
Background/description of issue	EQ-5D-5L data were collected in the trial.

	The company mapped this to EQ-5D-3L, and used a mixed-effects model to estimate utility values for the health states (0.810 for progression-free and 0.776 for progressed disease). In the company's model, the utility values were not treatment specific. The ERG considered that disutility associated with age was not fully captured in the utility values, and incorporated an age-related decrement in its base-case. It also included treatment as a covariate in the mixed-effects model to better capture any differences in incidence of adverse events (AEs) between the treatment arms (see Issue 5). The ERG highlighted that the utility value for the progression-free state was higher than the utility for the general population (0.80 for ages 55-64). It explored a lower progression-free utility value (0.73) taken from Ara and Brazier (2011) in a scenario analysis. The ERG considered that the utility decrement for transitioning to progressed disease (-0.034) was modest compared to the values found in the literature, and explored a decrement of 0.06 (based on values taken from Chouaid et al. [2013]) in a scenario analysis. Clinical expert advice indicated that the utility value of people in the progression-free state would be lower than in the general population, implying that the values used by the company are overestimated. Because of this, the technical team consider that the utility values taken from the literature are more appropriate.
Why this issue is important	Inaccurate utility values could bias estimates (although direction is unknown as overestimating the PFS utility may benefit durvalumab over standard care, and overestimating the progressed disease utility may benefit standard care over durvalumab). Scenarios exploring the alternative progression-free and progressed disease utilities taken from the literature increased the company's original base-case ICER by £1,300.
Technical team judgement before engagement	To avoid the problem of the progression-free health state utility value being higher than the utility value for the general population, it is preferable to use utilities taken from the literature for both health states. It is appropriate to capture age-related disutility in the model.

Summary of comments	Comments received from company: • Updated base-case applies age-related decrement of -0.004, derived from EQ-5D-3L index in Kind et al. (1999) • PACIFIC is the only source of EQ-5D data available for the population • Trial based health state utility values for patients in NICE technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531] were also higher than the UK population norm for people of the same age. However, in this appraisal it was acknowledged that a proportion of patients in the KEYNOTE-024 trial had an ECOG status of 0/1. Accounting for performance status of the trial population, the company does not consider that the progression-free utility value from PACIFIC lacks face validity. • Use of general utility values for 'cancer' is inappropriate when robust evidence from the PACIFIC study is available • Updated base-case uses the progression-free health state utility value from PACIFIC with scenario exploring value of 0.73 from Ara and Brazier (2011) • Company accept ERG's suggested change to the progressed disease health state utility value and use this in its updated base-case ERG considerations on new evidence received during technical engagement: • Using the utility estimate from PACIFIC for the progression-free health state and from Chouaid et al. (2013) for the progressed disease health state may overestimate the utility loss of progressed disease relative to remaining progression free
Technical team scientific judgement after engagement	The company's approach of modelling age-related disutility is acceptable. To ensure relative consistency in utility values when moving between health states, it is preferable to use

	health state utility values presented from the PACIFIC trial (with treatment-related decrement applied) for both progression-free and progressed disease health states.

Issue 5– Modelling of adverse events

This issue was resolved at technical engagement and is addressed in Table 3.

Issue 6– Vial sharing

This issue was resolved at technical engagement and is addressed in Table 3.

Issue 7– End of life considerations

Questions for engagement	12. Under standard care, is the life expectancy of adults with locally-advanced unresectable Stage III NSCLC whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based CRT more than 24 months? 13. Does durvalumab extend life for more than 3 months compared to standard care?
Background/description of issue	In its submission, the company suggest that durvalumab meets the end of life criteria (specified in NICE's guide to the methods of technology appraisal). The company cited evidence from the latest National lung Cancer Audit, data from Public Health England, the SOCCAR trial (a Phase 2 trial which compared overlapping CRT with sequential CRT in people with unresectable Stage III NSCLC) and clinical expert opinion, which suggested that average life expectancy for the population was less than 24 months. The company cited overall survival evidence from PACIFIC to argue that durvalumab extends life by more than 3 months compared to SoC (72.8% survival at 24 months in the durvalumab arm compared to 53.6% in the placebo arm; OS HR [95% CI] = 0.53 [0.36, 0.77]). The company's model

	predicts an extension to life of 66.8 months. The ERG's model predicts an extension to life of 30.5 months. The technical team noted that the evidence from the pivotal PACIFIC trial does not indicate that life expectancy in this population is less than 24 months. Median overall survival in the placebo arm was 29.1 months (95% CI: 17.7, NR). The technical team is aware that the issues with generalisability of the PACIFIC trial (see Issue 1) may mean that the life expectancy of the trial population is not representative of the population relevant to the appraisal. It would like to consider any available audit data to support estimates of life expectancy. Both the company and the ERG's models predict mean survival of 54.8 months in the standard care arm with a median of 28.5 months. Based on the evidence presented, the technical team do not consider that durvalumab meets the short life expectancy criteria.
Why this issue is important	The appraisal committee's judgements about the acceptability of the technology as an effective use of NHS resources will take into account whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'.
Technical team judgement before engagement	Durvalumab does not meet the end of life criteria specified in NICE's guide to the methods of technology appraisal.
Summary of comments	Comments received from company: • Although mean and median OS in PACIFIC indicate that durvalumab does not meet end-of-life criteria, UK-specific real world data should also be considered • People receiving sequential CRT are likely to have a poorer prognosis than the PACIFIC cohort who received overlapping CRT • Company highlight several UK based studies with median OS ranging from 18.4 to 22.3 months (see company response to technical engagement for more information)

	• Company cites evidence from PACIFIC to demonstrate a survival benefit of durvalumab over standard care of more than 3 months Comments received from Roy Castle Lung Cancer foundation: • National Lung Cancer Audit and other trial data shows that average life expectancy for locally advanced unresectable Stage III patients is less than 24 months. Comments received from BTOG-NCRI-ACP-RCP-RCR: • The standard of care arm in the RTOG 0617 study had a median survival of 28 months, but this study was in people offered overlapping CRT. In the UK population a median survival of around 24 months would be more realistic. • Durvalumab extends life for more than 3 months compared to standard care ERG considerations on new evidence received during technical engagement: • ERG does not consider durvalumab to meet the end of life criteria
Technical team scientific judgement after engagement	Data from PACIFIC is the best available evidence for this appraisal. Evidence from PACIFIC, and the economic model populated with PACIFIC trial data, indicate an extension to life of over 3 months. The technical team consider that durvalumab meets the extension to life criteria specified in NICE's guide to the methods of technology appraisal. Although the company has provided information about median OS from various real world data sources, the technical team have not seen enough information to determine whether populations in these studies reflect the population of interest. The technical team have not seen the mean OS from these studies and considers that there is still uncertainty about the spread of this survival data. Because of this, the technical team considers there is uncertainty associated with data from the real world studies. The technical team have preferred to use data from PACIFIC in other areas of uncertainty in the appraisal (for example, utility values and extension to life). The PACIFIC data do not

	indicate that life expectancy in this population is less than 24 months. The mean and median overall survival predicted by the company and ERG preferred models is higher than 24 months. Based on this evidence, durvalumab does not meet the short life expectancy criteria specified in NICE's guide to the methods of technology appraisal and therefore does not meet the end of life criteria.

Issue 8 – Cancer Drugs Fund (CDF)

Questions for engagement	14. Does durvalumab meet the criteria for inclusion in the Cancer Drugs Fund?
Background/description of issue	The technical team is aware of the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The technical team consider that there is clinical uncertainty that could be reduced through data collection via ongoing studies. For example, uncertainty about the generalisability of PACIFIC to clinical practice in the NHS due to the differences between overlapping and sequential CRT may be reduced through data collection from PACIFIC 6 (see Issue 1). However, taking into account its considerations about the end of life criteria, the technical team do not consider that durvalumab has plausible potential to be cost-effective at the offered price. In its original submission, the company did not express an interest in the treatment being considered for funding through the Cancer Drugs Fund in its submission.
Why this issue is important	The CDF is a potential option if there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid long delays, but would require information on its

	effectiveness before it can be considered for routine commissioning (when the guidance is reviewed).
Technical team judgement before engagement	The technical team considers that durvalumab does not meet the criteria for inclusion in the Cancer Drugs Fund.
Summary of comments	Comments received from company: • In response to engagement, company are pursuing Cancer Drugs Fund (with a focus on the population receiving durvalumab after sequential CRT) • Further clinical effectiveness data will be available in [redacted] through: o PACIFIC-6 study of durvalumab in people with prior sequential CRT o PACIFIC-R observation study (including follow-up of early access programme) o Final analyses from PACIFIC study (with ~five years of follow-up) • Conditional access to durvalumab through the CDF will give access to a population with significant unmet need and a small number of eligible patients while company collect additional relevant clinical trial data Comments received from Roy Castle Lung Cancer foundation: • There is an unmet need for this population, and PACIFIC trial suggests a large improvement in progression free survival with durvalumab • Whilst data matures and new data become available, hope that durvalumab can be available through the Cancer Drugs Fund
Technical team scientific judgement after engagement	At the current value proposition, durvalumab does not appear to have plausible potential for cost-effectiveness and therefore does not meet the criteria for inclusion in the Cancer Drugs Fund. However, if the committee were to accept modelling assumptions that resulted in a

	plausible range of ICERs with the lower end under £30,000 per QALY gained, durvalumab could be considered for the Cancer Drugs Fund.

3. Other issues for information

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

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

The company's updated base-case includes the following NICE technical team preferred assumptions:

- capturing of age-related disutility
- modelling a treatment-related disutility to capture differences in incidence of adverse events
- no vial sharing

Table 1 outlines the cumulative effect of all NICE technical team preferred assumptions on the cost-effectiveness estimate.

This estimate does not include the commercial arrangements for some of the relevant subsequent treatments (nivolumab, pembrolizumab, afatinib, erlotinib) because these are confidential and cannot be reported here. Estimates that include these commercial arrangements would be higher than those reported in Table 1.

Alteration	Technical team rationale	ICER	Change from base-case
Company base-case		**£28,433**	
1. 3 to 5 year treatment effect duration	Issue 2	£28,433 to £35,838	+£0 to +£7,405
2. Log-normal extrapolation of PFS in durvalumab arm and generalised gamma extrapolation of SoC (with 'cap' applied to prevent hazard curves crossing)	Issue 3	£46,615	+£18,182

3. Progression-free and progressed disease health state utility values taken from PACIFIC (with treatment-related decrement applied)	Issue 4	£29,378	+£945
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£48,631 to £48,649**	**+£20,198 to +£20,216**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Submission based on a more restricted population than the NICE scope	The population included in the NICE scope was restricted to align with the population given regulatory approval (adults with locally-advanced unresectable Stage III NSCLC whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based CRT). There is concern that the PACIFIC trial was not powered for the PD-L1≥1% subgroup. This subgroup was determined post-randomisation. Time-to-progression and post-progression survival analyses were not pre-specified.	Unknown. The technical team considers that this is a substantial area of uncertainty in the appraisal. However, the subgroup was selected by the regulatory body.
Demographics of trial population	The ERG highlighted that PACIFIC was not stratified by PD-L1 status, and that it	Data from the National Cancer Registration and Analysis Service

	only included 8 UK patients. This could affect the generalisability of the trial results to the UK population (further increasing the uncertainty discussed in Issue 1). **After technical engagement, the company provided data from the National Cancer Registration and Analysis Service to reduce uncertainty about the generalisability of PACIFIC.**	reduces some of the uncertainty about generalisability of the trial. However, uncertainty about the generalisability of the PACIFIC trial remains (see Issue 1).
Model structure	The company initially attempted a partitioned survival model, but the majority of extrapolation approaches led to the overall survival and progression-free survival curves crossing. The company instead used a 3-state semi-Markov model with model states derived from progression-free survival, time-to-progression and post-progression survival (therefore not using overall survival data directly). The company did not restructure the model to explicitly capture overall survival. In the company's model, post-progression survival (PPS) data from both treatment arms were pooled, implying that treatment effect was primarily seen in improvements in	The ERG state that the magnitude and direction of any bias are unclear.

	progression-free survival. The technical team consider that there is potential that this assumption could over-estimate survival in the durvalumab arm if the effect of subsequent immunotherapy is diminished in people treated with durvalumab maintenance at Stage 3 disease. The ERG highlighted that the model based on post-progression survival was informed by a smaller sample size than overall survival, increasing uncertainty. It was also concerned about risk of bias from imbalance in the groups (for example, post-progression survival contains more patients treated with placebo). The ERG highlighted that PPS data were based on people who progressed within the trial follow-up period, and that extrapolations could be biased if these people were not representative of people who progressed later.	

Table 3: Other issues for information

Issue	Comments
Modelling of adverse events (Issue 5)	In its original submission, the company modelled the costs of adverse events (AEs), but considered that the impact of AEs on health-related quality of life (HRQoL) was already captured in the utility estimates and so did not include them separately in the model. The technical team were aware that there was a higher incidence of serious adverse events (SAEs) in the durvalumab arm compared to the SoC arm, and considered that it was appropriate to have treatment-specific utility values. The technical team concluded that this could be achieved by deriving a treatment-related utility decrement from the mixed-effects model of the PACIFIC data and applying this decrement to the utility values. **Following technical engagement, the company updated its base-case to apply a treatment-related utility decrement derived from a mixed-effects model of the PACIFIC EQ-5D data.**
Vial sharing (Issue 6)	In its original submission, the company assumed vial sharing. It argued that this assumption is aligned with NHS England policy initiatives for immunotherapies. The technical considered that vial sharing was not realistic due to the low number of patients eligible to be treated with durvalumab. **Following technical engagement, the company updated its base-case to assume no vial sharing. The company explored a 30% vial sharing assumption in a scenario analysis.**
Modelling of subsequent treatment in line with PACIFIC	In PACIFIC, there was an imbalance in the proportion of patients who received subsequent therapy between treatment arms in the PD-L1≥1% group. A higher proportion of the placebo arm received subsequent immunotherapy. The company acknowledged that this imbalance could confound post-progression survival comparisons. However, it did not formally adjust for this in its base-case because it considered that the proportion of patients that received

	subsequent therapy reflected clinical practice. In the company's original model, subsequent therapy costs were included if they were used in 3% or more patients in either treatment arm. The ERG highlighted that there were more patients in the SoC arm, and this could lead to bias (for example, treatments received by 3% of patients in the durvalumab arm but not by patients in the SoC arm would not be costed in the analysis). **In response to technical engagement, the company removed the 3% threshold from its base-case. This change had a minimal impact on the company's base-case ICER.**
Stopping rule	The marketing authorisation for durvalumab states that it should be administered until disease progression or unacceptable toxicity, or for a maximum of 12 months.
Post-progression survival (PPS)	In its base-case, the company modelled PPS using data from PACIFIC. The company pooled PPS across both treatment arms, assuming no difference in PPS between durvalumab and SoC. The company extrapolated this data using an exponential distribution (based on statistical and visual assessment of fit, and validation of OS outcomes with other clinical sources). The company also explored extrapolations of PPS data from other clinical trials to explore the impact of differing levels of subsequent immunotherapy use. The ERG considered that there was substantial uncertainty about PPS due to immature PACIFIC data. It also considered that there was a risk of bias introduced through the model structure from imbalance in the groups (for example, PPS contains more patients treated with placebo). The ERG highlighted that PPS data was based on people who progressed within the trial follow-up period, and that extrapolations could be biased if these people were not representative of people who progressed later (see Table 2). However, in its base-case the ERG used an exponential extrapolation of the PACIFIC data, in line with the company's approach. Clinical expert advice indicated that the proportions of patients alive post-progression predicted by the ERG's model were reasonable.

Innovation	The company considers durvalumab to be innovative. However, the technical team considers that all relevant benefits associated with durvalumab are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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Technical engagement response form

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID1175]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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

Deadline for comments **5pm Monday 21 January 2019**

Thank you for your time.

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

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.

- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow and any information that is submitted under 'commercial arrangements' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

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

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About you

Your name	**Tina Sarbajna (Pricing and Market Access Lead, Immuno-oncology)**
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**

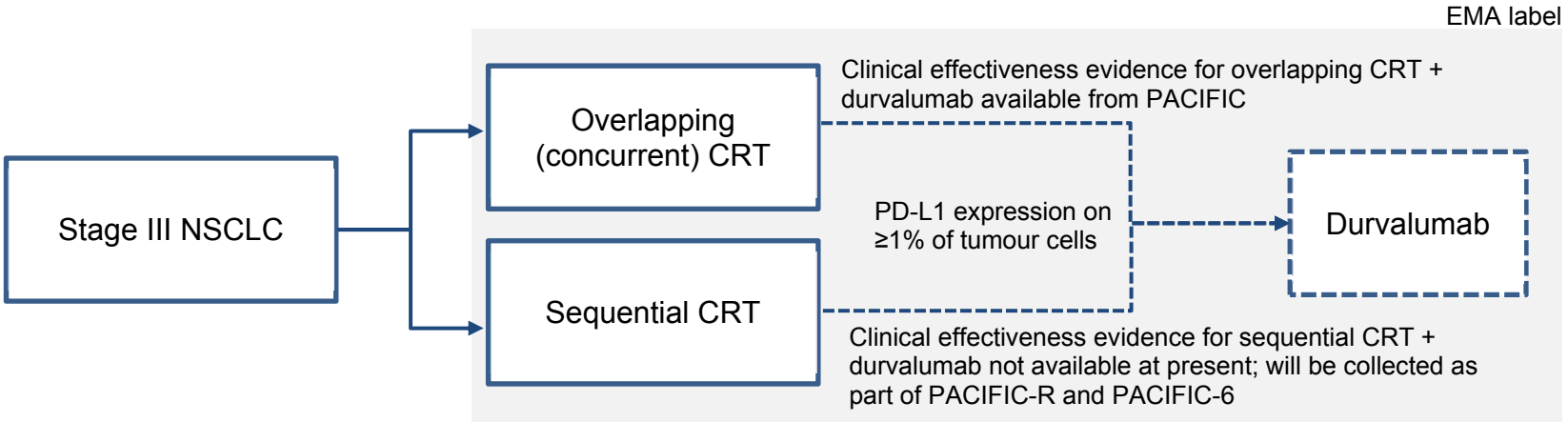
Summary of the revised AstraZeneca submission

We (AstraZeneca UK) have revised our initial submission, to reflect discussions with NICE and the ERG during the technical consultation period (including engagement meeting on 7 January 2019). Key aspects of this revised submission are briefly captured below:

Population

Per European Commission (EC) marketing authorisation, i.e. "adults with locally-advanced, unresectable, Stage III non-small cell lung cancer (NSCLC) whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (CRT)" (Figure 1)[1].

Figure 1. Positioning of durvalumab in the treatment pathway



The efficacy and safety of durvalumab in the PACIFIC study was evaluated after overlapping (i.e. concurrent), rather than sequential, CRT since the former is recognised as the **standard-of-care** for the treatment of locally-advanced, unresectable, Stage III NSCLC patients and is recommended as "treatment of choice" in the ESMO Clinical Practice Guidelines for early and locally-advanced NSCLC (see pages 23−25 of the Company submission,

Document B).[2] Consistent with this, data from the early access programme (EAP) show that [redacted] receive durvalumab after overlapping CRT (data as of 18 January 2019).

Real-world evidence from a cohort of [redacted] patients from the National Cancer Registration and Analysis Service (NCRAS) in England (who were diagnosed with Stage III NSCLC between 2013 and 2015 and received curative-intent overlapping CRT for their disease) highlight the generalisability of the PACIFIC population to UK patients in terms of demographics and disease characteristics (Table 1; see response to ERG clarification question A3, part A for further details). [redacted] (as discussed in the "strengths and limitations of the evidence base, and generalisability to the UK" section of the Company submission (pages 102–105; see reference 45 for supporting Data on File).

Table 1: Patient characteristics in the PACIFIC population versus a cohort of patients from the National Cancer Registration and Analysis Service (NCRAS) in England

Note: patients were diagnosed with Stage III NSCLC between 2013 and 2015 and received curative-intent overlapping CRT for their disease.

Patient characteristic	PACIFIC ITT population N=713	PACIFIC PD-L1 ≥1% population N=303	UK RWE (NCRAS data) N=[redacted]
Sex Male (n, %)	500 (70.1)	209 (69.0)	[redacted]
Median weight, kg	69 (range: 34−175)*	69 (range: 34−133)*	[redacted]
Median age, years	64	64	[redacted]
Disease stage IIIA IIIB	377 (52.9) 319 (44.7)	166 (54.8) 131 (43.2)	[redacted]
Tumour histological type, n (%) Squamous Non-squamous	326 (45.7) 387 (54.3)	150 (49.5) 153 (50.5)	[redacted]

[1]Imfinzi- EPAR – Medicine Overview. Available at: https://www.ema.europa.eu/documents/overview/imfizi-epar-medicine-overview_en.pdf (last accessed 18 Jan 2019).
[2]Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017; 28(suppl_4):iv1-iv21.

Performance status			
0	348 (48.8)	150 (49.5)	[redacted]
1	362 (50.8)	152 (50.2)	
2	-	-	
≥3	-	-	
Missing/invalid	3 (0.4)	1 (0.3)	

Abbreviations: ITT, intent to treat; NCRAS, National Cancer Registration and Analysis Service; PD-L1, programmed cell death ligand 1; RWE, real-world evidence.
*[redacted].
Source: PACIFIC 22 March 2018 DCO CSR (32), PACIFIC PD-L1 ≥1% DOF (14), and UK RWE, Public Health England (22). References numbers relate to Company Submission, Document B.

Whilst overlapping CRT is the standard of care for unresectable, Stage III NSCLC patients who are suitable for curative intent treatment, this may not be possible in all instances. Sequential approaches of induction chemotherapy followed by definitive radiotherapy are recommended as an alternative, if overlapping protocols are not possible for any reason[3]. We acknowledge that we do not at present have robust clinical trial data on the effectiveness of durvalumab after sequential CRT; however, we wish to highlight the following:

- The European Medicines Agency (EMA), after their assessment of durvalumab, granted marketing authorisation for all locally-advanced, unresectable NSCLC patients whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy, thus not restricting its use by specific types of CRT regimens. Durvalumab is currently being reviewed by multiple Health Technology Assessment agencies across Europe. On 15 January 2019, Germany's Institute for Quality and Efficiency in Health Care (IQWiG) published its benefit assessment of durvalumab, assigning it a benefit rating of 2 for the **full label population**. This follows a similar recommendation from the Swedish TLV in November 2018.
- Feedback from UK oncologists experienced in treating patients with durvalumab after both sequential and overlapping CRT as part of the EAP indicate that there are no apparent differences between these groups in terms of tolerability or radiological progression, and "*how they [patients] cope is identical*". This is consistent with clinical expert opinion quoted in the draft technical report (which states that "*differences in survival outcomes [associated with durvalumab] for overlapping compared to sequential CRT is likely to be small*"), and also resonates with the opinion of three other UK clinical experts who were consulted by AstraZeneca during the technical engagement period[4].
    - (Added in 25th January version) Preliminary analyses of a cohort of [redacted] patients from the NCRAS in England who were diagnosed with Stage III NSCLC between 2013 and 2015 and received curative-intent sequential CRT[5] highlight a [redacted]

[redacted]. The range of characteristics investigated is, however, not exhaustive; further analysis and validation of this data is currently underway.

Table 2. Characteristics of unresected, Stage III NSCLC patients in England (diagnosed between 2013 and 2015) who received either sequential or overlapping CRT for their disease

Patient characteristic	NCRAS – overlapping CRT N=[redacted]	NCRAS – sequential CRT N=[redacted]
Sex Male (n, %)	[redacted]	[redacted]
Median weight, kg	[redacted]	Not available at present
Median age, years	[redacted]	[redacted]
Disease stage IIIA IIIB	[redacted]	[redacted]
Tumour histological type, n (%) Squamous Non-squamous	[redacted]	Not available at present
Performance status 0 1 2 ≥3 Missing/invalid	[redacted]	[redacted]

- (Added in 25th January version) Audit data from the Royal Marsden Hospital (Sutton) presented at the 17th Annual British Thoracic Oncology Group conference (23rd−25th January 2019; Ireland, Dublin) showed that both overlapping (concurrent) and sequential CRT

[3]Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017; 28(suppl_4):iv1-iv21.

[4]1:1s with three UK clinicical oncologists conducted on 2nd and 4th of January 2019. Please also see related insights from UK clinicians submitted along with responses to ERG clarification questions.

[5]Patients were classified as having received sequential CRT if the first dose of radiotherapy (within six months of diagnosis) occurred after the final chemotherapy cycle (within six months of diagnosis). Only radiotherapy doses of ≥50Gy in ≥20 fractions were included.

resulted in prolonged lymphopenia in a cohort of 59 patients who had completed treatment, although this was *less* pronounced in sequential CRT patients. Since lymphopenia after CRT can reduce the benefit of durvalumab treatment (due to patients having fewer circulating lymphocytes that can be primed to attack cancer cells), the authors concluded that these results were supportive of durvalumab being "*equally beneficial in patients receiving sequential CRT*".[6]

- As highlighted in the Company submission (Document B, section B.2.11 "Ongoing studies"), the effectiveness of durvalumab 1500 mg Q4W following sequential CRT in unresectable Stage III NSCLC patients is being investigated in the open-label, multi-centre, international, Phase II safety study called PACIFIC-6. [redacted]. In addition, data on both overlapping and sequential CRT patients who participated in the EAP will also be analysed as part of the observational, non-interventional, PACIFIC-R study. Data from this study will also be available [redacted]. Collectively, PACIFIC-6 and PACIFIC-R studies will provide insights on the use of durvalumab after sequential CRT in both clinical trial and real-world settings in the near future.

Given the significant unmet clinical need in this population (5-year survival rates of 10.6%) and the small number of eligible patients, we request that the NICE committee consider granting conditional access to durvalumab after sequential CRT through the Cancer Drugs Fund (CDF). This will ensure the full licensed population can continue to benefit from this therapy, while AstraZeneca collect clinical effectiveness data through PACIFIC-6 and PACIFIC-R studies. To help the decision-making process, we have provided a simple cost-effectiveness analysis for durvalumab after sequential CRT (see Appendix B: The cost-effectiveness of durvalumab after sequential CRT). This analysis assumes the same risk reduction and health-related quality of life (HRQL) as the overlapping CRT population and uses data from the Auperin meta-analysis (2010)[7] and the START study (2014)[8] to account for the impact of prior sequential or overlapping CRT on PFS and PPS, respectively. In doing so, the model adjusts for the slightly worse PFS outcomes reported for sequential CRT versus overlapping CRT.

We are committed to working with NICE and NHS England throughout the next steps of the appraisal process to ensure we satisfy the necessary criteria to be considered for inclusion in the CDF.

[6]Westley et al. A retrospective analysis of lymphopenia rates during and after sequential and concurrent radical chemoradiotherapy for patients with stage III non-small cell lung cancer (NSCLC). Presented at the 17th Annual British Thoracic Oncology Group meeting (23rd–25th January; Ireland, Dublin).

[7]Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010; 28(13):2181-90.

[8]Butts C, Socinski MA, Mitchell PL, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014; 15(1):59-68.

Summary of key base-case assumptions and related sensitivity / scenario analyses

A summary of key model assumptions (relevant to issues raised by NICE) is provided below. The rationale for each of the following assumptions is described in detail in the following section.

Assumption	Rationale	Model element	Related scenario analyses
Overlapping CRT population:			
Durvalumab PFS curve: generalised-gamma	Per DSU guidance – this curve produces the best statistical fit, clinically-plausible outcomes, good visual fit	PFS extrapolation	Log-normal (ERG base-case)
SoC PFS curve: generalised-gamma	Per DSU guidance – this curve produces the best statistical fit, clinically-plausible outcomes, good visual fit	PFS extrapolation	Log-normal (per NICE technical team request)
NEW! Treatment effect duration (durvalumab) = 5 years	Clinical expert opinion, clinical plausibility of long-term PFS benefit estimated at 10- and 15-years (derived using generalised-gamma distributions for both arms), precedence from immunotherapy appraisals in the advanced metastatic (Stage IV) NSCLC setting	Treatment effect	Effect duration of up to 3 years and 10 years (per NICE technical team request)
Utility values			
NEW! Age-related utility decrement included	Appropriate considering the average starting age in the model (63.1 years), the time horizon of the analysis (lifetime; 40 years), and the curative intent with which treatment is given	Utilities	N/A
Progression-free (PF) health state: PACIFIC EQ-5D-5L, mapped to EQ-5D-3L	The PACIFIC study is the **only source** of PF health state utility data in the population of interest. As explained in detail in later sections of this response, we see no reason to question the face validity of these data, given the performance status of patients included in the trial	Utilities	PF health state utility of 0.73, taken from Ara and Brazier, 2011 (per NICE technical team request)

NEW! Progressed disease (PD) health state: 0.67 (taken from Chouaid *et al*., 2013)	ERG and NICE-technical team-preferred value; addresses concern that PD health state utility data from PACIFIC do not adequately capture the long-term HRQL decrement associated with disease progression	Utilities	N/A
NEW! Inclusion of treatment as a non-statistically significant covariate in mixed effects utility models	To adequately capture the potential impact of treatment-related AEs	Utilities	N/A
NEW! Costs of all subsequent treatment costs included	Addresses the concern that the use of an arbitrary 3% threshold may bias results obtained	Costs	N/A
NEW! No vial sharing	Addresses the ERGs' and NICE technical team's concern that vial sharing may not be realistic given the small patient population who are eligible for durvalumab	Costs	30% vial sharing (consistent with ERG scenario)
Sequential CRT population Note: see Appendix B for further information on methodology and results			
Same risk reduction and HRQL as PACIFIC overlapping CRT population	Clinical expert opinion and experience from the EAP	Key elements of model structure	N/A
Different (worse) PFS + same post-progression survival (PPS)	Based on the Auperin *et al*., meta-analysis (2010; PFS)[9] and the START study (2014; PPS)[10] Note: the meta-analysed hazard ratio (HR) for PFS from the Auperin *et al*., study (0.90) was applied to PFS curves for both placebo / standard-of-care and durvalumab arms; this analysis was based on 1,184 patients (1,074 events) from the six randomised trials		N/A

[9]Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010; 28(13):2181-90.

[10]Butts C, Socinski MA, Mitchell PL, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014; 15(1):59-68.

	directly comparing concomitant (i.e. overlapping) versus sequential CRT. Digitised data from the START study found no differences in PPS between overlapping and sequential CRT subgroups; therefore, no adjustments to PPS were made		
Same duration of treatment as PACIFIC overlapping CRT population	No evidence to the contrary		N/A
Same subsequent treatments after disease progression as PACIFIC overlapping CRT population	No evidence to the contrary		N/A

Rationale for key base-case assumptions

PFS extrapolations (generalised gamma distributions for both durvalumab and standard-of-care arms)

As per NICE DSU guidelines TSD 14[11], the overall fit of the different parametric models (i.e. exponential, generalised-gamma, Gompertz, log-logistic, log-normal, and Weibull) to PACIFIC clinical trial data was assessed using the Akaike's information criterion (AIC) and Bayesian information criterion (BIC) statistics (Table 3; Table 31 of Company submission), as well as visual fit. Based on these measures, the **generalised gamma for PFS was judged to be the best fit to PACIFIC data**. The log-normal distribution was the next-best statistical fit but produced clinically-implausible results for the standard-of-care arm (discussed further below).

Table 3: Summary of goodness of fit data for the parametric survival analysis of PFS data

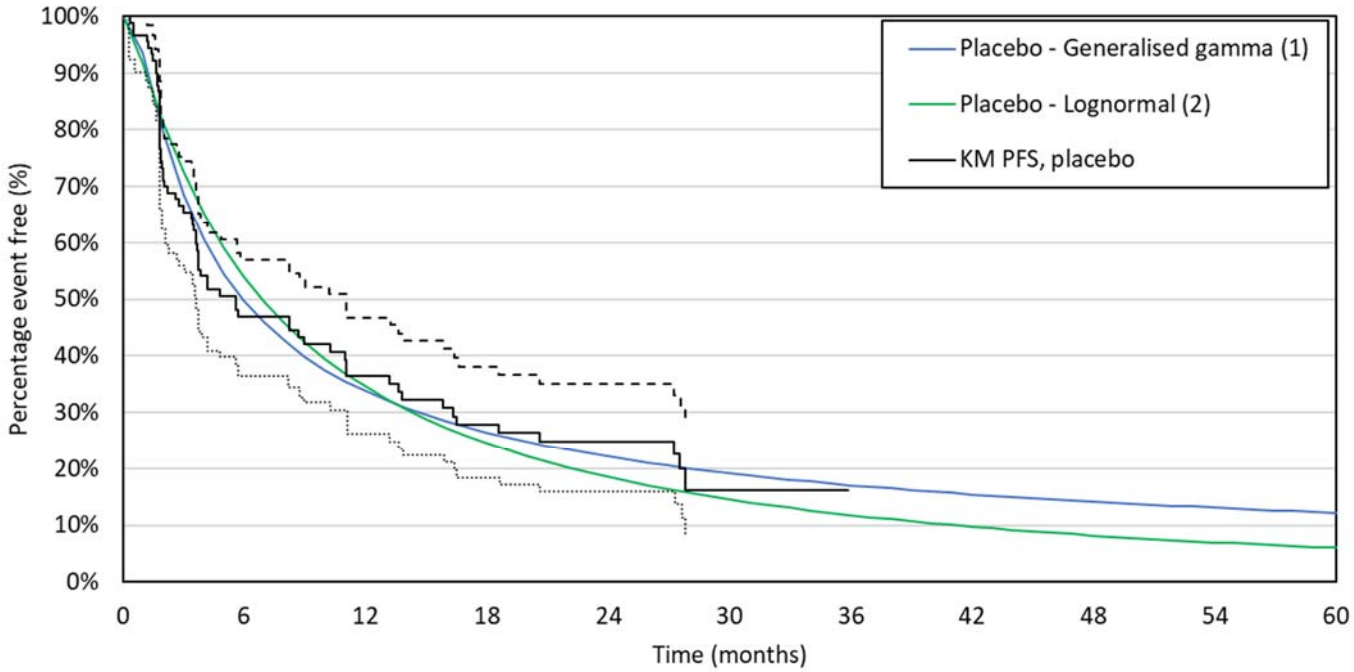
Distribution	Durvalumab		Placebo	
	AIC	BIC	AIC	BIC
Exponential	880.47	883.83	472.69	475.20
Generalised Gamma	**830.33**	**840.40**	**448.85**	**456.38**
Gompertz	867.34	874.05	460.98	466.00

[11]Decision Support Unit, Technical Support Document [TSD] 14, available at http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf

Log-logistic	869.38	876.10	458.26	463.28
Log-normal	860.46	867.18	454.51	459.53
Weibull	877.55	884.26	469.44	474.47

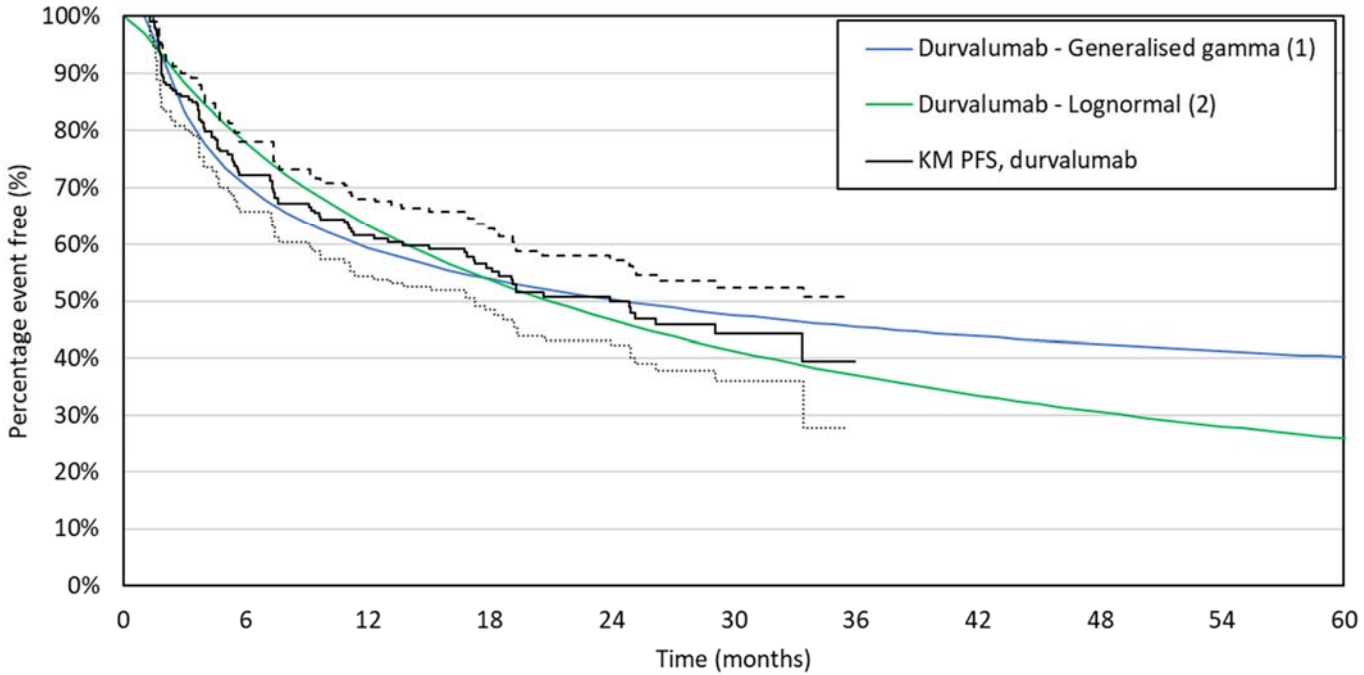
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
Note: **Bolded** values indicate the best scores.

Figure 2: Visual fit of PFS parametric functions to PACIFIC data; placebo arm, PD-L1 ≥1% group (generalised-gamma and log-normal* curves shown only to reflect the two best statistical fits)†



Note: *The log-normal curve produces long-term PFS rates that are too low to be clinically plausible (discussed further below). †Visual fits of all statistical curves considered is shown in Appendix A.

Figure 3: Visual fit of PFS parametric functions to PACIFIC data; durvalumab arm, PD-L1 ≥1% group (generalised-gamma and log-normal* curves shown only to reflect the two best statistical fits)†



Note: †Visual fits of all statistical curves considered is shown in Appendix A. Visual fit of PFS parametric functions to PACIFIC data (all statistical distributions considered).

The extrapolated curves were also compared against other relevant clinical studies, UK real-world data, and estimates of PFS sourced from clinical experts to assess their clinical validity.

- **Standard-of-care arm**:

  The generalised-gamma curve produced **clinically plausible** estimates of PFS on standard-of-care beyond the trial follow-up period, further validating its use in modelling survival outcomes. External validation conducted against relevant clinical trial evidence and UK clinical expert opinion is summarised in Table 4 (Table 33 of Company submission). While the log-normal distribution had good statistical fit, it produced clinically-implausible

estimates for long-term PFS on standard-of-care (i.e. placebo / active-follow-up), with estimates at 5 years and thereafter being substantially lower than the range of values reported from historical clinical trials in this setting, as well as UK clinical expert opinion.

Table 4: Comparison of extrapolated PFS outcomes on SoC against other clinical sources (survival measured from completion of CRT)

PFS	Median (months)	1 year	2 years	3 years	5 years	10 years	15 years	20 years
Modelled								
Exponential	9.2	41%	16%	7%	1%	0%	0%	0%
Generalised gamma	**6.0**	**34%**	**23%**	**17%**	**13%**	**8%**	**6%**	**5%**
Gompertz	6.4	35%	22%	17%	15%	14%	12%	9%
Log-logistic	6.4	33%	18%	12%	7%	3%	2%	1%
Log-normal	6.9	35%	19%	12%	6%	2%	1%	1%
Weibull	8.3	39%	20%	10%	3%	0%	0%	0%
Observed data from the PACIFIC study								
ITT	5.6	34%	24%	-	-	-	-	-
PD-L1 ≥1% group	5.6	36%	25%	16%*	-	-	-	-
Historical RCT data								
START[a]	8.3	42%	25%	20%	15%	-	-	-
GILT[b]	5.5	28%^	20%^	16%^	10%^	-	-	-
HOG LUN 01-24[c]	10.3	47%^	30%^	20%^	14%^	-	-	-
Carter 2012[d]	10.2	46%	32%	25%	25%	-	-	-
RTOG0617[f]					18.3%			
RTOG0214[g]						5%−12%		
UK clinical expert opinion (AstraZeneca data on file)								
Estimates for PACIFIC ITT population[e,146]	-	-	-	-	15%	9%	-	-

Key: CRT, chemoradiation therapy; ITT, intention to treat; KM, Kaplan–Meier; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RCT, randomised controlled trial; SoC, standard of care; -, not available.
Notes: *At 35.88 months. **At 35.94 months, ^digitised from source. Modelled values are shown at closest model cycle (14/28 days) to time point.
Sources: a, START[109, 110], ITT, KM data digitised, patients randomised upon completion of CRT; b, GILT[147], concurrent (overlapping) cisplatin + vinorelbine (pre-randomisation) followed by SoC, survival measured from randomisation on completion of concurrent cisplatin + vinorelbine therapy. Landmarks digitized from published KM curves, c, HOG[114], concurrent etoposide +

cisplatin (pre-randomisation) followed by observation, survival measured from randomisation on completion of concurrent etoposide + cisplatin. Landmarks digitised from published KM curves. d, Carter, 2012[148], induction or concurrent paclitaxel + carboplatin (pre-randomisation) followed by observation, survival measured from randomisation on completion of induction or concurrent paclitaxel + carboplatin. Landmarks obtained from publication, e, AstraZeneca data on file[146]. f, Bradley et al 2017. Long-Term Results of RTOG 0617: A Randomized Phase 3 Comparison of Standard Dose Versus High Dose Conformal Chemoradiation Therapy +/- Cetuximab for Stage III NSCLC.DOI: https://doi.org/10.1016/j.ijrobp.2017.06.250. g, Sun et al., 2018. 10-Year Updated Analysis of NRG Oncology/RTOG 0214: A Phase III Comparison of PCI vs. Observation in Patients with LA-NSCLC. DOI: https://doi.org/10.1016/j.jtho.2018.08.233. Reference numbers refer to Company submission, Document B.

- **Durvalumab arm:**

We note the ERGs' concern regarding the generalised-gamma distribution over-estimating PFS in the durvalumab arm relative to the PACIFIC KM-curve after 27 months (see Figure 3); however, we would like to reiterate that the sample size at the tail of the PFS distribution (where the predicted curve separates from the observed curve, albeit remaining within the 95% CI) is too small to be used as a reliable benchmark. Indeed, **at 36 months, data from PACIFIC are based on just one patient**. At the ERGs' request, we conducted an analysis wherein the parametric survival curves were refitted to PACIFIC data after removing the last 5% of patients from the durvalumab PFS curve (see response to clarification question B8, part c). The shape of the generalised-gamma curve for the durvalumab arm was unchanged in this analysis and it remained the best statistical fit (according to AIC/BIC) to PACIFIC data.

Following on from the receipt of the draft technical report, we consulted 6 UK clinical experts[12] to further understand the clinical plausibility of PFS estimates derived using a generalised-gamma distribution for durvalumab and placebo arms and assuming a 5-year (rather than 10-year) treatment effect for durvalumab (see Scenario 3; page 20).

Estimates of long-term PFS obtained using this approach were largely consistent with the range of values obtained from UK clinical experts, who predicted 10%−25% (percentage points) PFS benefit of durvalumab versus standard-of-care at 5 years, which would be sustained at later points of 10- and 15-years. Specifically, a generalised-gamma distribution for both arms (with a 5-year treatment effect assumption for durvalumab) predicts 10- and 15-year PFS rates of 25.6% and 19.6% for durvalumab, respectively, and 8.0% and 6.1% for placebo (i.e. standard-of-care, active follow-up). The PFS percentage-point benefit predicted by the model at both these timepoints (17.6% and 13.5%) approximates the mid-point of the range provided by experts. The 5-year PFS benefit predicted by the model is, however, above the upper end of the range provided by experts.

Whilst we firmly believe that the generalised-gamma distribution produces the most plausible PFS extrapolation for both standard-of-care and durvalumab arms based on the factors described above, we do acknowledge there is a degree of remaining uncertainty, which can only be addressed as data from

[12] 1:1s with five UK clinical oncologists and 1 UK medical oncologist conducted on 2nd–4th and 9th–10th of January 2019.

PACIFIC mature. Following on from discussions with NICE and ERG at the technical engagement meeting, we have provided two additional scenario analyses using the more conservative log-normal distribution for durvalumab arm.

We wish to highlight upfront that each of these analyses include key aspects that are clinically implausible and that the log-normal distribution underestimates long-term survival in both durvalumab and standard-of-care arms. To address this and following-on from feedback from clinical experts obtained at an advisory board conducted on 16 January 2019, we have also provided a third scenario that uses a simple averaged curve (with equal 50:50 weight applied to the log-normal and generalised-gamma curves), as a **middle-ground option between AstraZeneca and ERG base-cases** that maintains good visual fit versus observed data from PACIFIC and produces long-term estimates of PFS benefit that are aligned with the opinion of UK clinical experts (shown in Figure 7 and Figure 8).

- **Scenario 1: log-normal distribution for durvalumab and generalised-gamma distribution for standard-of-care (ERG base-case)**

  In their assessment, the ERG determined that the Company's base-case "*was likely to overestimate PFS for people receiving durvalumab*". They used the more conservative log-normal extrapolation in their base-case.

  Using the log-normal curve for the durvalumab arm produced progression hazards that were ***higher*** than that in the placebo arm (generalised-gamma distribution) from month ~39 onwards (Figure 4; note: revised AstraZeneca base-case shown in Figure 5 for reference). Analytically, this caused the cost effectiveness model to produce a seemingly spurious result wherein a shorter treatment effect for durvalumab (of 3 years) resulted in greater QALY gain, than a longer treatment effect duration (of 5 years).

  Clinically, this meant that rate of progression or death in the durvalumab arm became higher than the rate of progression or death in the placebo arm from ~39 months onwards. There is no evidence of this from PACIFIC data (maximum duration of follow-up = 40.5 months and 41.0 months in the durvalumab and placebo arms, respectively). The unanimous opinion from 6 clinical experts[13] who were asked to comment on the plausibility of hazard curves crossing after 39 months was that this scenario is **clinically implausible**. This was also the consensus opinion from 10 clinical experts who attended an advisory board in London on 16 January 2019.

[13] 1:1s with five UK clinical oncologists and 1 UK medical oncologist conducted on 2nd–4th and 9th–10th of January 2019.

Figure 4. The ERG base-case (generalised-gamma PFS distribution for standard-of-care and log-normal for durvalumab; 5-year treatment benefit duration of durvalumab)

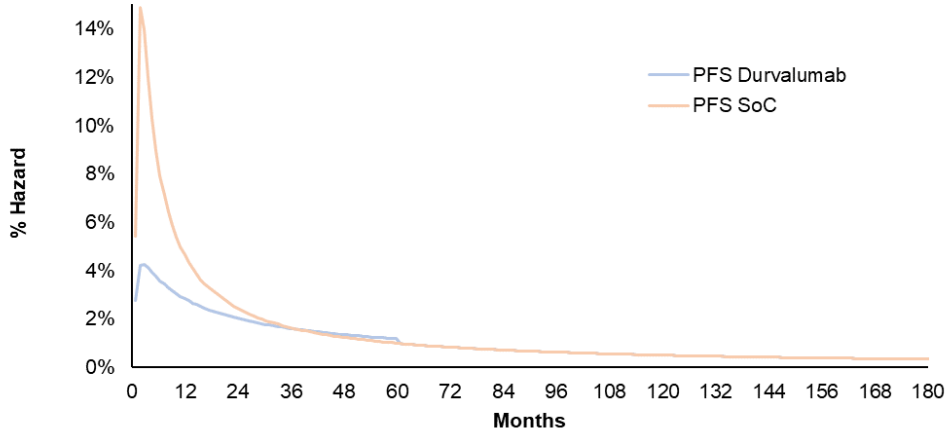
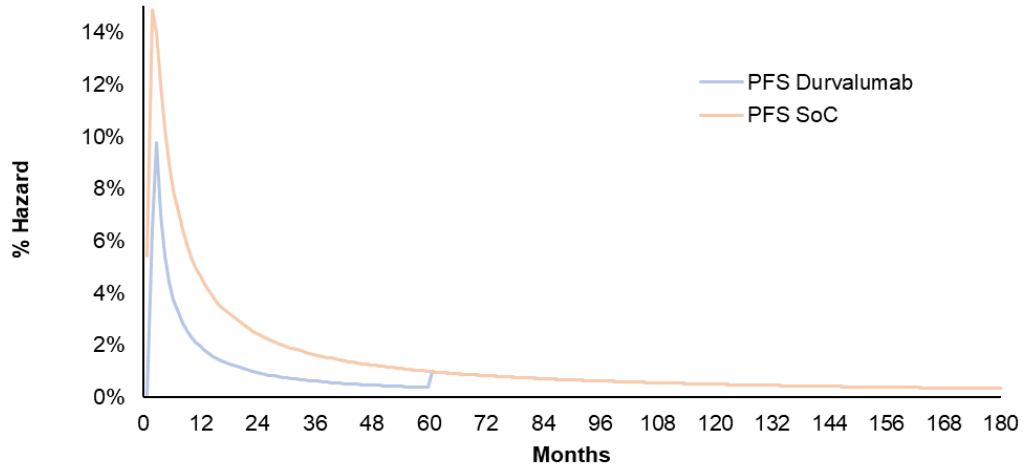


Figure 5. The revised AstraZeneca base-case (generalised-gamma PFS distribution for both arms; 5-year treatment benefit duration of durvalumab)



To ensure that the calculation in this scenario analysis is consistent with clinical expert opinion and does not produce spurious results, we introduced a logic check in the revised model whereby the progression hazard for the durvalumab arm was not allowed to exceed that for the placebo arm. The results of this analysis, which assumes equal risk of progression or death for durvalumab and placebo arms from the point at which the curves cross (~month 39 onwards) is shown in Note: minor changes to wording made in 25 January 2019 version
Table 7 (Appendix C (scenario 1): Cost-effectiveness analysis results using the ERGs' base-case (with model logic check included)*
It is worth noting that this treatment benefit duration (~39 months) contradicts observed data from PACIFIC and is substantially lower that the duration of benefit predicted by clinical experts.

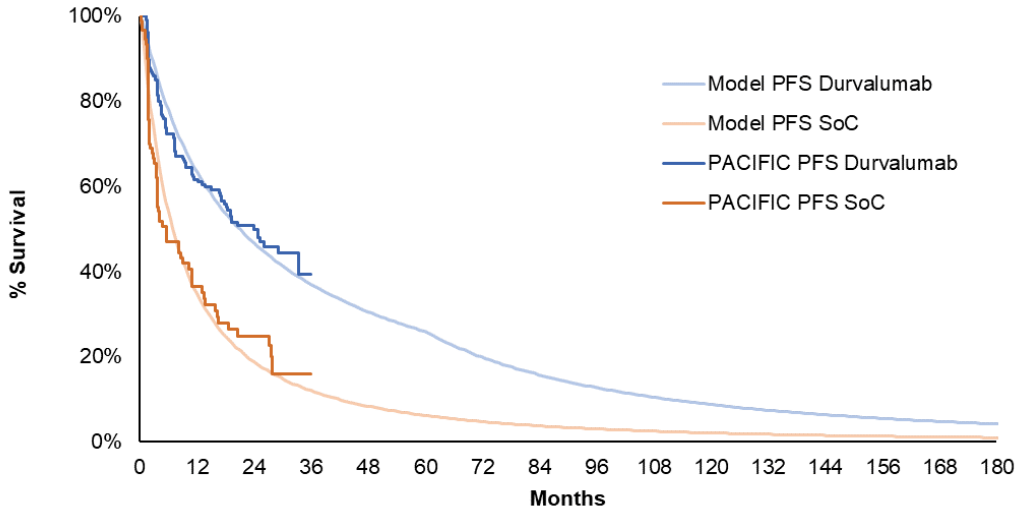
- **Scenario 2: log-normal distribution for both durvalumab and standard-of-care arms**

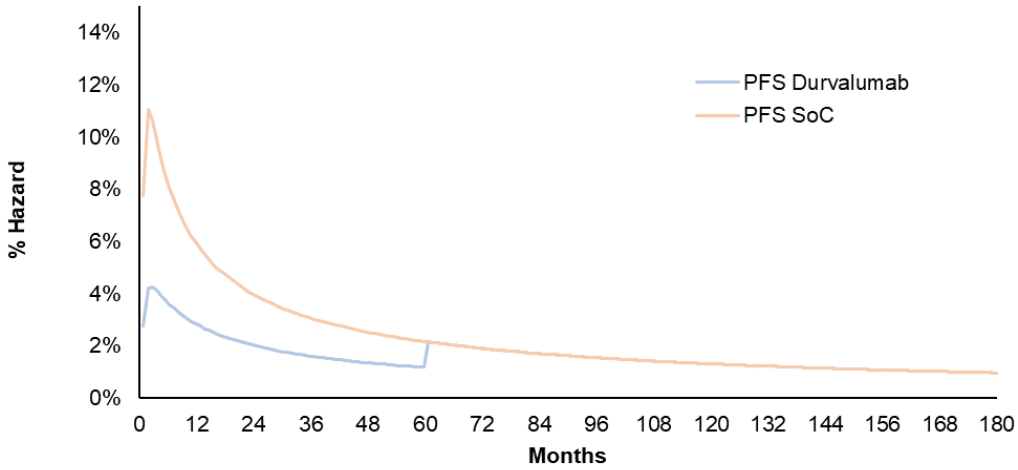
During the technical engagement meeting with NICE and the ERG, the technical team requested an additional scenario analysis using log-normal distributions for both durvalumab and standard-of-care arms, to overcome the issue of crossing hazard functions in the ERG base-case, whilst still modelling a conservative PFS benefit for durvalumab. Although using the same statistical fits for both arms avoids the crossing of hazard curves, this scenario nonetheless produces **clinically implausible** results since the log-normal distribution for standard-of-care severely underestimates long-term (5-year and 10-year) PFS rates relative to both historical clinical trial data and the opinion of UK experts (see Table 4). This was also the consensus opinion from 10 clinical experts who attended an advisory board in London on 16 January 2019, who agreed that the log-normal distribution for the standard-of-care arm was "*too pessimistic*".

Although we believe this scenario should not be used for decision-making, we nonetheless conducted this analysis for transparency at the request of the NICE technical team. Using log-normal PFS distributions for both durvalumab and placebo / standard-of-care arms (with other key assumptions being the same as the revised AstraZeneca base-case)[14] resulted in an ICER of £50,475 per QALY gained.

[14]Base-case assumptions = 5-year treatment benefit duration for durvalumab, age-related disutility included, PF health state utility from PACIFIC - 0.803 for durvalumab and 0.827 for placebo / standard-of-care (mixed effects models used to account for treatment-specific differences in AE rates), PD health state utility from Chouaid *et al.*, 2013 - 0.67 for both arms, costs of all subsequent treatments in PACIFIC included, no vial sharing, no "cure" assumption.

Figure 6. Survival and hazard curves using the log-normal PFS distributions for both durvalumab and standard-of-care arms (5-year treatment benefit duration assumed)





- **Scenario 3: simple average of generalised-gamma and log-normal distribution**

  In light of the NICE technical team's report, we consulted a number of (n=14) UK clinical experts[15] to obtain a range of long-term PFS estimates for durvalumab, given the benefit versus placebo observed to date. While the experts agreed that longer-term (10-year and 15-year) PFS rates predicted by the generalised gamma distribution were plausible, they felt that 3−5 year rates were slightly high. Conversely, consensus opinion was that whilst the log-normal distribution produced more realistic 3−5 year estimates, it underestimated long-term survival rates. Thus, to model a "middle-ground" scenario that produces reasonable PFS rates at both 3−5 years and also longer-term, we generated an additional average survival curve (calculated as a simple average of the log-normal, i.e. ERG base-case choice, and the generalised-gamma, i.e. AstraZeneca base-case choice). An equal weighting (50:50) was applied to the cumulative survival probabilities from the two distributions at each time point. The visual fit of the log-normal, generalised-gamma, and averaged survival curve to PACIFIC data are presented in Figure 7 and Figure 8; results from these analyses are presented in Table 8 (Appendix D (scenario 3): Cost-effectiveness analysis results using an average survival curve (obtained by assigning equal weight to log-normal and generalised-gamma distributions).

[15] 1:1s with five UK clinical oncologists and 1 UK medical oncologist conducted on 2nd–4th and 9th–10th of January 2019 and an advisory board conducted with 10 UK clinical experts on 16 January 2019.

Figure 7. Visual fit of PFS parametric functions to PACIFIC data; placebo arm, PD-L1 ≥1% group

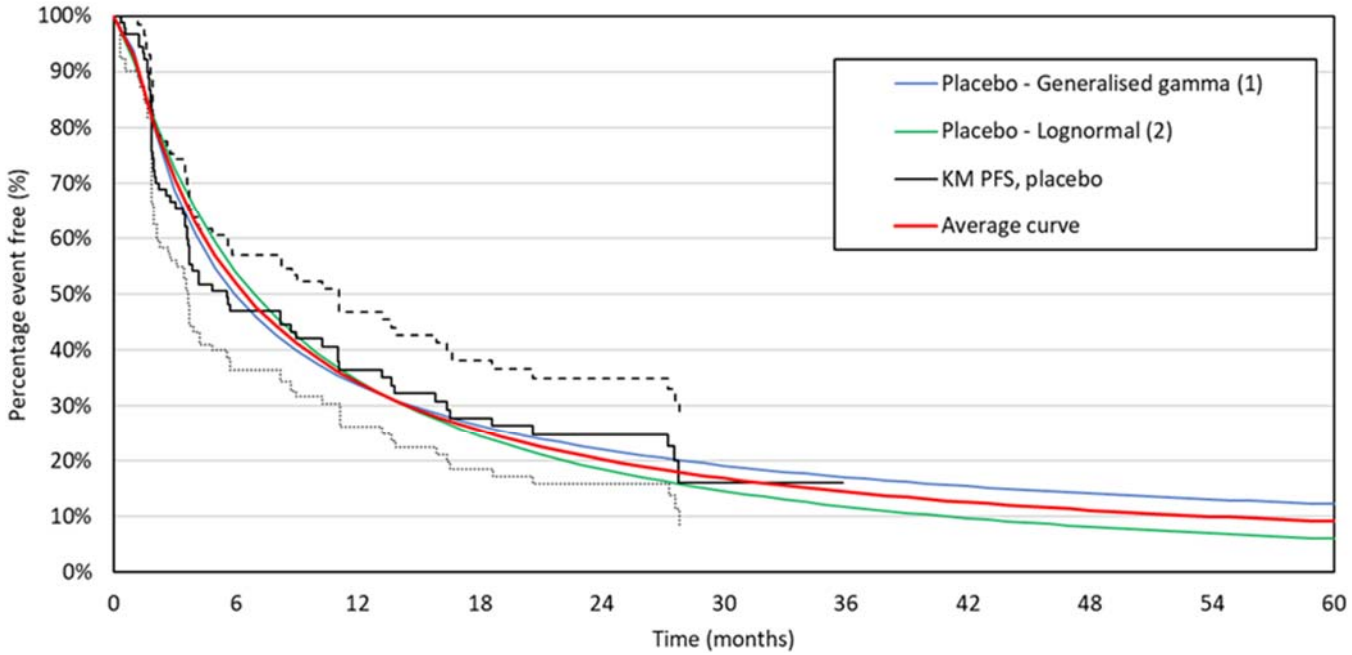
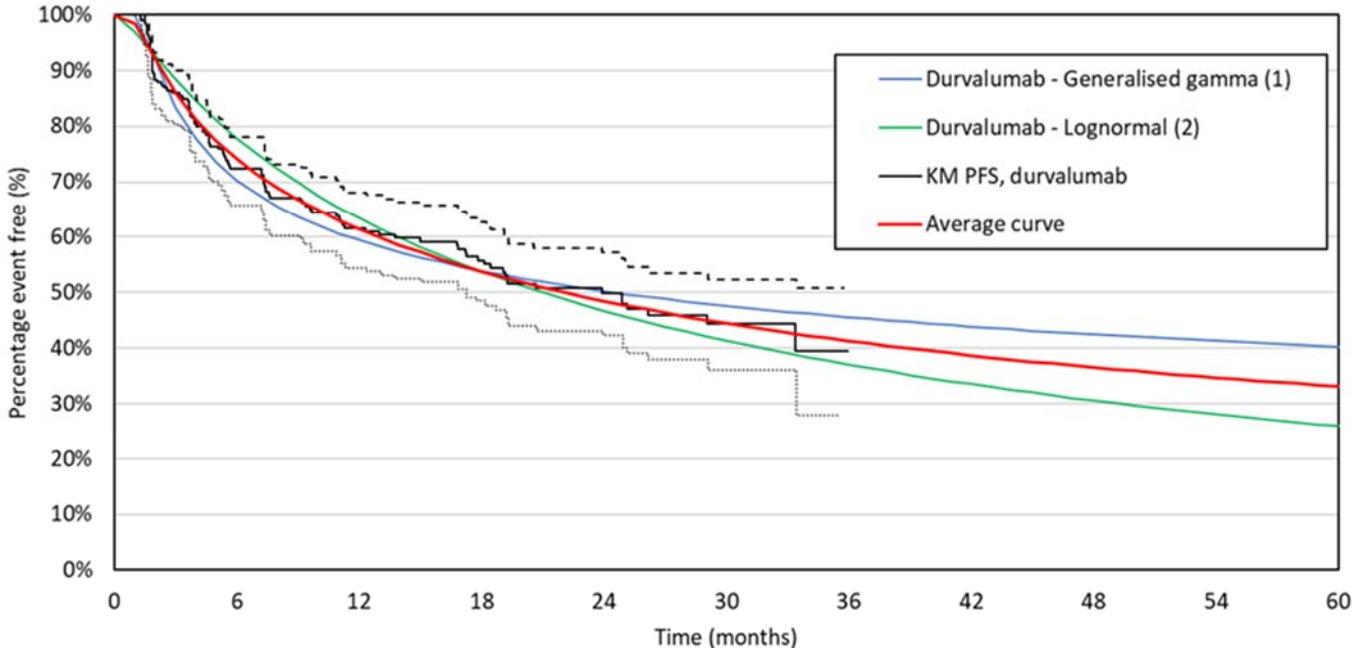


Figure 8. Visual fit of PFS parametric functions to PACIFIC data; durvalumab arm, PD-L1 ≥1% group



Treatment effect duration of 5 years for durvalumab monotherapy

At the time of the last data cut-off from PACIFIC (22 March 2018), maximum duration of follow-up was 40.5 months in the durvalumab arm and 41.0 months in the placebo arm. Patients in the durvalumab arm had lower hazards of progression or death compared to patients in the placebo arm, during the entire follow-up period (including the two years after completing durvalumab treatment). **These data support a durable and sustained treatment benefit of durvalumab even after discontinuation of treatment.**

How long this observed benefit will last is, however, presently unknown and will only be answered as data from PACIFIC mature. Final analyses from the PACIFIC study are expected in [redacted]; this data-cut will include approximately five years of follow-up and will provide a robust indication of the long-term benefit of durvalumab therapy. [redacted]

Our initial submission to NICE included a 10-year treatment benefit cut-off point for durvalumab. From this point onwards, the model assumed equal risk of progression or death in both durvalumab and placebo arms. This cut-off point produced valid OS estimates for durvalumab, which were in line with the survival benefit provided in NICE submissions for immunotherapies in the advanced metastatic Stage IV NSCLC setting (see Table 35 and Table 36 of the Company submission, Document B, for details).

Following feedback from the ERG and the NICE technical team and further discussions with clinical experts, we have revised our base-case to reflect a 5-year treatment effect.

Rationale for assuming a 5-year treatment effect is as follows:

- A treatment effect duration of five years is consistent with the opinion of the clinical expert consulted by NICE during this appraisal.
- During the technical engagement meeting, the clinical expert further explained that after five years, any new cancer that is detected is much more likely to be due to a new primary tumour and not a recurrence of the original radically-treated lung cancer. The odds of developing a new primary tumour at this stage are likely to driven by patient-specific factors (such as smoking and comorbidities) and are unlikely to vary by prior treatment received (i.e. CRT + active-follow-up or CRT + durvalumab). This is also consistent with the opinion of six other clinical experts[16] whose opinion was sought during the technical consultation period.
- As described above, assuming a 5-year treatment benefit (with generalised-gamma distributions for both durvalumab and placebo arms) produces clinically-plausible long-term (10-year and 15-year) estimates of PFS rates that are consistent with the range of values predicted by UK clinical experts.
- Finally, as highlighted in the draft technical report, a 5-year treatment effect (i.e. additional four years of benefit after treatment discontinuation) is within the range of what has been accepted by the NICE committee in immunotherapy appraisals in the advanced metastatic lung cancer setting. For instance, in TA520, the NICE committee accepted that a treatment benefit of atezolizumab could be sustained for up to 5 additional years following discontinuation of treatment. We note the technical team's concern that the treatment effect duration for durvalumab may be lower than that assumed in previous appraisals given the difference in maximum treatment duration (12 months for durvalumab versus 24 months for immunotherapies in the advanced metastatic setting). However, we wish to highlight that conversely, durvalumab is intended for patients with earlier-stage disease, where a curative outcome is still possible. Furthermore, the use of durvalumab directly after CRT harnesses the immune-priming effects of radiotherapy, maximising the potential to reinvigorate T-cells at a time when the volume of tumour burden is at its lowest. In this context, durvalumab may achieve greater systemic control, and therefore a prolonged treatment effect than what is achieved by immunotherapies approved in the advanced metastatic

[16] 1:1s with five UK clinical oncologists and 1 UK medical oncologist conducted on 2nd–4th and 9th–10th of January 2019.

setting. That said, we acknowledge that this is an area of remaining uncertainty, but one that can be addressed once five-year follow-up data from PACIFIC become available.

In the meantime, we have provided two sensitivity analyses at the request of the NICE technical team (one assuming a treatment effect duration of 10 years and another a duration of 3 years) to illustrate the impact of varying treatment benefit durations on ICERs. It is important to highlight that a three-year duration would contradict observed data from PACIFIC, which show no evidence of such a phenomenon from a maximum follow-up duration of 40.5 months in the durvalumab arm and 41.0 months in the placebo arm. As such, we consider it would be inappropriate to assume a three-year benefit duration in decision-making.

Modelling of AEs

Our initial company submission used the average utility values by health state for both arms. This decision was based on the following considerations:

- Our regression analyses did not identify any statistically-significant differences in utility between the durvalumab and placebo arms for PF or PD health states.
- Analysis of data from cancer-specific questionnaires (i.e. EORTC QLQ-C30 and EORTC QLQLC13) collected during the PACIFIC study showed there was no significant detrimental effect of durvalumab on patients' HRQL as compared to placebo.
- In the regression analysis for EQ-5D utility, the average difference in utility for durvalumab versus placebo was marginal (0.024 higher for placebo). The impact of including this non-statistically significant difference increased the company base-case by £951.

Based on feedback from the ERG and the NICE technical team, we have used mixed-effects models (which included treatment as a non-statistically significant covariate) in our revised base-case, to estimate PF health state utility values from PACIFIC clinical trial data that incorporate the impact of treatment-related AEs.

Utility values

Progression-free (PF) health state

We believe that EQ-5D data from PACIFIC is the most robust and reliable utility value for the PF health state:

- PACIFIC is a robust, Phase III, randomised, double blind, placebo-controlled study that included 303 patients with pre-CRT PD-L1 expression on ≥1% of tumour cells.
- PACIFIC is the **only** source of EQ-5D data that is available for the specific population that is being considered in the decision problem for this appraisal, i.e. adults with locally-advanced, unresectable, Stage III NSCLC whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based CRT).
- The average utility value for the PF health state derived from PACIFIC (0.815) is comparable to UK and UK-England population norms reported by Kind *et al.*,[17] 1999 (0.80) and Szende A, Janssen B, Cabases J, 2014[18] (0.81).

  This situation, where trial-based health-state utility values are either as high or higher than UK population norms for the same age, has been a consistent challenge for NICE appraisals in NSCLC. In TA531 (pembrolizumab for untreated PD-L1-positive metastatic NSCLC), the committee noted that the EQ-5D utility values collected in the KEYNOTE-024 trial appeared implausible, since the utility of patients with advanced metastatic lung cancer were higher at 360 days before death than the UK population norm for people of the same age. However, it was pointed out by the NHS England clinical lead that around 1/3 of patients in KEYNOTE-024 had an ECOG performance status of 0 (meaning these patients were fully active, able to carry on all pre-disease performance without restriction) and led relatively normal lives. The committee ultimately preferred the ERG-suggested approach of capping the trial-based EQ-5D utility values at 360 days before death to the UK population norm. Within the PD-L1 ≥1% group of PACIFIC, 49.5% and 50.2% of patients had a WHO performance-status score of 0 (meaning they were able to carry out all normal activity without restriction) and 1 (meaning patients were restricted in strenuous activity but ambulatory and able to carry out light work), respectively (see Table 4 of Document B). Taking this into account, we have no reason to believe that the PF health state utility values from PACIFIC lack face validity.

  Conversely, the ERGs' suggested PF health state utility value of 0.73 was sourced from the Ara and Brazier 2011[19] paper, which sought to provide health state utilities from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Table A4 of the supplementary information for this publication presents additional age / health condition stratified mean EQ-5D scores for prevalent health conditions. For patients aged 60 to ≤ 65 (n=2,739) with a history of health condition of '*General population irrespective of health status'*, the mean EQ-5D score (95% confidence interval, CI) was 0.8072 (0.793, 0.821). We believe this further validates the PF health state utility value from

[17]Kind P, Hardman G and Macran S. UK Population Norms for EQ-5D: Discussion paper 172. 1999. Available at: https://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf.

[18]Szende A, Janssen B, Cabases J, eds. Self-reported population health: an international perspective based on EQ-5D. Dordrecht: Springer, 2014 [accessed 20.9.18]. Available from: https://www.springer.com/gb/book/9789400775954

[19]Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health 2011;14(4):539-45.

PACIFIC, given the performance status of patients. For patients aged 60 to ≤ 65 (n=133) with a history of health condition of '*Cancer*', the mean EQ-5D score (95% CI) was 0.7297 (0.652, 0.807). No detail other than '*cancer*' is provided in the publication, and it is noted that a limitation of the data is that "*no information was collected that could be used to determine either the duration of the condition or the severity of the condition"*. We caution that this figure is not representative of the HRQL in the patient population of interest and should not be used in decision-making, especially when robust data from a Phase III randomised-controlled trial in the population of interest are available.

In summary, we believe that the PF health state utility value from PACIFIC is the most reliable source to inform economic modelling. This was also aligned with the opinion of 10 clinical experts who attended an advisory board in London on 16 January 2019. Therefore, our revised base-case still utilises PACIFIC data to inform the PF health state utility values, with treatment-specific differences captured using mixed-effects models (as described above; page 24).

Nonetheless, as per the NICE technical team's request, we have conducted a sensitivity analysis capping the PF health state utility value in the model to the ERGs' suggested value of 0.73. We are willing to collaborate with NICE to further investigate the potential discrepancies in trial-based and population-based utility values.

Progressed disease (PD) health state

We agree that the utility decrement for transitioning to PD health state (-0.034) is modest when compared with the values found in the literature and may not accurately describe the loss in HRQL upon disease progression, especially towards the end of life. In the PACIFIC study, utility data to inform the PD health state were collected only once (at the 30-day visit after confirmed radiologic progression) – therefore, we acknowledge that these data may not capture the worsening of HRQL over extended periods of time.

Given this potential limitation of PD health state utility data from the PACIFIC study, we consider using the ERGs' suggested value of 0.67 (i.e. utility associated with first-line progressed disease from Chouaid *et al*., 2013[20]) reasonable. However, it is important to bear in mind that the Chouaid *et al.* study included patients with more advanced disease than PACIFIC. At the time of the survey, the majority of patients in the study (82.1%) had Stage IV disease. It is conceivable that the HRQL decrement upon disease progression in the PACIFIC setting is less severe than that reported in the Chouaid *et al.* study.

[20]Chouaid C, Agulnik J, Goker E, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. *J Thorac Oncol*. 2013; 8(8):997-1003.

Subsequent therapies:

In our original submission, the costs of subsequent therapies were included in the model if they were used in more than 3% of patients in either treatment arm in the PACIFIC study. This arbitrary threshold has been removed from our revised base-case, as per the NICE technical team's request during the engagement meeting. The costs of all subsequent therapies in the PACIFIC study are now included. Including all subsequent therapies decreases the revised base-case ICER by £73 to £28,360 per QALY gained.

Vial sharing:

Our initial submission assumed the adoption of vial sharing in clinical practice (i.e. a situation where centres are able to optimise the administration of durvalumab and other chemotherapies so that no drug is wasted). This is aligned with policy initiatives for immuno- and chemo-therapy treatments put in place by NHS England. The impact of no vial sharing (i.e. total wastage) was tested in a sensitivity analysis.

In their draft report, the NICE technical team determined that a vial sharing assumption was unrealistic due to the small number of patients who are expected to be eligible for durvalumab therapy. During the technical engagement period, we consulted several (n=6) UK clinical experts[21] to understand whether vial sharing would be feasible in practice – the unanimous opinion was that this was a reasonable assumption considering the duration of durvalumab treatment. The exact level of vial sharing is however difficult to predict at this stage. In the interest of minimising uncertainty, we have removed the vial sharing assumption from our revised base-case and instead explored it in a scenario analysis (using the same 30% sharing assumption as the ERG).

Additional sensitivity analyses: mixed cure-rate models

Mixed cure-rate models (MCMs), as the name suggests, explicitly model survival as a mixture of two types of patients – those who are "cured" and those who are not. In their draft report, the NICE technical team noted they were mindful that a proportion of patients remained progression-free at 10 years in both the Company and the ERG models. Given this, the technical team queried if cure-rate models might be a relevant model structure for this appraisal.

[21] 1:1s with five UK clinical oncologists and 1 UK medical oncologist conducted on 2nd–4th and 9th–10th of January 2019.

We agree these models are appropriate in this appraisal context for a number of reasons (described in detail in our response to question 7) and have used two different approaches for modelling cure:

- The first is a 'simple approach' where patients who are alive and progression-free (i.e. show no evidence of disease) after a certain time point are considered "cured". From this point onwards, the hazard of progression (and future cancer death) becomes zero. Patients in this health state are only subjected to the hazard of death (from any cause) derived from age-matched UK life tables.
- The second approach uses a parametric mixture cure-rate model. Mixture cure-rate models assume that there are different event risk profiles within a study population, with a proportion of patients have a reduced risk of disease, and the remainder following a typical survival distribution for that particular disease. The generalised-gamma distribution was the best statistical fit but produced a clinically-implausible predicted cute rate of ~0%. Hence, the second-best statistical fit, i.e. the log-normal distribution was used for both placebo / standard-of-care and durvalumab arms. This produced a more plausible cure rate of [redacted]. It is worth noting, however, that the generalised-gamma function is flexible in itself and may have already captured the different hazard structure for the cured patients. Full details of the mixture cure-rate model are provided in Appendix E: use of mixture cure-rate model to estimate long-term survival with durvalumab in unresectable, Stage III NSCLC patients. Results from these analyses are provided in Table 14.

Top-line results:

Note: The following table shows revised AstraZeneca base-case results in the overlapping CRT population, aligned to the PACIFIC clinical trial. For results in the sequential CRT population, please see Appendix B: The cost-effectiveness of durvalumab after sequential CRT.

Table 5. AZ revised base-case (overlapping CRT population)

Assumptions	Rationale	ICER	Change from revised base case	Change from submission base case
AZ revised base-case				
Generalised-gamma PFS extrapolations for both arms, 5-year treatment benefit duration, age-related disutility included, PF health state utility from PACIFIC (mixed effects models used to account for treatment-specific	As described above	£28,433	N/A	+ £9,113

differences in AE rates - 0.803 for durvalumab and 0.827 for placebo / standard-of-care, PD health state utility from Chouaid *et al*., 2013 - 0.67 for both arms, costs of all subsequent treatments in PACIFIC included, no vial sharing, no "cure" assumption				
Sensitivity analyses (no "cure" assumption)				
Treatment effect duration (durvalumab)				
3 years	Minimum duration requested by the NICE technical team (note: this contradicts observed data from PACIFIC, which show no evidence of such a phenomenon from a maximum follow-up duration of 40.5 months in the durvalumab arm and 41.0 months in the placebo arm)	£35,838	+ £7,405	+ £16,518
10 years	Rationale as provided in initial AZ submission (this cut-off point produces valid OS estimates for durvalumab, that are in line with the survival benefit provided in NICE submissions for immunotherapies in the advanced metastatic Stage IV NSCLC setting)	£22,528	- £5,905	+ £3,208
Utility (note: age-related decrement has been included in both scenarios) Note: values corrected in 25 January 2019 version				
PF = 0.73 for both arms; PD = 0.67 for both arms; disutility of AEs included (see Document B, Appendix P for further details)	ERG-preferred utility values sourced from the literature	£30,978	+ £2,545	+ £11,658
PF = 0.73 for placebo / standard-of-care and 0.706 for durvalumab; PD = 0.67 for both arms	ERG-preferred utility values sourced from the literature (same as above), but with treatment-related decrement from PACIFIC added to capture difference in incidence of AEs	£33,137	+ £4,704	+ £13,817

Vial sharing				
30% vial sharing included	Scenario explored by the ERG; reflects a degree of vial sharing consistent with UK clinical expert opinion (see page 27 for further details)	£27,931	- £502	+ £8,611
AZ revised base-case with assumption that patients who are progression-free at 5 years are clinically "cured"				
See "AZ revised base-case". Includes assumption that patients who are progression-free at 5 years are "cured"	One of two cure fraction modelling approaches explored as per the technical team's suggestion	£22,503	- £5,930	+ £3,183
Sensitivity analyses using AZ revised base-case + assumption that patients who are progression-free at 5 years are clinically "cured"				
Treatment effect duration			Difference relative to cure at 5 years base-case	
3 years	As described above	£29,138	+ £6,635	+ £9,818
10 years		£22,503	£0	+ £3,183
Utility (note: age-related decrement has been included in both scenarios) Note: values corrected in 25 January 2019 version				
PF = 0.73 for both arms; PD = 0.67 for both arms; disutility of AEs included (see Document B, Appendix P for further details)	As described above	£24,592	+ £2,089	+ £5,272
PF = 0.73 for placebo / standard-of-care and 0.706 for durvalumab; PD = 0.67 for both arms		£26,286	+ £3,783	+ £6,966
Vial sharing				
30% vial sharing included	As described above	£22,094	- £409	+ £2,774
AZ revised base-case with assumption that patients who are progression-free at 10 years are clinically "cured"				
See "AZ revised base-case". Includes assumption that patients who are progression-free at 5 years are "cured"	One of two cure fraction modelling approaches explored as per the technical team's suggestion	£27,576	- £857	+ £8,256
Sensitivity analyses using AZ revised base-case + assumption that patients who are progression-free at 10 years are clinically "cured"				

Treatment effect duration			Difference relative to cure at 10 years base-case	
3 years	As described above	£34,889	+ £7,313	+ £15,569
10 years		£21,684	- £5,892	+ £2,364
Utility				
PF = 0.73 for both arms; PD = 0.67 for both arms; disutility of AEs included (see Document B, Appendix P for further details)	As described above	£30,060	+ £2,484	+ £10,740
PF = 0.73 for placebo / standard-of-care and 0.706 for durvalumab; PD = 0.67 for both arms		£32,154	+ £4,578	+ £12,834
Vial sharing				
30% vial sharing included	As described above	£27,087	- £489	+ £7,767

Questions for engagement

Issue 1: Overlapping vs sequential prior chemoradiation therapy (CRT) and generalisability of PACIFIC trial	
1. Are the results of the PACIFIC trial generalisable to clinical practice in the NHS?	We believe that PACIFIC trial data are broadly generalisable to patients who will be treated with durvalumab in clinical practice within the NHS. • As mentioned above, data from the EAP show that [redacted] **overlapping**, [redacted], **CRT in real-world practice** [redacted], i.e. the population included in the PACIFIC clinical trial. • A comparison of patient characteristics in the PACIFIC population versus a cohort of patients from the National Cancer Registration and Analysis Service in England show [redacted] age, gender, disease stage, and performance status distributions in the two datasets (presented in Table 1). Generalisability of the PACIFIC population to UK Stage III NSCLC patients who receive curative-intent overlapping CRT was also confirmed by UK clinical experts (see evidence submitted in response to ERG clarification questions).

2. Are clinical outcomes likely to differ between overlapping and sequential chemoradiation therapy? Does this affect the generalisability of the trial?	In the absence of clinical trial evidence, the opinion of clinical experts and real-world experience are the most reliable sources of information to address this. As stated in the draft technical report, "*clinical expert advice indicates that the differences in survival outcomes [associated with durvalumab] for overlapping compared to sequential CRT is likely to be small*". This is consistent with the insights from three clinical experts[22] obtained by AstraZeneca during the technical consultation period, feedback from UK oncologists (n=2) experienced in treating patients with durvalumab after both sequential and overlapping CRT as part of the EAP, and the conclusion of authors who studied the occurrence of lymphopenia after sequential and overlapping CRT to understand implications on the benefit derived from durvalumab in these two populations[23]. Ultimately, this question will be answered by evidence collected as part of PACIFIC-R and PACIFIC-6 studies (data read-outs from both are expected [redacted]). Given the opinion of clinical experts and real-world experience (described in the previous paragraph), evidence shown in Table 2 (showing a comparison of demographic and disease characteristics of sequential and overlapping CRT patients from the NCRAS) and data from the EAP, which show that durvalumab tends to be used after overlapped CRT in [redacted] UK patients in any case, we do not anticipate significant generalisability concerns from inclusion of sequential patients in this decision-problem.
Issue 2: Treatment effect duration	
3. Is a 3 to 5 year treatment effect duration for durvalumab appropriate?	In the absence of long-term follow-up data from PACIFIC, we consider a 5-year treatment effect duration reasonable, based on insights from UK clinical experts, clinical plausibility of predicted long-term (10- and 15-year) PFS benefit* versus standard-of-care, and precedence from previous immunotherapy appraisals in the advanced metastatic setting (described in detail above; see rationale for "Treatment effect duration of 5 years for durvalumab monotherapy"). However, it is worth highlighting that there is no evidence to suggest that the treatment effect duration is not longer than 5 years. To address this, we have included a scenario analysis where a treatment effect duration of 10 years is applied. As noted previously, this cut-off point produces valid OS estimates for durvalumab, which were in line with the survival **benefit** provided in NICE submissions for immunotherapies in the advanced metastatic Stage IV NSCLC setting.

[22] 1:1s with three UK clinicical oncologists conducted on 2nd and 4th of January 2019.

[23] Westley et al. A retrospective analysis of lymphopenia rates during and after sequential and concurrent radical chemoradiotherapy for patients with stage III non-small cell lung cancer (NSCLC). Presented at the 17th Annual British Thoracic Oncology Group meeting (23rd–25th January; Ireland, Dublin).

	At the request of the NICE technical team, we have also provided a scenario analysis that includes 3-year treatment effect duration. However, as emphasised above, this contradicts observed data from PACIFIC and is thus not appropriate for use in decision-making. **Using generalised-gamma distributions for both durvalumab and standard-of-care arms*
Issue 3: Progression-free survival (PFS) extrapolation	
4. Is it reasonable to use a model that predicts that 37%, 26% and 14% of the durvalumab arm would be progression free at 3, 5 and 10 years respectively? (This is the log-normal distribution used to extrapolate PFS in the durvalumab arm)	Clinical experts consulted by AstraZeneca during this technical consultation period stated that the longer-term (10- and 15-year) benefit of durvalumab predicted using generalised-gamma distributions for both arms and assuming a 5-year treatment benefit for durvalumab were "*reasonable*"[24]. As explained above, using the log-normal PFS distribution for durvalumab and the generalised-gamma distribution for placebo leads to a clinically implausible scenario where hazards functions for durvalumab and placebo arms cross at ~39 months. In this scenario, the hazard of progression or death in the durvalumab arm becomes higher than the hazard of progression or death in the placebo arm from the point at which the hazard curves cross (Figure 4). There is no evidence of such a phenomenon from PACIFIC data (maximum duration of follow-up = 40.5 months and 41.0 months in the durvalumab and placebo arms, respectively). Clinical experts consulted by AstraZeneca during the technical consultation period[25] confirmed there is **no clinical rationale** to support a crossing of durvalumab and placebo hazard curves. It is also worth noting that even without the issue of crossing hazard curves, the long-term PFS benefit predicted using the log-normal curve for durvalumab and generalised gamma for standard-of-care* (8.6% and 6.6% at 10 years and 15 years, respectively) is below the range predicted by 6 UK clinical experts (10%−25%; confirmed at an advisory board held on 16 January 2019 with 10 UK clinical experts). This log-normal distribution may thus underestimate the PFS tail, comprising patients who achieve good long-term outcomes on overlapping CRT followed by durvalumab.

[24] 1:1s with five UK clinical oncologists and 1 UK medical oncologist conducted on 2nd–4th and 9th–10th of January 2019 and an advisory board conducted with 10 UK clinical experts on 16 January 2019. Note: experts believed that the 3- and 5-year PFS (percentage point) benefit for durvalumab versus placebo predicted by the generalised-gamma curve was slightly high. See Scenario 3 for more information on how this was addressed.

[25] 1:1s with five UK clinical oncologists and 1 UK medical oncologist conducted on 2nd–4th and 9th–10th of January 2019 and an advisory board conducted with 10 UK clinical experts on 16 January 2019.

	**Assuming equal risk of progression or death in durvalumab and placebo arms from the point at which hazard curves cross.*
5. Is it reasonable to use a model that predicts that 17%, 12% and 8% of the standard care arm would be progression free at 3, 5 and 10 years respectively? (This is the generalised gamma distribution used to extrapolate PFS in the standard care arm).	Yes. As shown in Table 4, these values are consistent with evidence from historical clinical trials in this setting and estimates from UK clinical experts. The generalised-gamma curve for standard-of-care also achieves the best statistic fit and visual fit to PACIFIC data. We believe that this is the most plausible parametric survival curve for the standard-of-care arm and should be used in decision-making.
6. The Decision Support Unit (DSU) advise that fitting separate distributions to treatment arms should be justified using clinical expert judgement, biological plausibility and robust statistical analysis (DSU Technical Support Document 14). Have the DSU criteria been sufficiently met to justify	The proposed ERG base-case of fitting two different distributions to the treatment arms to extrapolate observed PFS data within PACIFIC leads to a situation where the hazards of progression or death for durvalumab and standard-of-care cross at approximately month 39 within the model (with the hazard for durvalumab being higher than that for standard-of-care). The crossing of the projected hazards contradicts observed data from PACIFIC and is considered clinically implausible by both oncologists[26] and external health economics experts whose opinions were sought during the technical consultation period. This paradoxical crossing of progression hazard violates the minimal internal validity requirement that is emphasised in the DSU TSD 14 for robust statistical analyses. As such, we do not believe there is sufficient rationale to justify fitting different statistical distributions to durvalumab and standard-of-care arms.

[26] 1:1s with five UK clinical oncologists and 1 UK medical oncologist conducted on 2nd–4th and 9th–10th of January 2019 and an advisory board conducted with 10 UK clinical experts on 16 January 2019.

fitting different model types per treatment arm?	
7. Would a mixture cure rate model be appropriate for this topic?	We agree that cure models are a sensible approach given the appraisal context. Durvalumab is indicated for the treatment of locally-advanced, unresectable, Stage III NSCLC patients who have completed radical overlapping or sequential CRT. Treatment-intent in this setting is curative and a fraction of patients achieve good long-term outcomes on the current standard-of-care (i.e. active follow-up). In real-world UK practice, patients who are alive and progression-free five years after CRT are effectively considered to be "cured" and discharged to their GP's care, given the low risk of relapse and disease progression (from the primary lung cancer) at this time point. The addition of durvalumab following CRT (i.e. the "PACIFIC regimen") represents a vital opportunity to prevent / significantly-delay systemic disease spread, harnessing the immune-priming effects of CRT at a time when tumour burden is at its lowest. Although 5-year data from PACIFIC are not yet available, available PFS and OS analyses support the notion that durvalumab will substantially increase the proportion of patients who are alive and progression-free five years after receiving treatment and are thus effectively "cured". As noted in the draft technical report, this is also reflected in extrapolations of observed data from PACIFIC, regardless of whether AstraZeneca's or the ERG's base-case is used. Cure models are also appropriate from a methodological perspective. In clinical situations where subsets of patients are not subject to disease progression, the average hazard function is likely to become more complex than what can be adequately accounted for by a single survival function. In these situations, a cure fraction model can provide a suitable statistical framework that allows the application of different hazard functions for "cured" and "not cured" fractions. Mixture cure-rate models, in particular, can produce more-coherent statistical fits and clinically-justifiable extrapolations. In doing so, these models can reduce the level of uncertainty in decision-making in instances where the observed survival curves demonstrate complex underlying hazards (as is the case for the durvalumab arm in PACIFIC).
Issue 4: Utility values	
8. Should utility values incorporate an age-related disultility?	We agree that given the average starting age in the model (63.1 years), the time horizon of the analysis (lifetime; 40 years), and the curative intent with which treatment is given, the utility values should incorporate an age-related disutility as reflected by the general population.

	In our revised base-case, mean health state utility values over the lifetime time horizon are adjusted by age-related decrements, to reflect the aging of the cohort. The decrement applied (-0.004) was calculated as the difference between the weighted health state EQ-5D-3L index by age and sex presented in Kind 1999[27] for the cohort of individuals aged 55−64 (0.79) and those aged 75+ (0.74), i.e. 0.79 - 0.74 = -0.004. This decrement was applied additively in each cycle of the model.
9. Is the utility value for the progression-free state taken from the literature appropriate (0.73)?	As explained above (see Utility values, page 24), robust and reliable PF health state utility data were collected in the PACIFIC study (based on 1,740 completed EQ-5D-5L questionnaires from 291 patients). This is the **only** source of utility data in the population of interest, i.e. adults with locally-advanced, unresectable, Stage III NSCLC whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based CRT. The PF health state utility value from PACIFIC (0.815) is comparable to UK and UK-England population norms reported by Kind *et al.*,[28] 1999 (0.80) and Szende A, Janssen B, Cabases J, 2014[29] (0.81) and we see no reason to question the face validity of this data considering the performance status of patients included in the PACIFIC study. As such, we feel the use of general utility values for "cancer" is inappropriate when robust evidence from the PACIFIC study is available, especially considering that the authors of the study from which the ERG's preferred value was derived themselves caution that "*no information was collected that could be used to determine either the duration of the condition or the severity of the condition*".
10. Is the utility value for the progressed disease state taken from the literature appropriate (0.67)?	We acknowledge the ERGs' and NICE technical team's concern that the utility decrement for transitioning to progressed disease (-0.034) derived from PACIFIC is modest when compared with the values found in the literature and that this value may not adequately capture the loss in HRQL experienced upon disease progression, especially over prolonged time-frames and towards the end of life. Given the limitations of PD health state utility data from PACIFIC (described above; see Utility values), we agree that applying the utility value sourced from literature (i.e. the Chouaid *et al.*, 2013 study) is understandable. However, we caution that these data were captured in a population of patients with more advanced disease (82.1% of patients had

[27] Kind P, Hardman G, Macran S. UK population norms for EQ-5D 1999 [Available from: https://www.york.ac.uk/che/pdf/DP172.pdf.

[28] Kind P, Hardman G and Macran S. UK Population Norms for EQ-5D: Discussion paper 172. 1999. Available at: https://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf.

[29] Szende A, Janssen B, Cabases J, eds. Self-reported population health: an international perspective based on EQ-5D. Dordrecht: Springer, 2014 [accessed 20.9.18]. Available from: https://www.springer.com/gb/book/9789400775954

	advanced metastatic Stage IV NSCLC at time of survey) [30] and may therefore over-estimate the deterioration in HRQL that is likely to be experienced by patients in the PACIFIC setting.
Issue 5: Modelling of adverse events (AEs)	
11. Should utility values be treatment specific to capture the full impact of treatment-related AEs?	We acknowledge the ERGs' concern that the full impact of treatment-related AEs may not have been captured in the base-case health-state utility values. To address this, we have used the ERG's base-case mixed-effects models (which included treatment as a non-statistically significant covariate) to estimate PF health-state utility values from PACIFIC clinical trial data. This approach addresses the ERG's concern regarding the inclusion of the full impact of treatment-related AEs, whilst using PACIFIC data (focusing on the population of interest) to inform utility values for the PF health state.
Issue 6: Vial sharing	
12. Is it appropriate to assume no vial sharing?	As mentioned previously, the unanimous opinion from clinical experts consulted during the technical engagement period (n=6) was that vial sharing is a reasonable assumption, considering the maximum duration of durvalumab treatment (12 months), i.e. patients who commence treatment at different times are likely to overlap during their treatment period. Nonetheless, in the interest of minimising uncertainty, we have removed the vial sharing assumption from our revised base-case and instead explored it in a scenario analysis (using the same 30% sharing assumption as the ERG).
Issue 7: End of life considerations	
13. Under standard care, is the life expectancy of adults with locally-advanced unresectable Stage III NSCLC whose tumours express PD-L1 on ≥1% of tumour cells	We have provided multiple sources of UK-specific data in our submission, all of which indicate that life expectancy in the population of interest is <24 months. These data are reiterated below for reference (the Public Health England data are of particular note since these capture the suboptimal real-world survival outcomes in the specific population of interest): • NLCA (2016 audit period)[8] – Average 1-year survival rate from diagnosis (all Stage III) = 42.5% • Møller *et al* audit (patients treated with radical radiotherapy)[117] – 2-year survival probability from diagnosis = <25%

[30] At the time of the survey, the majority of patients in the study (82.1%) had Stage IV disease.

and whose disease has not progressed following platinum-based CRT more than 24 months?	• RCR audit[56] – Median OS (radical radiotherapy) = 22 months; 2-year survival rate = 44% – 2-year survival rate (overlapping CRT) = 46% • Public Health England (NHS digital)[45] – Median OS (unresected Stage III patients who had received overlapping CRT) = [redacted] months • SOCCAR RCT[111] – Median OS from ***start*** of overlapping CRT = 24.3 months – Median OS from ***start*** of sequential CRT = 18.4 months • UK KEE opinion[44] – Median OS (mean of 10 responses = 22.3 months) We note the technical team's preliminary judgement that durvalumab does not meet the end-of-life criteria specified by NICE given the median OS of 29.1 months (95% CI: 17.7, NR) in the placebo arm of PACIFIC (PD-L1 ≥1% group). However, **given the end-of-life criteria are a UK-specific consideration, we believe that UK data should be taken into account in decision-making**. We also urge the committee to consider the generally poorer prognosis of patients who receive sequential CRT when deliberating on the applicability of end-of-life criteria to this appraisal. Finally, we are conscious that this situation is not unique to the durvalumab appraisal and feel that this topic warrants a broader discussion with NICE. We would be happy to collaborate to identify a way of reconciling the use of trial versus real-world survival data for decision-making purposes.
14. Does durvalumab extend life for more than 3 months compared to standard care?	We consider this criterion met on account of the following evidence: Durvalumab met the overall survival (OS) primary endpoint in the PACIFIC study, demonstrating a significant survival benefit versus placebo in both the ITT population (HR 0.68; *P*-value=0.0003) and the PD-L1 ≥1% group (HR 0.54; *P*-value=0.0003). Median OS was not reached in the durvalumab arm in either the ITT population or the PD-L1 ≥1% group; however, the lower bound of the 95% CI (of 34.7 months) for durvalumab indicates a benefit of **at least six months** versus the median OS for placebo (22.9 months) in the ITT population. Evidence on the OS benefit of durvalumab is presented in the Section B.2.6 of the Company submission and also summarised below (information taken from Document A, Table 11):

	PACIFIC RCT OS data (durvalumab versus active follow-up): • **ITT** – HR (95% CI), *P*-value = 0.68 (0.53, 0.87), *P*=0.003 – Median OS ▪ Durvalumab: NR (95% CI 34.7, NR); lower bound indicates OS benefit of 6 months versus median OS for placebo (below) ▪ Placebo: 28.7 (22.9, NR) • **PD-L1 ≥ 1% group** – HR (95% CI), *P*-value = 0.54 (0.35, 0.81), *P*=0.003 – Median OS ▪ Durvalumab: NR (95% CI NR, NR); lower bound not reached in durvalumab arm, verses 17.7 months for placebo ▪ Placebo: 29.1 (95% CI 17.7, NR) – OS24 ▪ Durvalumab: 72.8% (95% CI 66.2, 78.4) ▪ Placebo: 53.6% (95% CI 42.5, 63.4)
Issue 8: Cancer drugs fund (CDF)	
15. Does durvalumab meet the criteria for inclusion in the Cancer Drugs Fund?	As stated in the draft technical report, the "CDF is a potential option if there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies". We acknowledge there is "remaining clinical uncertainty" relating to the long-term efficacy of durvalumab in both sequential and overlapping CRT populations. For the overlapping CRT population, this relates to the long-term survival benefit of durvalumab versus standard-of-care and whether this is best captured by the ERGs' or AstraZeneca's base-case, or indeed a middle-ground approach (represented in the average survival curve scenario). This will ultimately be answered as data from PACIFIC mature [redacted]. In the

	meantime, we have provided results using as many as six[31] different frame-works (with supporting sensitivity analyses) to help the NICE committee establish the most-plausible ICER / range of ICERs for decision-making: • Revised company base-case (generalised-gamma for both arms, no "cure" assumptions) • Revised company base-case (generalised-gamma for both arms) with patients who are progression-free at five years assumed to be "cured" • Revised company base-case (generalised-gamma for both arms) with patients who are progression-free at ten years assumed to be "cured" • Mixed cure-rate model (using log-normal distributions for both arms) • The ERG base-case with model logic check (generalised-gamma for standard-of-care and log-normal for placebo) • A "middle-ground" average survival curve approach (assigning equal weights to generalised-gamma and log-normal PFS curves). For the sequential CRT population, the main source of uncertainty stems from the lack of clinical trial data at present. This will be addressed in [redacted] also, as results from PACIFIC-R and PACIFIC-6 studies become available. In the meantime, we request that the NICE committee consider granting conditional access to durvalumab (through the CDF) in this population, given significant unmet need and a small number of eligible patients. This will ensure that the full licensed population can continue to benefit from this curative-intent therapy over the next two years, as AstraZeneca collect relevant clinical trial data. As mentioned previously, **we are committed to working with NICE and NHS England throughout the next steps of the appraisal process to ensure we satisfy the necessary criteria to be considered for inclusion in the CDF**.

[31] In addition, a scenario that uses log-normal PFS distributions for both durvalumab and standard-of-care arms (with no "cure" assumptions) was provided for transparency.

Appendix A. Visual fit of PFS parametric functions to PACIFIC data (all statistical distributions considered)

Figure 9. Placebo arm, PD-L1 ≥1% group

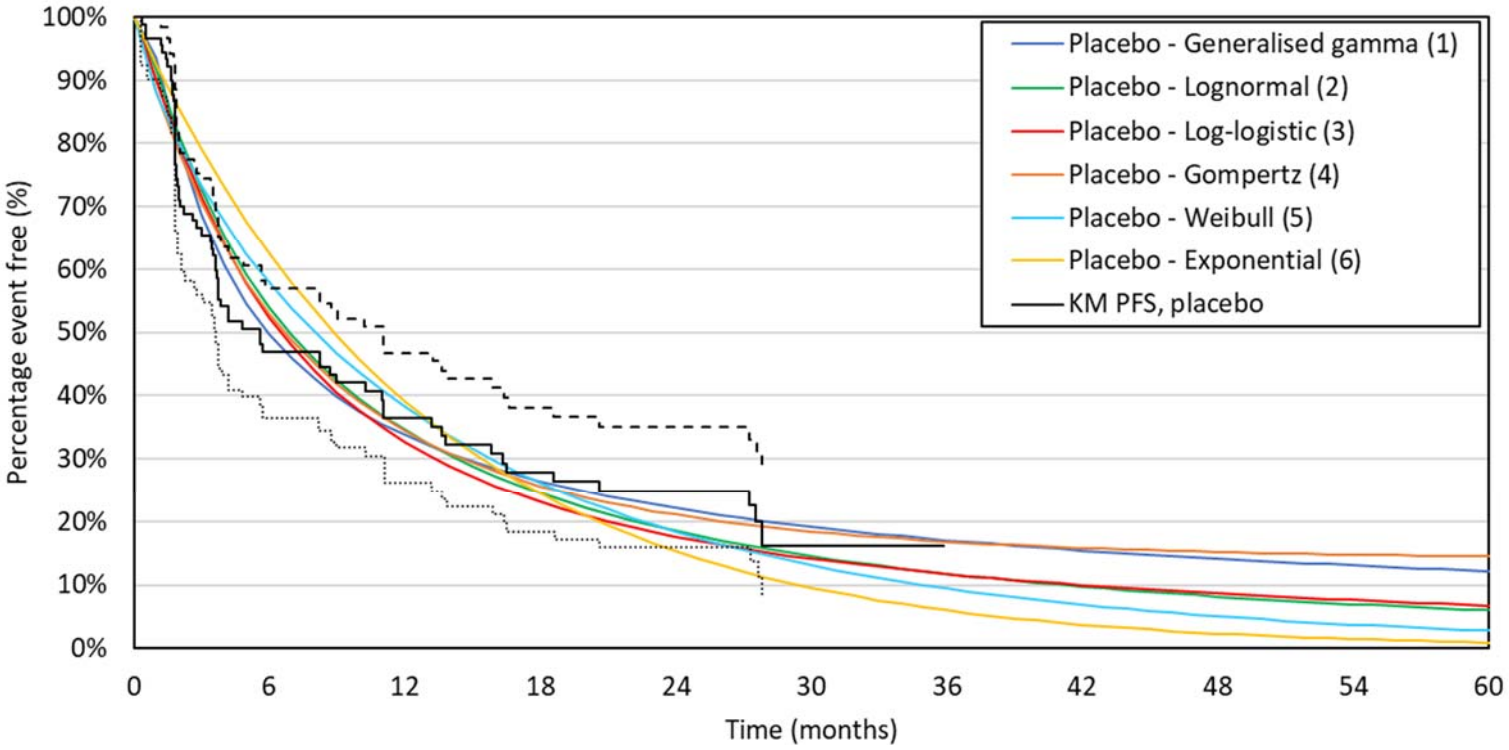
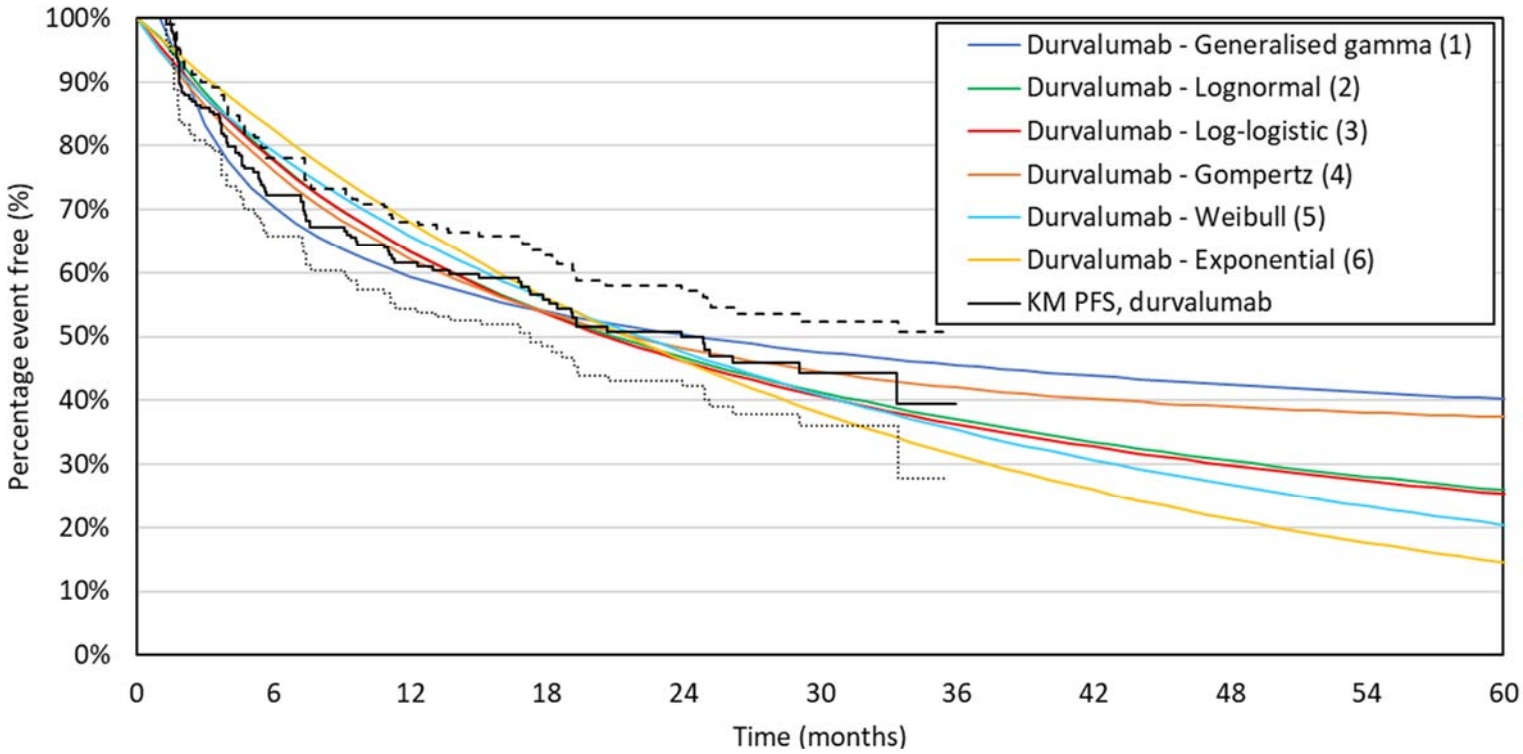


Figure 10. Durvalumab arm, PD-L1 ≥1% group



Appendix B: The cost-effectiveness of durvalumab after sequential CRT

Methodology

The cost-effectiveness analysis for durvalumab after sequential CRT uses the same semi-Markov approach as the revised AZ base-case in the overlapping CRT population. The analysis is based on the following key assumptions:

- The same percent risk reduction for durvalumab versus placebo as in the overlapping CRT population
- The same HRQL, level and type of subsequent therapy use, and incidence of AEs as the overlapping CRT population.

Data sources used to model PFS in patients who receive sequential CRT (Auperin *et al*., 2010)

In 2010, the NSCLC Collaborative Group published a meta-analysis of randomised trials directly comparing concomitant / concurrent (i.e. overlapping) CRT versus sequential CRT. The analysis included 1,205 patients across six studies; median duration of follow-up was 6 years. The study showed a significant PFS benefit associated with concomitant versus sequential CRT (HR, 0.90; 95% CI, 0.79 to 1.01; *P*=0.07). The supporting PFS curves are shown in Figure 2, part B of the publication.

This meta-analysis is the primary source of evidence cited in the ESMO clinical practice guidelines recommending the use of concurrent CRT as treatment of choice for unresectable Stage III NSCLC[32] and is a reliable source of PFS after sequential CRT in the unresected Stage III NSCLC population.

The HR of 0.9 between concomitant (i.e. overlapping) CRT and sequential CRT reported in the Auperin (2010) meta-analysis was applied to the PACIFIC placebo / standard-of-care PFS survival function, to capture the slightly worse PFS outcomes reported in the latter (i.e. sequential CRT patients). Same HR is also applied to the time-to-progression (TTP) survival function.

To maintain the same percent risk reduction in the durvalumab arm relative to the placebo arm as in the overlapping CRT population, the same HR (0.9) was applied. The application of this HR to the durvalumab PFS survival function is non-parametric and agnostic to distribution assumptions.

[32]Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017; 28(suppl_4):iv1-iv21.

Data sources used to model PPS in patients who receive sequential CRT (Butts *et al.*, 2014)

Patient-level data for the placebo arm of the START trial[33] were used to model PPS in the sequential CRT population. Using this approach, we found no difference in PPS between sequential and overlapping CRT subgroups (detailed analysis results are presented below). No adjustments to PPS were therefore made.

- **Semi-parametric analysis**

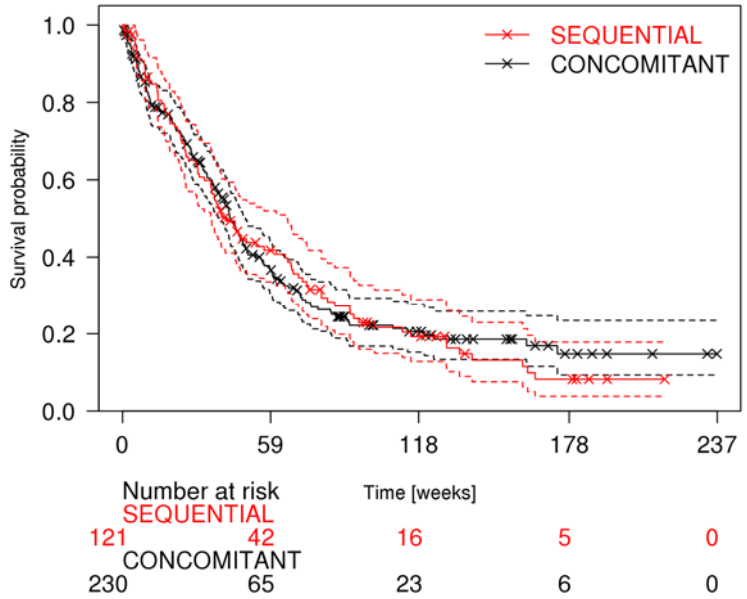
Total number of events and median time-to-event (if defined, otherwise N/A):

	Sequential CRT (total=121)	Concomitant / overlapping CRT (total=230)	Ratio	Difference
			Sequential: concomitant	Sequential-concomitant
Total number of events	95	159	1.67	-64
Median time to event	41.00	43.00	1.05	-2.00
95% lower CI	35.14	38.71	1.10	-3.57
95% upper CI	64.86	49.00	0.76	15.86

[33]Butts C, Socinski MA, Mitchell PL, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014; 15(1):59-68.

- **Kaplan Meier (KM) plot**

KM survival curve per arm with confidence intervals:



- **Logrank test(s)**

Logrank test(s):

	Statistic	df	p-value
No stratification	0.018	1	0.892

Cost-effectiveness model results

Table 6. AZ base-case (sequential CRT population)

Assumptions	Rationale	ICER	Change from revised base case (overlapping CRT)	Change from submission base case
AZ base-case for the sequential CRT population				
Same as AZ revised base-case for the overlapping CRT population (described in Table 5) with HR of 0.9[34] applied to placebo / standard-of-care and durvalumab PFS curves	As described above in the Appendix B "Methodology" section	£30,433	+ £2,000	+ £11,113
Sensitivity analyses (no "cure" assumption)				
Treatment effect duration				
3 years	Same as for the overlapping CRT population (see Table 5)	£38,428	+ £9,995	+ £19,108
10 years		£24,040	- £4,393	+ £4,720
Utility (note: age-related utility decrement has been included in both scenarios)				
PF = 0.73 for both arms; PD = 0.67 for both arms; disutility of AEs included (see Document B, Appendix P for further details)	Same as for the overlapping CRT population (see Table 5)	£33,235	+ £4,802	+ £13,915
PF = 0.73 for placebo / standard-of-care and 0.706 for durvalumab; PD = 0.67 for both arms		£35,432	+ £6,999	+ £16,112
Vial sharing				
30% vial sharing included	Same as for the overlapping CRT population (see Table 5)	£29,898	+ £1,465	+ £10,578

[34]Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010; 28(13):2181-90.

Appendix C (scenario 1): Cost-effectiveness analysis results using the ERGs' base-case (with model logic check included)*

Note: minor changes to wording made in 25 January 2019 version

Table 7. ERGs' base-case results with model logic check and related sensitivity analyses

Assumptions	Rationale	ICER	Change from AZ revised base-case	Change from AZ submission base case
ERG base-base with model logic check (no other adjustments made)				
Generalised-gamma PFS distribution for placebo / standard-of-care and log-normal PFS distribution for durvalumab, equal risk of progression or death from the point at which PFS curves crossed in ERG base-base originally provided (i.e. at ~39 months without logic check), mixed effects model including a treatment covariate, age-adjusted disutility included, no vial sharing, 3% threshold for subsequent treatments, no "cure" assumptions included	Per ERG base-case, with model logic check added to prevent durvalumab and standard-of-care hazard curves from crossing	£48,373	+ £19,940	+ £29,053
Sensitivity analyses performed by the ERG (with any changes highlighted)				
Treatment effects duration				
NEW! N/A	Equal risk assumed from 39 months	N/A		
Utility				
PF = 0.73 for both arms; PD = 0.67 for both arms; disutilities from AEs included	Per ERG analysis and report	£49,772	+ £21,339	+ £30,452
Vial sharing				
30% vial sharing included	Per ERG analysis and report	£47,539	+ £19,106	+ £28,219
Subsequent therapies				
NEW! Costs of all subsequent treatments in PACIFIC included	Per the NICE technical team's request	£48,631	+ £20,198	+ £29,311

Assumptions	Rationale	ICER	Change from AZ revised base-case	Change from AZ submission base case
Simple cure fraction modelling approach				
NEW! Base-case + patients who are progression-free at 5 years assumed to be clinically "cured"	Per the NICE technical team's suggestion	£40,219	+ £11,786	+ £20,899
NEW! Base-case + patients who are progression-free at 10 years assumed to be clinically "cured"		£47,241	+ £18,809	+ £27,921

*Note: the model logic check does not allow durvalumab PFS and TTP conditional survival probabilities to go below those of standard-of-care.

Appendix D (scenario 3): Cost-effectiveness analysis results using an average survival curve (obtained by assigning equal weight to log-normal and generalised-gamma distributions)

Note: "change from revised base-case" values corrected in 25 January 2019 version

Table 8. Cost-effectiveness results using an "average" PFS survival curve

Assumptions	Rationale	ICER	Change from revised base case	Change from submission base case
Average PFS survival curve approach				
Average PFS survival curves for durvalumab and placebo / standard-of-care obtained by assigning equal (50:50) weights to log-normal (ERG base-case) and generalised-gamma (AZ base-case) distributions. All other assumptions same as the AZ revised base-case	Based on UK clinical expert feedback; to model a "middle-ground" scenario that produces more-conservative 3−5 PFS (percentage point) benefit for durvalumab versus standard-of-care than the generalised-gamma curve, as well as more optimistic estimates of longer-term survival tails (at 10 years and beyond) than the log-normal curve	£35,298	+ £6,865	+ £15,978

Assumptions	Rationale	ICER	Change from revised base case	Change from submission base case
Sensitivity analyses (no "cure" assumption)				
Treatment effect duration				
3 years	As described previously for the revised AZ base-case (see Table 5)	£44,073	+ £15,640	+ £24,753
10 years		£28,756	+ £323	+ £9,436
Utility (note: age-related decrement has been included in both scenarios)				
PF = 0.73 for both arms; PD = 0.67 for both arms; disutility of AEs included (see Document B, Appendix P for further details)	As described previously for the revised AZ base-case (see Table 5)	£38,410	+ £9,977	+ £19,090
PF = 0.73 for placebo / standard-of-care and 0.706 for durvalumab; PD = 0.67 for both arms		£41,055	+ £12,622	+ £21,735
Vial sharing				
30% vial sharing included	As described previously for the revised AZ base-case (see Table 5)	£34,685	+ £6,252	+ £15,365

Appendix E: use of mixture cure-rate model to estimate long-term survival with durvalumab in unresectable, Stage III NSCLC patients

In response to the NICE technical team's consideration that cure-rate models might be a "relevant model structure for the company to explore", this analysis aimed to examine the mixture cure-rate model (MCM) as a statistical approach for interpreting and extrapolating PFS data for durvalumab versus placebo in the PACIFIC trial.

The MCM assumes that the study includes patients with a reduced risk of an event (i.e. "cure" group[35]) and patients at an increased risk of event (i.e. the "non-cure" group).

MCMs were fitted to observed PFS data from PACIFIC according to study arm, and standard parametric distributions were evaluated: Weibull, log-logistic, log-normal, exponential, Gompertz, and generalised-gamma. Based on PFS data, evidence of a statistical cure was found for both arms (durvalumab and placebo); this was in line with clinical expectations for patients with unresectable, Stage III NSCLC undergoing curative-intent treatment.

The MCM for PFS is presented in Equation 1.

Equation 1 MCM for PFS (PACIFIC)

$$PFS = survival\ of\ general\ population * (p_{cured} + [1 - p_{cured}] * PFS_{uncured})$$

Where survival of the general population is based on UK life tables (age- and gender-adjusted)[36]. p_{cured} represents the statistical "cured" fraction of patients, who are only subject to general mortality. $PFS_{uncured}$ represents the survival function for PFS among the "non-cured" fraction, which is parameterised by the listed parametric distributions.

Following guidance from the NICE DSU, "best fitting" models were chosen based on assessment of:

- Internal validity
    - Internal goodness-of-fit statistics: AIC
    - Visual inspection of the model fit to PACIFIC KM-curves
- External validity
    - Assessment of the clinical plausibility of the modelled extrapolations
    - Comparison of outcomes against survival data available from PACIFIC, the wider clinical literature, UK real-world evidence, and clinical expert opinion.

[35]Note: this refers to statistical cure; no clinical definition is applied in the model.

[36] United Kingdom, 2014-16. 2017. (Updated: 27 September 2017) Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Accessed: 12 April 2018.

A summary of the AIC statistics for each distribution explored is provided in Table 9. A plot of the survival functions is shown in Figure 11 and Figure 12 for visual assessment of fit; survival rates predicted by these curves is shown in

Table 10.

The estimated statistical cure percentages from the standard survival distributions are presented in Table 11. Table 12 presents a comparison of the extrapolated curves against other relevant clinical studies, real-world data, and estimates of PFS sourced from clinical experts.

Table 9. Summary of goodness-of-fit data for the parametric survival analysis of PFS data

Distribution	AIC	Rank
Durvalumab arm		
Generalised-gamma	825	1
Log-normal	847	2
Log-logistic	855	3
Gompertz	862	6
Weibull	860	4
Exponential	860	5
Placebo arm		
Generalised-gamma	449	1
Log-normal	450	2
Log-logistic	455	3
Gompertz	460	6
Weibull	460	5
Exponential	459	4

Figure 11. Visual fit of PFS MCMs to PACIFIC data; placebo arm, PD-L1 ≥1% group

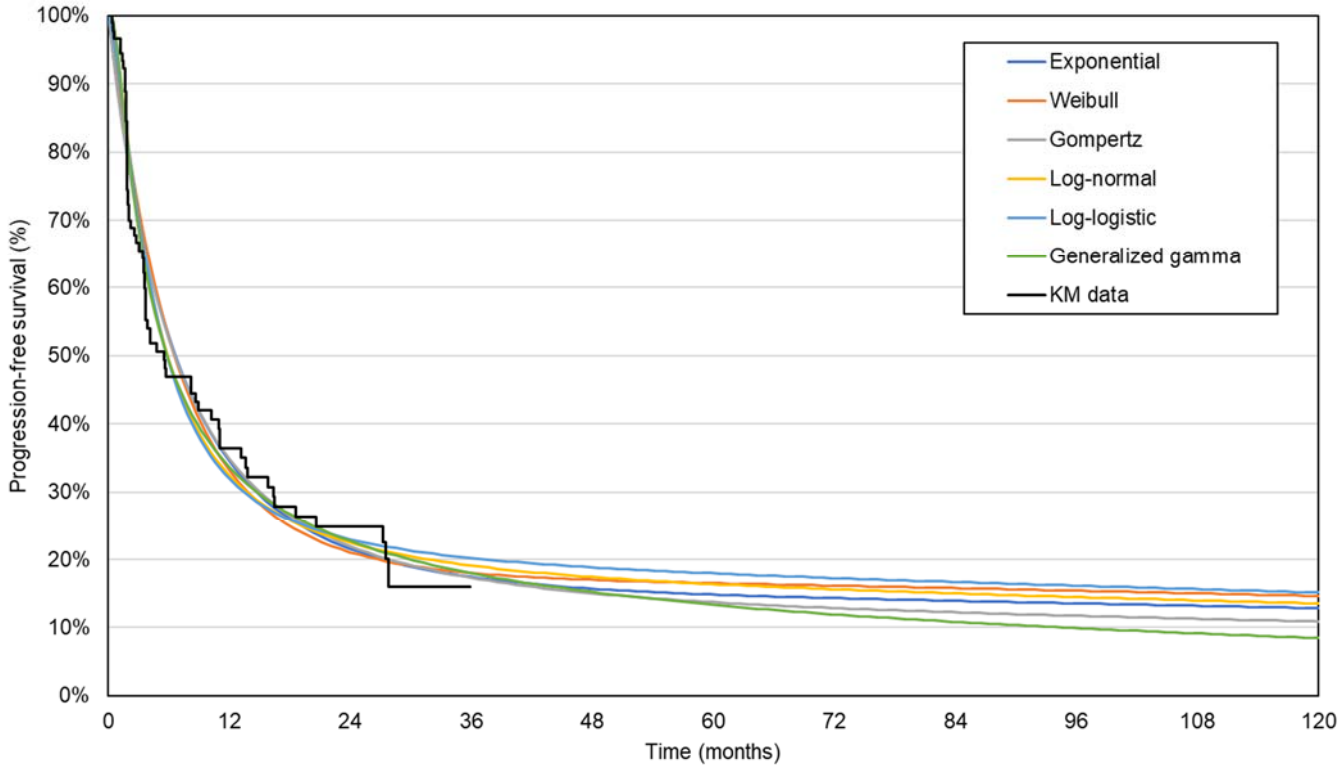


Figure 12. Visual fit of PFS MCMs to PACIFIC data; durvalumab arm, PD-L1 ≥1% group

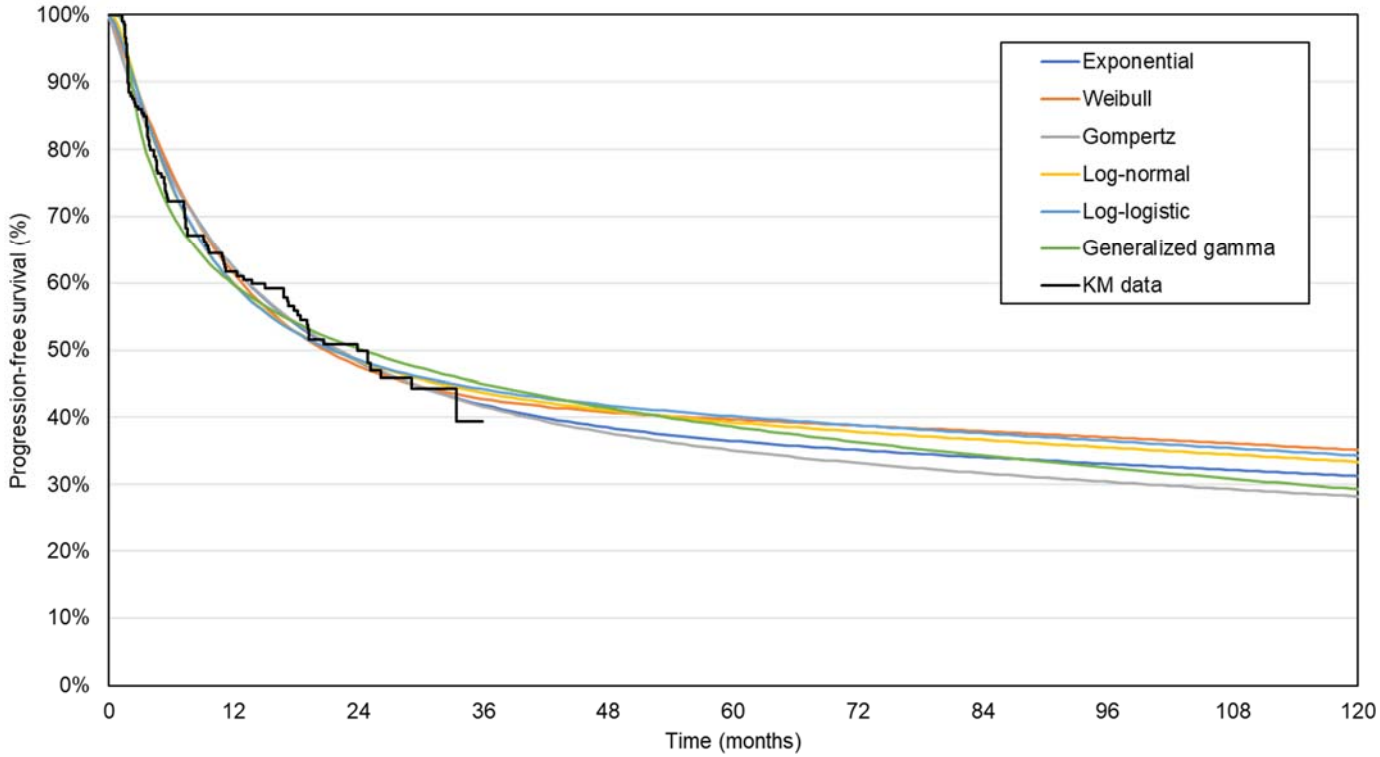


Table 10. Comparison of predicted PFS against data from PACIFIC PD-L1 ≥1% group

Distribution (fit*)	% PF 1 year		% PF 2 years		% PF 3 years	
	Durvalumab	Placebo	Durvalumab	Placebo	Durvalumab	Placebo
PACIFIC study	**61.6% At risk (106)**	**36.4% At risk (27)**	**49.9% At risk (57)**	**24.8% At risk (15)**	**39.4% [1] At risk (1)**	**16.0% [2] At risk (1)**
Generalised gamma (1)	59.8%	33.7%	50.2%	22.7%	45.1%	18.0%
Lognormal (2)	60.0%	32.5%	48.5%	22.5%	43.7%	19.1%
Loglogistic (3)	59.9%	32.0%	48.5%	23.0%	44.2%	20.2%
Weibull (4)	61.5%	33.2%	47.7%	21.1%	42.8%	18.0%
Exponential (5)	62.4%	34.6%	48.3%	21.6%	41.9%	17.4%
Gompertz (6)	62.5%	34.9%	48.5%	22.0%	41.7%	17.3%

Abbreviations: PD-L1, programmed cell death ligand 1; PF, progression-free; PFS, progression-free survival.
Notes: Numbers in brackets (1-6; column 1) refer to statistical goodness-of-fit. Modelled values are shown at closest model cycle (14/28 days) to time point. *By Akaike information criterion (AIC), [1]at 35.94 months, [2]at 35.88 months.

Table 11. Estimated statistical cure percentages by treatment according to standard distribution models

Distribution	Statistical cure (%)	
	Durvalumab	Placebo
Generalised-gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Table 12. Comparison of extrapolated PFS outcomes on standard-of-care against other clinical sources (survival measured from completion of CRT)

PFS	Median (months)	1 year	2 years	3 years	5 years	10 years	15 years	20 years
Modelled								
Exponential	6.44	34.6%	21.6%	17.4%	14.9%	12.8%	10.8%	8.3%
Generalised-gamma	5.98	33.7%	22.7%	18.0%	13.4%	8.5%	5.9%	4.0%
Gompertz	6.44	34.9%	22.0%	17.3%	13.7%	10.9%	9.0%	6.9%
Log-logistic	5.98	32.0%	23.0%	20.2%	18.0%	15.1%	12.5%	9.6%
Log-normal	5.98	32.5%	22.5%	19.1%	16.4%	13.5%	11.2%	8.6%
Weibull	6.44	33.2%	21.1%	18.0%	16.5%	14.6%	12.3%	9.5%
Observed from the PACIFIC study								
ITT	5.6	34%	24%	-	-	-	-	-
PD-L1 ≥1% group	5.6	36%	25%	16%*	-	-	-	-
Historical RCT data								
START[a]	8.3	42%	25%	20%	15%	-	-	-
GILT[b]	5.5	28%^	20%^	16%^	10%^	-	-	-
HOG LUN 01-24[c]	10.3	47%^	30%^	20%^	14%^	-	-	-
Carter 2012[d]	10.2	46%	32%	25%	25%	-	-	-
UK clinical expert opinion (AstraZeneca data on file)								
Estimates for PACIFIC ITT population[e,146]	-	-	-	-	15%	9%	-	-

Key: CRT, chemoradiation therapy; ITT, intention to treat; KM, Kaplan–Meier; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RCT, randomised controlled trial; SoC, standard of care; -, not available. Notes: *At 35.88 months. **At 35.94 months, ^digitised from source. Modelled values are shown at closest model cycle (14/28 days) to time point. Sources: a, START[37], ITT, KM data digitised, patients randomised upon completion of CRT; b, GILT[38], concurrent (overlapping) cisplatin + vinorelbine (pre-randomisation) followed by SoC, survival measured from randomisation on completion of concurrent cisplatin + vinorelbine therapy. Landmarks digitised from

[37] Butts C, Socinski MA, Mitchell PL, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2014; 15(1):59-68. Mitchell P, Thatcher N, Socinski MA, et al. Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: updated overall survival and biomarker analyses. Ann Oncol. 2015; 26(6):1134-42

[38] Flentje M, Huber RM, Engel-Riedel W, et al. GILT--A randomised phase III study of oral vinorelbine and cisplatin with concomitant radiotherapy followed by either consolidation therapy with oral vinorelbine and cisplatin or best supportive care alone in stage III non-small cell lung cancer. *Strahlenther Onkol*. 2016; 192(4):216-22.

published KM curves, c, HOG[39], concurrent etoposide + cisplatin (pre-randomisation) followed by observation, survival measured from randomisation on completion of concurrent etoposide + cisplatin. Landmarks digitised from published KM curves. d, Carter, 2012[40], induction or concurrent paclitaxel + carboplatin (pre-randomisation) followed by observation, survival measured from randomization on completion of induction or concurrent paclitaxel + carboplatin. Landmarks obtained from publication, e, AstraZeneca data on file[41].

For both the placebo and durvalumab arms, all distributions in the MCM resulted in similar fitted curves (Figure 11 and Figure 12).

All distributions approximated the observed data well and predicted a narrow range of 5-year PFS estimates of between 35−40% for the durvalumab arm and between 13−18% for the placebo arm (Table 10 and Table 12). The best statistical fit (according to AIC) is the generalised-gamma; however, the predicted statistical cure is close to zero in both arms and is lower in the durvalumab arm compared to the placebo arm. This result is judged to be clinically implausible (note that the generalised-gamma function is flexible and may have already captured the difference in hazard structure for the cured and non-cured patients, meaning that a cure fraction is not explicitly required to capture “cure” in the generalised-gamma distribution).

The log-normal distribution was the second-best statistical fit and predicted clinically-plausible cure rates of [redacted] in the durvalumab arm and [redacted] in the placebo arm. It was thus chosen as the most plausible distribution for MCM. As per NICE DSU guidelines, the same distribution was chosen to inform the PFS extrapolation for both arms.

Pre-progression mortality

The PFS curve is used to determine the rate at which patients leave the PF health state. These patients could either have experienced disease progression (i.e. transitioned to the PD health state) or died.

To determine the proportion of patients who transition to PD in each cycle, parametric curves were fitted to TTP data (where deaths were censored). The transition probability of patients moving from PF to PD was calculated as 1 – probability of remaining progression-free. In this analysis (similarly to the base-case analysis), the TTP distribution was set to the same as for PFS (i.e. log-normal).

[39]Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol*. 2008; 26(35):5755-60.
[40]Carter DL, Garfield D, Hathorn J, et al. A randomized phase III trial of combined paclitaxel, carboplatin, and radiation therapy followed by weekly paclitaxel or observation for patients with locally advanced inoperable non-small-cell lung cancer. Clin Lung Cancer. 2012; 13(3):205-13
[41]AstraZeneca. Clinical expert opinion on long-term survival outcomes with SoC. (DOF-IMF-004-AUG18) 25 August 2018. Data on File.

This approach was chosen because at the time of the latest DCO (22 March 2018), only a small number of patients in the PD-L1 ≥1% group of the PACIFIC study had died before progression: 13 patients in the durvalumab arm, and 8 patients in the placebo arm among uncensored PFS events[42], making parametric fits to PFS and TTP very similar.

TTP

As with PFS, MCMs were fitted to observed TTP data from PACIFIC according to study arm; the following standard parametric distributions were evaluated: Weibull, log-logistic, log-normal, exponential, Gompertz, and generalised-gamma.

A summary of AIC statistics for each distribution explored is provided in Table 13. A plot of the survival functions is shown in Figure 13 and Figure 14 for visual assessment of fit.

Table 13. Summary of goodness-of-fit data for the parametric survival analysis of TTP data

Distribution	AIC	Rank
Durvalumab arm		
Generalised-gamma	748	1
Log-normal	759	2
Log-logistic	765	3
Gompertz	771	6
Weibull	770	5
Exponential	770	4
Placebo arm		
Generalised-gamma	408	1
Log-normal	410	2
Log-logistic	415	3
Gompertz	420	6
Weibull	419	5
Exponential	418	4

Note: in cure model for TTP, the variance-covariance matrix for generalised gamma distribution did not converge under the default optimisation algorithm using the 'flexsurvcure' module in R package. Modifications to the optimisation algorithm were introduced to force the convergence.

[42] AstraZeneca. Number of deaths (prior to progression) among uncensored PFS events: Full Analysis Set - Subgroup PDL>=1% only. 2018.

Figure 13. Visual fit of TTP MCMs to PACIFIC data; placebo arm, PD-L1 ≥1% group

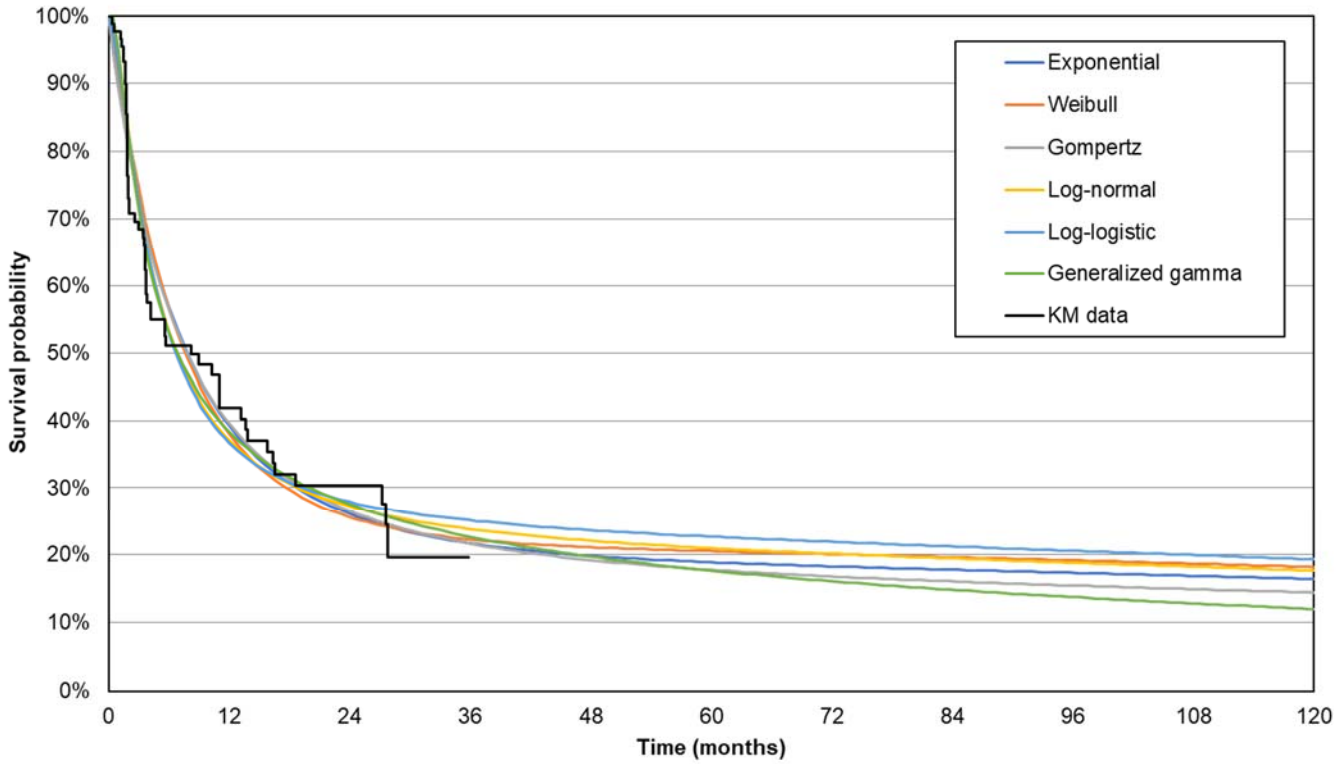


Figure 14. Visual fit of TTP MCMs to PACIFIC data; durvalumab, PD-L1 ≥1% group

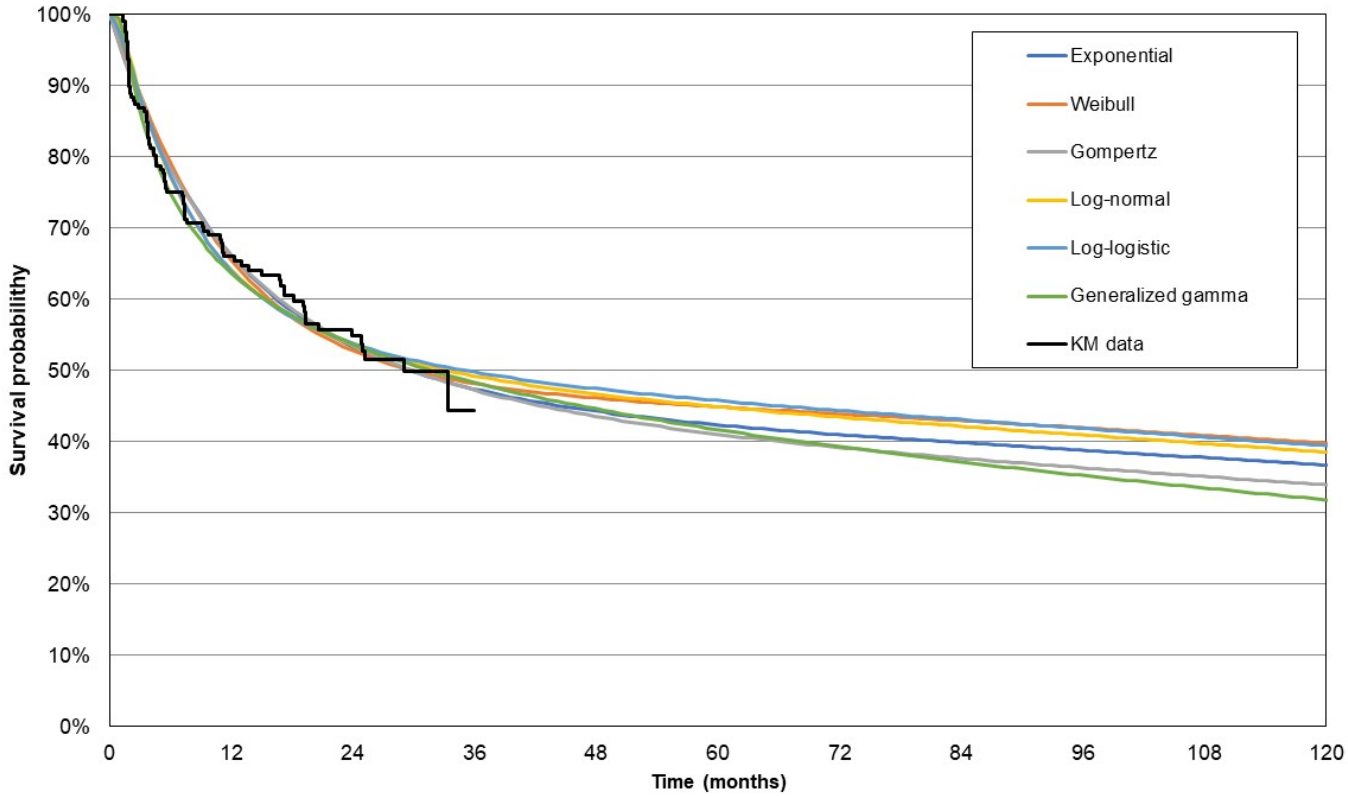


Table 14. Cost-effectiveness results using mixed cure-rate models (MCM)

Assumptions	Rationale	ICER	Change from revised base case	Change from submission base case
MCM base-case				
Log-normal PFS distributions for both arms; other assumptions same as revised AZ base-case	One of two cure fraction modelling approaches explored as per the technical team's suggestion	£28,307	- £126	+ £8,987
Sensitivity analyses (MCM base-case)				
Treatment effect duration				
3 years	As described previously for the revised AZ base-case (see Table 5)	£30,235	+ £1,802	+ £10,915
10 years		£27,435	- £998	+ £8,115
Utility (note: age-related decrement has been included in both scenarios)				
PF = 0.73 for both arms; PD = 0.67 for both arms; disutility of AEs included (see Document B, Appendix P for further details)	As described previously for the revised AZ base-case (see Table 5)	£30,652	+ £2,219	+ £11,332
PF = 0.73 for placebo / standard-of-care and 0.706 for durvalumab; PD = 0.67 for both arms		£33,085	+ £4,652	+ £13,765
Vial sharing				
30% vial sharing included	As described previously for the revised AZ base-case (see Table 5)	£27,805	- £628	+ £8,485

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 [ID1175]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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

Deadline for comments **5pm Monday 21 January 2019**

Thank you for your time.

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

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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

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

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

About you

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

Questions for engagement

Issue 1: Overlapping vs sequential prior chemoradiation therapy (CRT) and generalisability of PACIFIC trial	
1. Are the results of the PACIFIC trial generalisable to clinical practice in the NHS?	**Yes, we think so. We note that the majority of UK patients have sequential chemoradiation, If durvalumab were made available for maintenance after overlapping chemoradiation (as in PACIFIC), then practice would likely to change**
2. Are clinical outcomes likely to differ between overlapping and sequential chemoradiation therapy? Does this affect the generalisability of the trial?	**We note the clinical expert advice, that differences in clinical outcome between the two, would be small. And thus, not have any significant effect on generalisability of the trial.**
Issue 2: Treatment effect duration	
3. Is a 3 to 5 year treatment effect duration for durvalumab appropriate?	**We don't have anything to add to the discussion in the draft. However, a treatment effect duration of up to 5 years seems reasonable.**
Issue 3: Progression-free survival (PFS) extrapolation	
4. Is it reasonable to use a model that predicts that 37%, 26% and 14% of the durvalumab arm would be progression free at 3, 5 and 10 years respectively? (This is the log-normal distribution used to extrapolate PFS in the durvalumab arm)	
5. Is it reasonable to use a model that predicts that 17%, 12% and 8% of the standard care	

arm would be progression free at 3, 5 and 10 years respectively? (This is the generalised gamma distribution used to extrapolate PFS in the standard care arm).	
6. The Decision Support Unit (DSU) advise that fitting separate distributions to treatment arms should be justified using clinical expert judgement, biological plausibility and robust statistical analysis (DSU Technical Support Document 14). Have the DSU criteria been sufficiently met to justify fitting different model types per treatment arm?	
7. Would a mixture cure rate model be appropriate for this topic?	
Issue 4: Utility values	
8. Should utility values incorporate an age-related disultility?	
9. Is the utility value for the progression-free state taken from the literature appropriate (0.73)?	
10. Is the utility value for the progressed disease state taken from the literature appropriate (0.67)?	
Issue 5: Modelling of adverse events (AEs)	
11. Should utility values be treatment specific to capture the full impact of treatment-related AEs?	

Issue 6: Vial sharing	
12. Is it appropriate to assume no vial sharing?	
Issue 7: End of life considerations	
1. Under standard care, is the life expectancy of adults with locally-advanced unresectable Stage III NSCLC whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based CRT more than 24 months?	We agree with the clinical expert opinion, that National Lung Cancer Audit and other trial data shows that average life expectancy for locally advanced unresectable Stage III patients is less than 24 months.
2. Does durvalumab extend life for more than 3 months compared to standard care?	We have no data to add, beyond that publicly available from the PACIFIC study.
Issue 8: Cancer drugs fund (CDF)	
3. Does durvalumab meet the criteria for inclusion in the Cancer Drugs Fund?	We note the obvious unmet need in this patient population and the clinical benefit for patients, as seen in the PACIFIC study – in patient terms, half of those tumours not treated with immunotherapy, had begun to grow again within six months, whilst half of those, who had received Durvalumab, remained stable or in remission at almost one year and five months. For patients this is really important. We appreciate the uncertainty in modelling and data immaturity. As such, we would hope that whilst data matures and new data becomes available, that compromise could be

	reached on cost, between NICE, NHSE and the manufacturer, in order that Durvalumab would, in the meantime, be available through the Cancer Drugs Fund.

NICE National Institute for Health and Care Excellence

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- Do not use abbreviations.
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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)	**BTOG-NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[redacted]

Questions for engagement

Issue 1: Overlapping vs sequential prior chemoradiation therapy (CRT) and generalisability of PACIFIC trial	
1. Are the results of the PACIFIC trial generalisable to clinical practice in the NHS?	Yes, in the patients fit for concurrent chemo-radiotherapy treatment.
2. Are clinical outcomes likely to differ between overlapping and sequential chemoradiation therapy? Does this affect the generalisability of the trial?	Yes. In general patients treated with sequential chemoradiotherapy will a little older, have little more in the way of co-morbidities resulting in a worse performance status when compared to the cohort of patients treated in the PACIFIC study. Although you would hope that there will be a benefit for maintenance immunotherapy following treatment you would expect an increase in toxicity. The size of that increase in toxicity and the extent of that benefit from treatment in the sequential patient population is unknown and should not be extrapolated from the PACIFIC trials. Other studies, like PACIFIC 6, are needed to give robust data to support the extension of maintenance treatment into this population.
Issue 2: Treatment effect duration	
3. Is a 3 to 5 year treatment effect duration for durvalumab appropriate?	
Issue 3: Progression-free survival (PFS) extrapolation	
4. Is it reasonable to use a model that predicts that 37%, 26% and 14% of the durvalumab arm would be progression free at 3, 5 and 10 years respectively? (This is the log-normal	

distribution used to extrapolate PFS in the durvalumab arm)	
5. Is it reasonable to use a model that predicts that 17%, 12% and 8% of the standard care arm would be progression free at 3, 5 and 10 years respectively? (This is the generalised gamma distribution used to extrapolate PFS in the standard care arm).	
6. The Decision Support Unit (DSU) advise that fitting separate distributions to treatment arms should be justified using clinical expert judgement, biological plausibility and robust statistical analysis (DSU Technical Support Document 14). Have the DSU criteria been sufficiently met to justify fitting different model types per treatment arm?	
7. Would a mixture cure rate model be appropriate for this topic?	
Issue 4: Utility values	
8. Should utility values incorporate an age-related disutility?	
9. Is the utility value for the progression-free state taken from the literature appropriate (0.73)?	
10. Is the utility value for the progressed disease state taken from the literature appropriate (0.67)?	

Issue 5: Modelling of adverse events (AEs)	
11. Should utility values be treatment specific to capture the full impact of treatment-related AEs?	
Issue 6: Vial sharing	
12. Is it appropriate to assume no vial sharing?	
Issue 7: End of life considerations	
1. Under standard care, is the life expectancy of adults with locally-advanced unresectable Stage III NSCLC whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based CRT more than 24 months?	The standard arm of RTOG 0617 study had a median survival of 28 months for stage III patients treated with concurrent chemo-radiotherapy. However, the inclusion criteria mean patients are selected for such a study and in the less selected UK population of patients offered concurrent chemo-radiotherapy a median survival of around 24months would be more realistic.
2. Does durvalumab extend life for more than 3 months compared to standard care?	Yes
Issue 8: Cancer drugs fund (CDF)	
3. Does durvalumab meet the criteria for inclusion in the Cancer Drugs Fund?	

Question by Gary McVeigh on 08/02/2019

In reviewing other trials that have used consolidation therapy of various types following cCRT for stage III NSCLC, I note the PFS of 5.6 months in PACIFIC is very low C/W other trials (e.g. START trial that used Tecemotide as consolidation the PFS for cCRT was 11.4 months; similarly RTOG-0619 PFS following cCRT (average high vs low dose radiation 10.7 months) and all others (see table in Mc Call et al ...Beyond concurrent chemoradiotherapy...) have better PFS Vs the SoC in PACIFIC. A difference of 6 months is significant and in part may be due to difference in definition of PFS.....in prior trials from initiation of CRT to progression in PACIFIC from time of randomisation to Durvulmab to progression (this could be up to 6 weeks)

Table 1. Table 1 of McCall 2018 Clin Cancer Res

Table 1. Multi-institutional phase III trials of consolidative or induction systemic therapy after concurrent chemoradiation for unresectable stage III NSCLC

Trial	Induction or consolidative therapy with cCRT	PFS (months) (*P*)	OS (months) (*P*)
CALGB-39801 (5)	Carboplatin + paclitaxel (induction)	7 vs. 8 (NS)	12 vs. 14 (NS)
HOG LU-0124 (6)	Docetaxel (consolidation)	10.8 vs. 10.3 (NS)	24.2 vs. 26.1 (NS)
Korean Cancer Study Group - LU05-04 (2)	Cisplatin + docetaxel (consolidation)	9.1 vs. 8.1 (NS)	21.8 vs. 21.6 (NS)
RTOG-0617 (3)[a]	Cetuximab (consolidation)	10.8 vs. 10.7 (NS)	25 vs. 24 (NS)
SWOG-S0023 (7)	Docetaxel followed by gefitinib (consolidation)	8.3 vs. 11.7 (NS)	23 vs. 35 ($P = 0.013$)
START (8)[b]	Tecemotide (consolidation)	14.2 vs. 11.4 ($P = 0.02$)	30.8 vs. 20.6 ($P = 0.016$)
PACIFIC (28)	Durvalumab (consolidation)	16.8 vs. 5.6 ($P < 0.0001$)	Ongoing

NOTE: All values from clinical trials are presented as experimental arm value versus control arm value.
Abbreviation: NS, not statistically significant.
[a]Data are shown regardless of irradiation to 60 or 74 Gy.
[b]Data from patients who received prior concurrent chemoradiation are shown.

Table 2. Comparison of characteristics of studies from Table 1 above

Study	Population	Definition/analysis/results of PFS
CALGB-39801	"Eligible patients had histologic or cytologic documentation of NSCLC. Patients had previously untreated unresectable or inoperable stage III disease. Patients with N3 disease were eligible if all gross disease could be encompassed in the radiation boost field, but patients with scalene, supraclavicular, or contralateral hilar lymph node involvement, direct invasion of the vertebral body, or with a pleural effusion were ineligible." Age (median, range): 63, 37-35 Stage: IIIA (49%), IIIB (47%)	"Failure-free survival (FFS) was defined as the time between random assignment and disease relapse or death." Sample size was based on overall survival (OS) KM curves, treatments were compared with a log-rank test At median follow-up of 38 months FFS was not significantly different (median 7 vs. 8 mths, p = 0.2)
HOG LU-0124	"Patients with histologic or cytologic confirmation of NSCLC with unresectable stage IIIA or IIIB disease were assessed for eligibility. Unresectable stage IIIA disease was defined by multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT) scan such that, in the opinion of the treating investigator, the patient was not a candidate for surgical resection. N2 disease must have been documented by biopsy, fluorodeoxyglucose positron emission tomography (PET), or CT if nodes were more than 2 cm. Stage IIIB patients must have had N3 or T4 status. N3 status must have been documented by the presence of a contralateral (to the primary tumor) mediastinal lymph node or supraclavicular or scalene lymph node proven by biopsy, fluorodeoxyglucose PET, or more than 2 cm on CT scan. Patients with disease extending into the cervical region were not eligible. (…) Eligibility for consolidation therapy required completion of initial chemoradiotherapy within 4 to 8 weeks of random assignment without local progression or distant metastases, ECOG PS of 0 to 2 at random assignment, adequate bone marrow and hepatic function (same as baseline requirements), and absence of symptomatic peripheral neuropathy before random assignment."	No details Sample size was based on OS (259 patients) Trial was stopped for futility for OS after an interim analysis of the first 203 patients (p = 0.9087) PFS was a secondary outcome KM curves, no other details After median follow-up of 41.6 months there no significant difference in PFS (p = 0.96)

Study	Population	Definition/analysis/results of PFS
	Age (median, range): 63, NR Stage: IIIA (40%) no further details	
Korean Cancer Study Group - LU05-04	"Patients with histologically documented NSCLC with inoperable stage IIIA or IIIB disease, which was proven by computed tomography (CT), magnetic resonance imaging, and/or positron emission tomography (PET), were eligible. N2 orN3 disease must have been confirmed by pathology orPET. Patients were age 18 years or older and had an Eastern Cooperative Oncology Group performance status of 0 to 1 at baseline. Eligible patients also met the following criteria: measurable disease based on RECIST; no prior chemotherapy, RT to the chest, immunotherapy, or biologic therapy; forced expiratory volume in 1 second 0.8 L by spirometry; and adequate bone marrow, renal, and hepatic function. Female patients were also excluded if they were pregnant or lactating, had not taken a pregnancy test within 14 days before the first administration, or had childbearing potential and were not willing to use adequate contraception" Age (median, range): 61, 31-79 (CCRT only); 61, 35-79 (CCRT + consolidation) Stage: IIIA CCRT only (25.1%) CCRT + consolidation (19.1%) IIIB CCRT only (74.4%) CCRT + consolidation (80.4%)	"PFS was defined as the time from random assignment to the first documentation of disease progression or death, whichever came first." Sample size was based on PFS ("the consolidation arm would increase median PFS by 40% from 12 mths reported in Park") and 434 patients gave 90% power. KM curves, treatments were compared with a log-rank test, univariable and multivariable Cox regression After median follow-up of 50.7 mths Median PFS CCRT + consolidation 9.10 (95% CI 7.92 to 10.94) CCRT only 8.05 (7.56 to 8.90) = 0.410
RTOG-0617	"Eligibility criteria included having stage IIIA or IIIB non-small-cell lung cancer, no previous invasive cancer during the previous 3 years, Zubrod performance status score of 0–1, less than 10% weight loss (in the month before study entry), and pulmonary function (before or after bronchodilation) of 1·2 L per s or higher. Tumour histology was classified as squamous cell, adenocarcinoma, large-cell carcinoma, or non-small-cell lung cancer not otherwise specified. Specific mutational analyses were not necessary for trial entry. Patients with contralateral hilar or supraclavicular adenopathy or Pancoast tumours were excluded	"Endpoints of overall survival, progression-free survival, local failure, and distant metastasis were measured from the date of randomisation." This was a factorial trial comparing standard-dose vs. high-dose chemoradiotherapy and cetuximab vs. no cetuximab (4 treatment groups with 2 comparisons). High-dose radiation group was closed due to futility at an interim analysis, the futility boundary for cetuximab was crossed at the third interim analysis but met the planned sample size.

Study	Population	Definition/analysis/results of PFS
	because of the risk of lung or brachial plexus toxic effects. Minimum pleural effusions were allowed if they were transudative and cytologically negative by thoracentesis." Age (median, range): 64, 38-83 Stage: IIIA (65%), IIIB (35%)	Sample size was based on OS KM curves, treatments were compared with a log-rank test, and Cox regression After median follow-up of 21.2 mths (IQR 10.5 to 30.3) Median PFS Cetuximab 10.8 (95% CI 9.8 to 12.3) No cetuximab 10.7 (95% CI 9.3 to 13.2)
SWOG-S0023	"Adult patients with pathologically confirmed and inoperable stage IIIA or IIIB NSCLC were eligible to participate in this study. Patients with pleural or pericardial effusions or patients with multiple tumors within the lung were excluded. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 to 1; measurable or non-measurable disease; no prior systemic therapy, radiation therapy, or complete surgical resection; and adequate organ function. Patients with a forced expiratory volume in 1 second (FEV1) of less than 2.0 L were eligible if they had a minimum FEV 1 of 800 mL in the contralateral lung." Age (median, range): 61, 20-83 Stage: IIIA gefitinib (45%), placebo (51%) IIIB gefitinib (55%), placebo (49%)	From randomisation. No definition of progression or PFS (although progression after initial radiation therapy was assessed with RECIST) Sample size was based on OS. It was assumed that 20% of patients would not be randomised to gefitinib or placebo due to disease progression or toxicity during 3 cycles of docetaxel. Trial was closed early due to results from the ISEL trial which showed that gefitinib did not improve survival (243 out of planned 840 were recruited). KM curves, treatments were compared with Cox regression stratified by disease stage, measurable/non-measurable disease and squamous subtype. After median follow-up of 27 mths Median PFS Gefitinib 8.3 (95% CI 6 to 14) Placebo 11.7 (95% CI 9 to 17)

Study	Population	Definition/analysis/results of PFS
START	"Eligible patients were those aged 18 years or older with histologically or cytologically unresectable stage III non-small-cell lung cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Stage was confirmed and documented by CT, MRI, or PET. We did not require pathological confirmation of mediastinal nodal involvement and we included all histological subtypes of non-small-cell lung cancer. Between 4 and 12 weeks before randomisation, patients had to have completed at least two cycles of platinum-based chemotherapy (given sequentially or concurrently) with a minimum of 50 Gy of radiation, and have received confirmation of stable disease or an objective response after chemoradiotherapy. All patients underwent brain imaging during screening to exclude brain metastases. Exclusion criteria included: having undergone any therapy for lung cancer (other than primary chemoradiotherapy), including surgery; receipt of any immunotherapy 28 days before randomisation; and having metastatic disease or any autoimmune disease." Age (median, range): Tecemotide 61, 19-89, placebo 61.5, 24-83 Stage: IIIA (39%), IIIB (61%)	Time to disease progression assessed by investigators using RECIST 1.0 "Although RECIST 1.0 had to be followed for classification of disease progression, no formal imaging schedule was required after randomisation and it was done according to institutional practice." **This is not the same outcome as PFS** Sample size was based on OS. In March 2010 tecemotide trials (including START) were put on hold due to a safety concern in another trial. Patients randomised in the 6 mths before the clinical hold were excluded in a modified ITT analysis (n = 274). KM curves, treatments were compared with Cox regression After median follow-up of 39 mths (IQR 19.9 to 49.7) Median time to progression Tecemotide 10.0 (95% CI 9.1 to 11.5) Placebo 8.4 (95% CI 7.2 to 10.8)
PACIFIC	In the PACIFIC study, in order to be included patients had to be adults who had histologically- or cytologically-confirmed unresectable Stage III NSCLC who had not progressed following platinum-based CRT. The patients also had to receive at least two overlapping cycles of CRT without disease progression upon completion. Trial treatment was started within 42 days of competing CRT.	PFS defined as time from randomisation to disease progression (using BICR assessments and RECIST 1.1) or death whichever occurred first. Trial was ongoing at the time of the company submission. Patients who progressed could restart study treatment for up to 12 mths but no crossover was allowed. Sample size was based on PFS and OS (co-primary outcomes). Primary PFS analysis was planned after 458 PFS events had occurred.

Study	Population	Definition/analysis/results of PFS
	All patients (n = 713) Age (median, range): 64, 23-90 Stage: IIIA (52.9%), IIB (44.7%) PD-L1 ≥ 1% subgroup (n = 303) Age (median, range): 64, 36-90 Stage: IIIA (54.8%), IIB (43.2%)	KM curves, treatments were compared with Cox regression After median follow-up of 26.9 mths (range 0.5 to 40.5) durvalumab and 21.2 mths (range 0.5 to 41 for placebo) Median PFS (All patients) Durvalumab 16.8 (95% CI 13.0 to 18.1) Placebo 5.6 (95% CI 4.6 to 7.8) Median PFS (PD-L1 ≥ 1%) Durvalumab 17.8 (95% CI 13.0 to not reached) Placebo 5.6 (95% CI 3.6 to 11.0)

Further thoughts and observations:

1. I think PACIFIC has a more favourable population than some of the other trials regarding disease stage and previous treatments. 53% were stage IIIA , all others were lower than this apart from RTOG-0627 which had 65% stage IIIA. They had also had to have had at least 2 platinum-based CRT without progressing, the only other trial with this criteria appears to be START. However START did not measure PFS, it was time to progression so cannot be compared to PACIFIC. START was also placebo-controlled like PACIFIC the only other placebo-controlled trial was SWOG-S0023 but I don't think they had any previous CRT. START and PACIFIC seem the most comparable and also have the most comparable PFS for the placebo arm. START is 8.4 (95% CI 7.2 to 10.8) and PACIFIC is 5.6 (95% CI 4.6 to 7.8).
2. PACIFIC was one of only 2 trials to have the sample size based on PFS, the other was the Korean Cancer Study Group LU05-04, all the others were powered to detect differences in overall survival only. However this was a more severe population (77% Stage IIIB) and they had not had previous chemotherapy, RT to the chest, immunotherapy or biologic therapy).
3. A few trials were stopped early due to futility (trial would never find a significant difference in the primary endpoint): HOG LU-0124, and safety concerns (SWOG-S0023) which could affect PFS estimates. START was affected by a clinical hold due to a safety concern with tecemotide in a different phase II trial.
4. RTOG-0617 was a different design to all other trials, it was a factorial 2 x 2 design compared to parallel group designs in the others. It compared high with low-dose CRT and cetuximab with no cetuximab. One group was stopped early due to futility (high-dose CRT).

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

ERG Response to technical engagement responses by AstraZeneca and the Roy Castle Lung Cancer Foundation

The ERG has taken note of the responses to the technical engagement of both, AstraZeneca UK Ltd and the Roy Castle Lung Cancer Foundation. However, given tight timelines and the considerable amount of information and analyses reported, particularly in the response by AstraZeneca, the ERG focussed its response on certain main issues.

Population: Overlapping vs. sequential CRT

The ERG noted the comment made by Jesme Fox on behalf of the Roy Castle Lung Cancer Foundation, i.e. "that the majority of UK patients have sequential chemoradiation. If durvalumab were made available for maintenance after overlapping chemoradiation (as in PACIFIC), then practice would likely to change". Jesme continued to argue that as per "the clinical expert advice, (…) differences in clinical outcome between the two, would be small. And thus, not have any significant effect on generalisability of the trial" (page 3 of the technical engagement response form).

Similarly, while the company acknowledged that "clinical effectiveness evidence for sequential CRT + durvalumab [is] not available at present" (page 4 of the technical engagement response form), the company also highlighted that "feedback from UK oncologists experienced in treating patients with durvalumab after both sequential and overlapping CRT as part of the EAP indicate that there are no apparent differences between these groups in terms of tolerability or radiological progression, and 'how they [patients] cope is identical'" (page 6 of the technical engagement response form).

While the ERG acknowledges the statement by the clinical experts, it would like to emphasise once more the uncertainty regarding the generalisability of the PACIFIC trial as the assumption of comparability of sequential + CRT and overlapping + CRT treatment, respectively, is largely based on expert opinion rather than on more robust clinical trial data.

End of life considerations

The ERG noted the response to issue 7 (end of life considerations) on pages 36 and 37 of the technical engagement document prepared by AstraZeneca in which the company reiterated its view on meeting the end of life criteria. However, the ERG felt that its position was adequately reflected in preliminary report produced by the NICE Technical team and that no change is required.

Cancer drugs fund (CDF)

The ERG took note of the "request that the NICE committee consider granting conditional access to durvalumab (through the CDF) in this population [patients receiving sequential CRT], given significant unmet need and a small number of eligible patients".

The ERG report discussed a number of issues, some of these related to the immaturity of the available data. Furthermore, the ERG noted that, according to page 39 of the technical engagement document submitted by AstraZeneca, "this will be addressed in [redacted] also, as results from PACIFIC-R and PACIFIC-6 studies become available".

Revised base-case of the company

The revised base-case proposed by the company is equal to the ERG base-case in many aspects, but different where it concerns the PFS curve for durvalumab, the utility score for progressed disease, and the inclusion threshold for costs of subsequent treatment. These three issues will be discussed below.

- The company chose to maintain the generalized gamma for the PFS curve of durvalumab, using the same arguments that were used in the original company submission, complemented with additional

clinical expert opinion. The ERG does not see any new evidence concerning PFS, and will therefore maintain their argumentation as stated in the ERG report. The ERG's main reasoning for using a lognormal PFS curve for the durvalumab arm is that the generalized gamma likely overestimates PFS in PACIFIC, and the end of the KM-curve was based on only very few patients, making extrapolations highly uncertain. As PFS is the model aspect with the most significant impact on the ICERs, these uncertain extrapolations have substantial consequences (for details see pages 54-57 of the ERG report and Figures 5.2 and 5.3 from the ERG report, also replicated below as Figures 1 and 2).

- The company acknowledged the concerns that PD utility value from PACIFIC may not adequately capture the long-term HRQoL decrement associated with disease progression, and decided to use the utility value proposed by the ERG, which was taken from literature. Although the same concerns were present regarding the high utility score for the PF state, the company did not address these concerns here because of the fact that 'the PACIFIC study is the **only source** of PF health state utility data in the population of interest'. Also, in the response to clarification,[1] the company stated they deemed the Chouaid value not suitable for the PD health state as in Chouaid et al.[2] it concerned a population of advanced metastatic disease. According to the ERG using the utility estimate from PACIFIC for PF and from Chouaid for PD may overestimate the utility loss of progressed disease relative to remaining progression free.
- To address concerns that the use of an arbitrary 3% threshold for inclusion of costs of subsequent treatment may bias results obtained, the company decided to remove this threshold and include all subsequent treatment costs. The ERG appreciates this as it increases transparency, and decided to update their own base-case to also include all subsequent treatments.

Figure 1: PFS using generalised gamma for durvalumab and SoC (CS base-case)

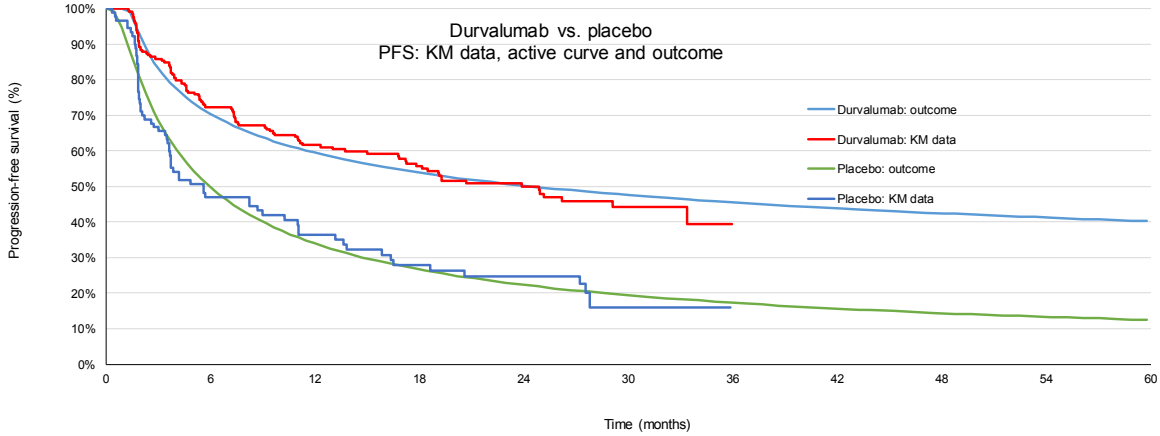
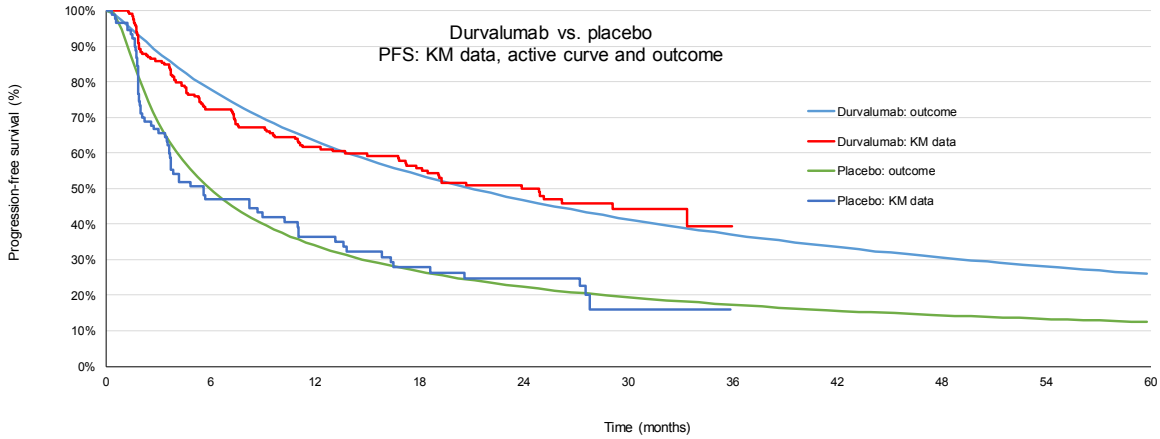


Figure 2: PFS using lognormal for durvalumab and generalised gamma for SoC (ERG base-case)



Sequential CRT population

The company provided a separate analysis for the sequential CRT population (Appendix B, Table 5, page 45 of the AZ technical engagement response form), as evidence shows PFS may be worse than in the overlapping CRT population. A HR of 0.9 was applied to PFS of both SoC and durvalumab. All other parameters, such as PPS, HRQoL, and subsequent treatments, remained the same, most with the argument that there was no evidence to the contrary. Given the lack of information on this issue, the ERG considers this a reasonable approach to provide some insight into the cost-effectiveness of durvalumab in the sequential CRT population, although the use of the generalized gamma for PFS in durvalumab will suffer from the same uncertainties as in the main analysis for the overlapping population.

Model logic check

The company performed an analysis using the ERG base-case including a so-called 'model logic check' which would not allow durvalumab PFS and TTP conditional survival probabilities to go below those of SoC (Appendix C, Table 6, page 46 of the AZ technical engagement response form). Consequently, in the differential PFS curves for durvalumab and SoC that the ERG applied, hazards for durvalumab could at certain time points be above those of SoC. To avoid this slightly counterintuitive phenomenon, the company amended the model. Compared to the original ERG base-case, the ICER decreased with around £2,000 to £48,373. The ERG considers this a useful amendment to the model and included it in their updated base-case.

Average survival curve

To reflect a 'middle ground' scenario regarding the PFS extrapolations, the company provided an analysis using an average survival curve obtained by assigning equal weight to log-normal and generalized gamma distributions (Appendix D, Table 7, page 47 of the AZ technical engagement response form). The ERG regards this scenario indeed to reflect a middle ground, but does not see scientific or clinical reasons to adopt this approach in any main analysis.

Cure fraction modelling approaches

As per the NICE technical team's suggestion, the company explored the use of cure fraction modelling approaches. One of these approaches was an assumption that all patients who are progression free at a certain time point (i.e. 5 or 10 years) would be clinically 'cured', that is they would not progress anymore after that moment (see Table 4 AZ revised base-case sensitivity analyses, page 27 of the AZ technical engagement response form). The other approach was a mixture cure model (Appendix E of the AZ technical engagement response form). The ERG considers the first approach, which assumes all progression free at some point to be cured, to be overly optimistic, as a clinical basis for this assumption is lacking. As for the mixture cure model, although a well-known method, it requires mature data to be able to distinguish the cured fraction from the non-cured. Othus et al (2017) for instance, have applied it to a population of melanoma patients for which the cured fraction had an OS of 26 years.[3] The data in PACIFIC are not mature enough to reliably apply a mixture cure mode. Moreover, the ICER was only minimally affected when using the mixture cure model. Therefore, the ERG considers the mixture cure model analysis to be of limited use.

Revised ERG base-case

The ERG reconstructed the company's amended base-case and was able to reproduce the ICER as reported in the response. The ERG also performed a probabilistic sensitivity analysis for the company's amended base-case (see table 1). Then, the ERG amended the ERG base-case to include costs of all subsequent treatments and the 'model logic check' proposed by the company. Results are presented in tables 2-4 and in Figure 3.

Table 1: ICER resulting from company's amended base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic company amended base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	2.26	£28,433
SoC	[redacted]	[redacted]			
Probabilistic company amended base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	2.07	£31,387
SoC	[redacted]	[redacted]			
ERG = Evidence Review Group = ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care					

Table 2: ICER resulting from ERG's preferred assumptions

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic ERG amended base-case					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	1.36	£48,631
SoC	[redacted]	[redacted]			
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			

ERG = Evidence Review Group = ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care

Figure 3: cost-effectiveness acceptability curve for ERG amended base-case probabilistic analysis

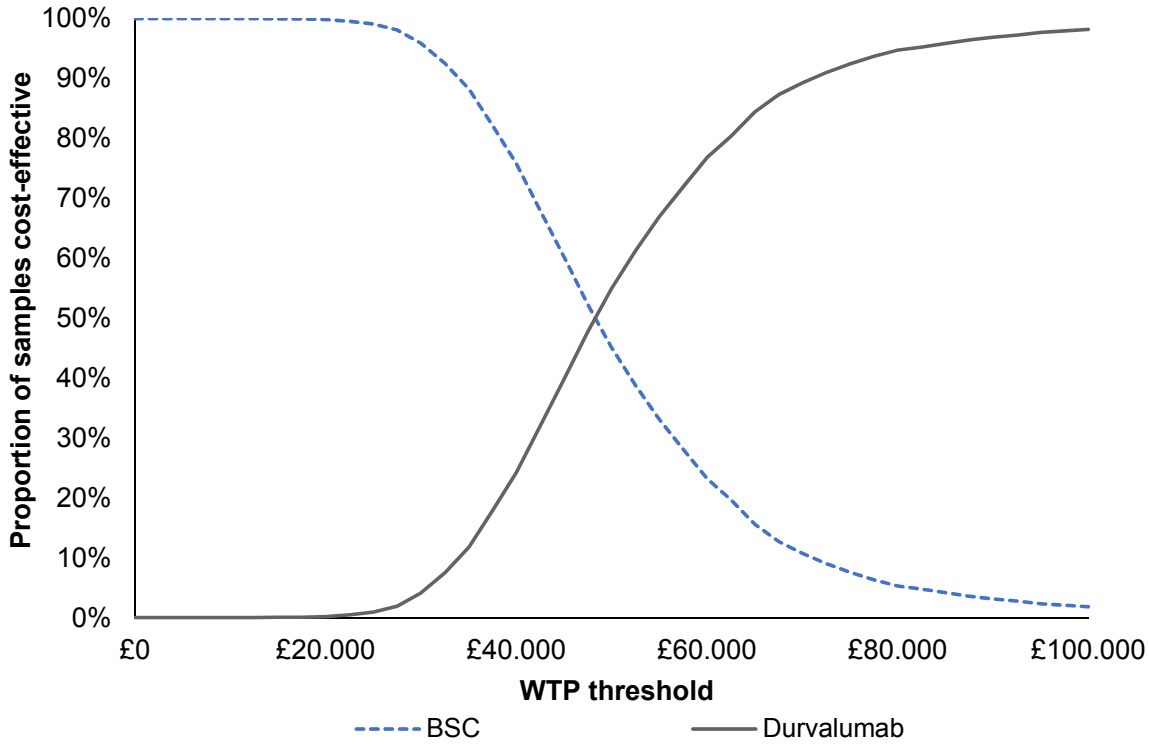


Table 3 Additional scenario – as company amended base-case <u>but</u> with lognormal PFS curve for durvalumab, model logic check (hazard cap), and utility scores from literature (PF 0.73, PD 0.67) including treatment decrement from PACIFIC utilities mixed model (-0.024). Results shown for both duration of treatment effect of 3 and 5 years

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic scenario: treatment effect 3 years					
Durvalumab	[redacted]	[redacted]	[redacted]	1.22	£54,334
SoC	[redacted]	[redacted]			
Deterministic scenario: treatment effect 5 years					
Durvalumab	[redacted]	[redacted]	[redacted]	1.22	£54,315
SoC	[redacted]	[redacted]			
Probabilistic scenario: treatment effect 3 years					
Durvalumab	[redacted]	[redacted]	[redacted]	1.19	£55,805
SoC	[redacted]	[redacted]			
Probabilistic scenario: treatment effect 5 years					
Durvalumab	[redacted]	[redacted]	[redacted]	1.23	£54,015
SoC	[redacted]	[redacted]			

ERG = Evidence Review Group = ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care

Table 4: Exploratory analyses undertaken by the ERG

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG amended base-case					
Durvalumab	[redacted]	[redacted]	[redacted]	1.36	£48,631
SoC	[redacted]	[redacted]			
Alternative PFS distributions both arms, generalised gamma (1)					
Durvalumab	[redacted]	[redacted]	[redacted]	2.19	£29,378
SoC	[redacted]	[redacted]			
Alternative PFS distributions both arms, lognormal (2)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.27	£52,680
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as ERG base-case (3a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.36	£48,649
SoC	[redacted]	[redacted]			
Treatment waning at 3 years, PFS as scenario 2 (3b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.04	£65,040
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as ERG base-case (4a)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.36	£48,631
SoC	[redacted]	[redacted]			
Treatment waning at 7 years, PFS as scenario 2 (4b)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.41	£47,320

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]			
PACIFIC PPS, but generalised gamma (5)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.37	£48,268
SoC	[redacted]	[redacted]			
Company's KEYNOTE-024 PPS scenario, with errors corrected (6)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.14	£57,112
SoC	[redacted]	[redacted]			
Adverse events with amended incidence and including impact on HRQoL (7)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.36	£48,680
SoC	[redacted]	[redacted]			
Alternative PF utility score (8)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,264
SoC	[redacted]	[redacted]			
Alternative PF and PD utility scores (9)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.32	£50,045
SoC	[redacted]	[redacted]			
Vial sharing possible at 30% (10)					
Durvalumab	[redacted]	[redacted]	[redacted]	1.36	£47,779
SoC	[redacted]	[redacted]			

ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; PD = progressed disease; PF = progression-free; PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year; SoC = standard of care

References

[1] AstraZeneca. *Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation - Response to request for clarification from the ERG*: AstraZeneca, 2018. 73p.

[2] Chouaid C, Agulnik J, Goker E, Herder GJ, Lester JF, Vansteenkiste J, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. *J Thorac Oncol* 2013;8(8):997-1003.

[3] Othus M, Bansal A, Koepl L, Wagner S, Ramsey S. Accounting for cured patients in cost-effectiveness analysis. *Value Health* 2017;20(4):705-9.

Progression free survival in durvalumab arm

Proportion progression free with treatment effect duration 5 yrs	3 years	5 years	10 years
Generalised gamma for both arms, patients progression-free at 5 years assumed 'cured'	45.53%	40.21%	35.78%
Generalised gamma for both arms, patients progression-free at 10 years assumed 'cured'	45.53%	40.21%	25.58%

Proportion progression free with treatment effect duration 3 yrs	3 years	5 years	10 years
Generalised gamma for both arms, patients progression-free at 5 years assumed 'cured'	45.53%	32.79%	29.17%
Generalised gamma for both arms, patients progression-free at 10 years assumed 'cured'	45.53%	32.79%	20.86%

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

ERG addendum post-PMB

February 8th 2019

Upon request of the NICE technical team the ERG performed a number of additional analyses exploring various assumptions for PFS extrapolation and for the population having received sequential CRT.

All analyses presented below were, unless stated otherwise, performed departing from the NICE technical team's preferred assumptions, using utility scores from PACIFIC including treatment decrement and age-related decrement, hazard cap, 3-5 yr treatment effect duration (from start of treatment).

Table 1 Exploration of progression-free survival modelling

	Probabilistic ICER (£/QALY, 1000 simulations)	
	3yr tx effect duration	5yr tx effect duration
Generalised gamma for both arms	£ 40,781	£ 32,407
Log-normal durvalumab & generalised gamma SoC*	£ 49,290	£ 47,963
Log-normal for both arms*	£ 65,662	£ 53,448
Average of generalised gamma & log-normal for durvalumab & generalised gamma for SoC*	£ 45,445	£ 39,745
Generalised gamma for both arms, patients progression-free at 5 years assumed 'cured'	£ 33,349	£ 24,884
Generalised gamma for both arms, patients progression-free at 10 years assumed 'cured'	£39,919	£ 30,997
Mixture cure rate model with log-normal for both arms (implies [redacted] durvalumab & [redacted] SoC 'cured')	NA*	NA*

* performing PSA not possible for this scenario as model returned error (#N/A) values

Table 2 Exploration of analysis for sequential CRT (PFS extrapolation log-normal for durvalumab, and generalized gamma for SoC)

	ICER (£/QALY, PSA with 1000 simulations)			
	3yr tx effect duration		5yr tx effect duration	
	deterministic	probabilistic	deterministic	probabilistic
ERG preferred utilities (from PACIFIC data, with treatment decrement and age-related decrement applied)	£ 52,193	£ 53,419	£ 52,175	£ 51,203
Utilities from literature (lower than from PACIFIC, reflecting the fact that sequential CRT population are sicker than population eligible for overlapping CRT. Treatment decrement and age-related decrement still applied)	£ 58,156	£ 59,305	£ 58,135	£ 56,650

Dear NICE team,

Subject: AstraZeneca response to provisional technical report shared on 7 February 2019

Many thanks for sharing the provisional technical report for us – we are extremely grateful for your understanding and flexibility on this.

We wish to raise one critical factual inaccuracy and one critical logical inconsistency in the provisional report (detailed below). In the context of these points, the **£18 difference** in the range of ICERs (£48,631–£48,649) proposed by the technical team **precludes relevant and clinically-plausible scenarios** (highlighted by NICE, clinical experts, and other stakeholders) – we therefore urge the technical team to reconsider the lower bound of plausible range of ICERs in the technical report. **We remain committed to working collaboratively with NICE to ensure a productive committee meeting on 14 February and have outlined a brief proposal below, which we are keen to discuss with the NICE team ahead of the committee meeting.**

Critical factual inaccuracy and logical inconsistency:

1. We have identified a key **factual inaccuracy** in the way in which clinical expert feedback on the predicted long-term PFS benefit of durvalumab vs SoC has been interpreted[1]. Clinical experts commented on the **percentage-point benefit** in PFS for durvalumab vs SoC – **this has been misinterpreted as the absolute (modelled) PFS rate in the durvalumab arm at 5-, 10-, and 15-years.** This has important implications on the ERG's and technical team's conclusions on the clinical plausibility of the revised AstraZeneca base-case, as well as several of the scenario analyses.

    - In our response to the technical report, we highlight that "*estimates of long-term PFS obtained using this approach [i.e. generalised-gamma for both treatment arms; 5-year treatment benefit duration for durvalumab] were largely consistent with the range of values obtained from UK clinical experts[2], who predicted **10%–25% (percentage point) PFS benefit** of durvalumab versus standard-of-care at 5 years, which would be sustained at later points of 10- and 15-years*". Based on the accepted modelled PFS in the SoC arm, this would predict the following PFS rates in the durvalumab arm:

	5 years	10 years	15 years
PFS rates modelled for SoC (using generalised-gamma distribution)	12.5%	8.0%	6.1%
Corresponding PFS rates for durvalumab assuming a **10–25 percentage-point benefit** (versus SoC) predicted by experts	22.5%–37.5%	18%–33%	16.1%–31.1%

[1]Note: a further factual inaccuracy relating to interpretation of the average-curve approach is detailed in page 7 (see table legend).

[2]Range obtained from 1:1s with six UK clinical experts conducted on 2nd–4th and 9th–10th of January 2019. Further validated at an advisory board conducted with 10 UK clinical experts on 16 January 2019.

- In light of this, the following statements are incorrect:
    - Page 18 of provisional technical report: "*The predicted PFS at 10 years from the log-normal extrapolation is 14%, which falls within the 10 to 25% estimate predicted by the company's clinical experts".* **14% PFS rate at 10 years for durvalumab corresponds to a 6%-point PFS benefit vs SoC, which is lower than the 10%–25%-points PFS benefit predicted by experts**. This log-normal distribution thus underestimates the PFS tail, comprising patients who achieve good long-term outcomes on overlapping CRT followed by durvalumab. This is also stated in our response to the draft technical report (page 33).
    - Page 18 of provisional technical report: *"[…] the company's preferred generalised gamma extrapolation is not plausible because its predictions are more optimistic that the expected survival predicted by the clinical experts*". As stated in our response to the draft technical report (page 15), **the longer-term (10-year and 15-year) PFS rates for durvalumab predicted by the generalised-gamma extrapolation are in fact within the range predicted by experts**: "*a generalised-gamma distribution for both arms (with a 5-year treatment effect assumption for durvalumab) predicts 10- and 15-year PFS rates of 25.6% and 19.6% for durvalumab, respectively, and 8.0% and 6.1% for placebo (i.e. standard-of-care, active follow-up). The PFS percentage-point benefit predicted by the model at both these timepoints (17.6% and 13.5%) approximates the mid-point of the range provided by experts*".

2. The **logical inconsistency** relates to how the cumulative effect of all NICE technical team preferred assumptions on the cost-effectiveness estimate are calculated in Table 1. The technical team in their assessment acknowledge that "*it is plausible that the actual treatment effect duration could be up to 5 years*". This is consistent with clinical expert opinion and stakeholder comments provided in the technical report. Yet, the technical team combine alteration point 1 with point 2, **essentially negating the possibility of the treatment benefit duration being anything >39 months**, at which point the "cap" comes into effect using the ERG-preferred PFS distributions, and equal treatment effect is assumed for durvalumab and SoC arms.

   The range of ICERs provided by the technical team thus precludes *any* scenarios reflecting a treatment benefit duration of up to 5 years, and thus does not represent the full spectrum of clinically-plausible scenarios recognised in the technical report. Rather, it is based almost entirely on an approach that:

    - Is not in line with the DSU methods guide (TSD 14).
    - Requires a cap within the model engine to ensure a clinically-**im**plausible scenario (where progression hazards in the durvalumab arm are higher than that in the placebo arm) does not occur.
    - Directly contradicts observed data from PACIFIC, invoking a scenario where all of the treatment benefit of durvalumab suddenly disappears at 39 months

(there is no evidence of such a phenomenon from 40.5 months and 41.0 months maximum follow-up in durvalumab and placebo arms, respectively).

- Produces long-term estimates of PFS benefit vs SoC that is less than the minimum value predicted by UK clinical experts (as detailed in point 1).
- Contradicts trends in KM survival curves from PACIFIC, other durvalumab studies, as well as other immunotherapies, which show improved / maintained survival rate in later data-cuts (relative to the survival tail observed at earlier timepoints). This is explained in further detail in a supporting Appendix to this response.

As mentioned previously, we are keen to work collaboratively with the NICE team to maximise chances of a productive committee meeting; however, the **artificially narrow range of ICERs of just £18.00 difference, proposed by the technical team, does not reflect the full range of clinically-plausible scenarios in play and anchors cost-effectiveness to an overly pessimistic scenario proposed by the ERG.** We propose using items 1+3 or 2+3 **separately**, to obtain a range of ICERs that includes a scenario allowing for up to 5-year treatment benefit duration for durvalumab:

	Technical team rationale	ICER	Change from base case
Company base case	-	£28,433	-
Alterations			
1a. 5-year treatment effect duration	Issue 2	£28,433	£0
1b. 3-year treatment effect duration		£35,838	+ £7,405
2. Log-normal extrapolation of PFS in durvalumab arm and generalised gamma extrapolation of SoC (with logic-check applied to prevent hazard curves crossing; treatment effect can never be longer than 39 months)	Issue 3	£46,615	+ £18,182
3. Progression-free and progressed disease health state utility values taken from PACIFIC (with treatment-related decrement applied)	Issue 4	£29,378	+ £945
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate			
1a (60 months' [5-year] treatment effect) + 3	-	£29,378	+ £945
1b (36 months' [3-year] treatment effect) + 3	-	£37,157	+ £8,724
2 (39 months' treatment effect) + 3	-	£48,631	+ £20,198
Range of ICERs	**-**	**£29,378–£48,631**	**+ £945–£20,198**

While we firmly believe in our revised base-case, we recognise there is remaining uncertainty while we wait for five-year follow-up data from PACIFIC ([redacted]), and acknowledge that a more conservative outcome, that is still aligned with the range of values predicted by clinical experts, is plausible. To understand this, we have adopted a similar approach to the NICE technical team and considered the remaining scenarios that produce long-term PFS values within the range predicted by clinical experts:

	Scenario		Modelled PFS / %-point difference		
			5 year	10 year	15 year
1	**(AstraZeneca base-case)** Generalised gamma for both arms	Placebo	13%	8%	6%
		Durvalumab	40%	26%	20%
		difference (%-point)	*28%*	*18%*	*14%*
	Clinical benefit in line with KEE opinion (10%–25%-points difference)?		No	Yes	Yes
2	**(ERG base-case)** Log-normal durvalumab & generalised gamma SoC	Placebo	13%	8%	6%
		Durvalumab	27%	17%	13%
		difference (%- point)	*14%*	*9%*	*7%*
	Clinical benefit in line with KEE opinion (10%–25%-points difference)?		Yes	No	No
Additional scenarios explored					
3	Average of generalised gamma & log-normal for durvalumab ~~& generalised gamma for~~ SoC* - **more conservative than cure-rate models (scenarios 4 to 6)**	Placebo	9%	5%	4%
		Durvalumab	33%	18%	13%
		difference (%-point)	*24%*	*13%*	*9%*
	Clinical benefit in line with KEE opinion (10%–25%-points difference)?		Yes	Yes	No
4	Generalised gamma for both arms, patients progression-free at 5 years assumed 'cured'	Placebo	13%	11%	9%
		Durvalumab	40%	36%	30%
		difference (%-point)	*28%*	*25%*	*21%*
	Clinical benefit in line with KEE opinion (10%–25%-points difference)?		No	Yes	Yes
5	Generalised gamma for both arms, patients progression-free at 10 years assumed 'cured'	Placebo	13%	8%	7%
		Durvalumab	40%	26%	21%
		difference (%-point)	*28%*	*18%*	*15%*
	Clinical benefit in line with KEE opinion (10%–25%-points difference)?		No	Yes	Yes
6	Mixture cure-rate model with log-normal for both arms (implies 39.9% durvalumab & 16.0% SoC 'cured')	Placebo	16%	14%	11%
		Durvalumab	39%	33%	27%
		difference (%-point)	*23%*	*19%*	*16%*
	Clinical benefit in line with KEE opinion (10%–25%-points difference)?		Yes	Yes	Yes

*In the "summary of comments" section for Issue 3, it states the following *"Scenario with durvalumab arm extrapolated using a distribution that is a 50:50 average of generalised gamma and log-normal, with generalised gamma extrapolation of SoC"*. This is incorrect – in the analysis undertaken by AstraZeneca, the average PFS survival curves for **both durvalumab and placebo/ standard of care** were obtained by assigning equal (50:50) weights to log-normal (ERG base case) and generalised gamma (AZ base-case) distributions. All other assumptions were same as the AZ revised base case (this is stated in Table 8, page 48 of our response to the draft technical report).

Of the remaining scenarios (excluding the AstraZeneca and ERG base-cases), the mixture cure-rate model and the average-curve approach produced clinically-plausible long-term PFS estimates, without needing to invoke additional logic checks (note: the 15-year %-point benefit for durvalumab vs SoC is <1% lower than the range provided by experts).

[redacted]

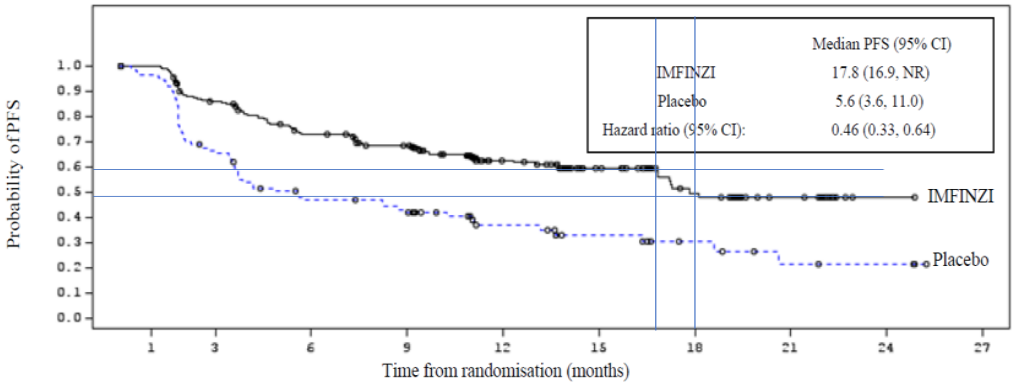
[redacted] **We wish to urgently discuss the inclusion of this proposal in the 14 February 2019 committee meeting for ID1175.**

In the meantime, we have attach a marked-up version of the provisional technical report highlighting the key issues detailed above, as well as corrections to confidentiality markings and minor corrections (errors / misrepresentations).

Appendix A

As we have noted in our response to the draft technical repot, the very last drop in the KM curve for durvalumab (at ~33 months) is driven by just **one event** from a small pool of remaining patients at risk (N=16). We reiterate again that this KM-tail is not a reliable benchmark to guide the choice of parametric survival curves for decision making. For context, we present the example of an ~10% drop in PFS that was observed at 18 months in the primary PFS analysis from PACIFIC (13 February 2017; PD-L1 ≥1% group). As PFS data from PACIFIC matured (22 March 2018 data-cut), the HR for PFS improved from 0.46 to 0.44 and the previous 10% drop in PFS shrunk to ~2−3% (as shown in supporting KM-curves below).

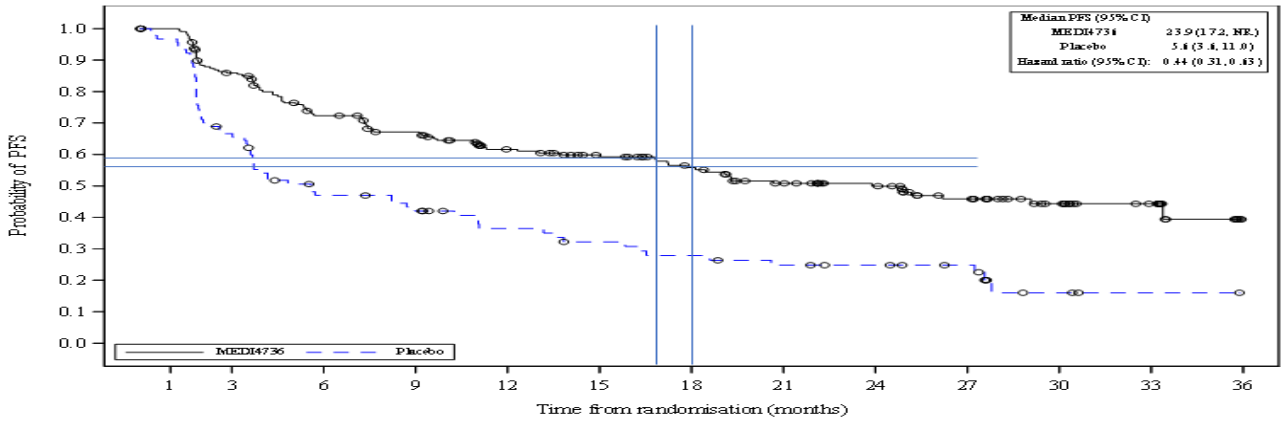
13 February 2017 data cut-off: note ~10% drop in PFS at 18 months (solid blue lines)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27
IMFINZI	212	174	143	127	82	52	30	14	1	0
Placebo	91	59	39	34	20	13	8	4	3	0

22 March 2018 data cut-off: note drop in PFS observed in 13 February 2017 data cut-off is smaller (~2%) in this more-mature data-set



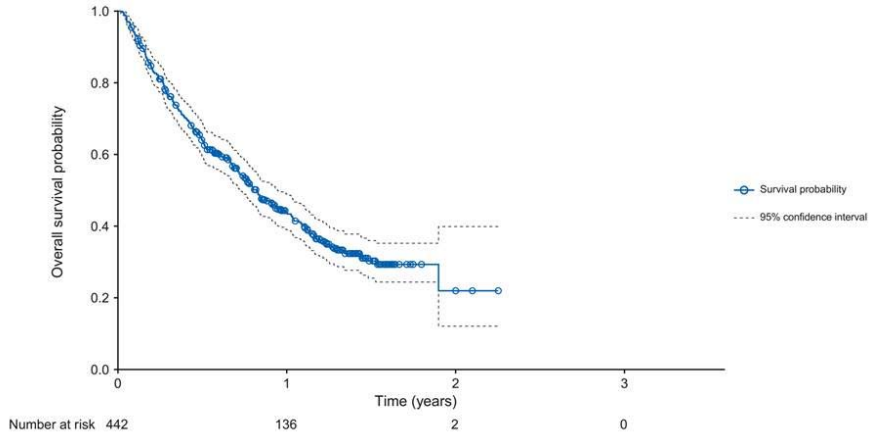
Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36
MEDI4736	212	174	142	127	105	94	81	67	56	41	26	16	0
Placebo	91	59	39	34	26	22	19	16	14	11	3	1	0

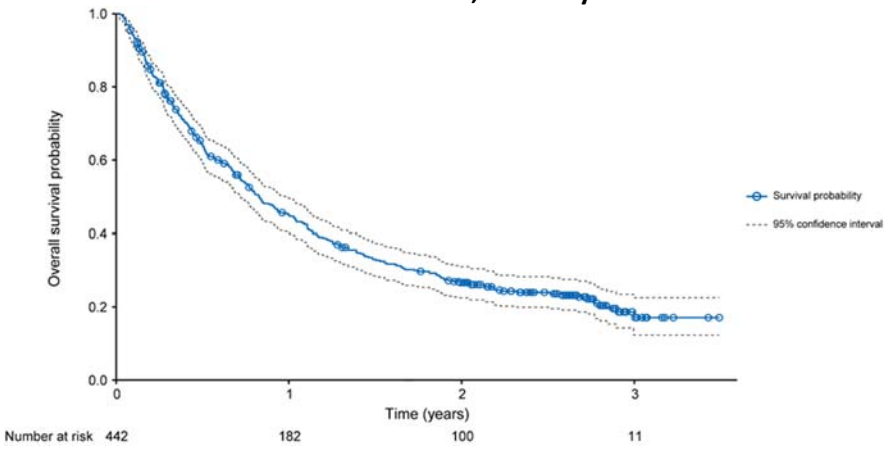
A similar phenomenon was seen in the ATLANTIC study (NCT02087423), a Phase II, open-label, single-arm trial of durvalumab in patients with Stage IIIB–IV NSCLC and WHO PS of 0 or 1, who had received at least two prior systemic treatment regimens (including one platinum-based regimen). Initial analysis of OS was performed on 3 June 2016 and a follow-up analysis on 7 November 2017. As evident

from the KM-curves below, the dip in OS observed at 2 years in the 3 June 2016 data-cut completely disappeared in the 7 November 2017 follow-up analysis. Furthermore, all parametric fits based on the June 2016 read-out under-predicted the observed outcomes in the more-mature dataset (last graph in series presented below).

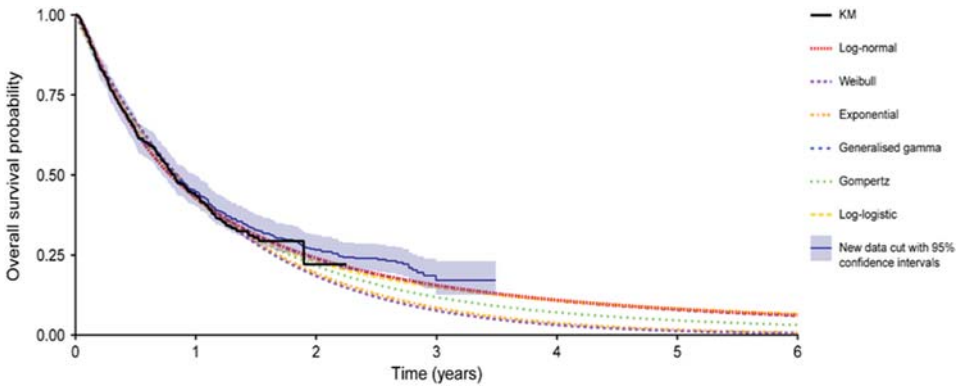
ATLANTIC - 3 June 2016 data-cut, OS analysis



ATLANTIC - 7 November 2017 data-cut, OS analysis

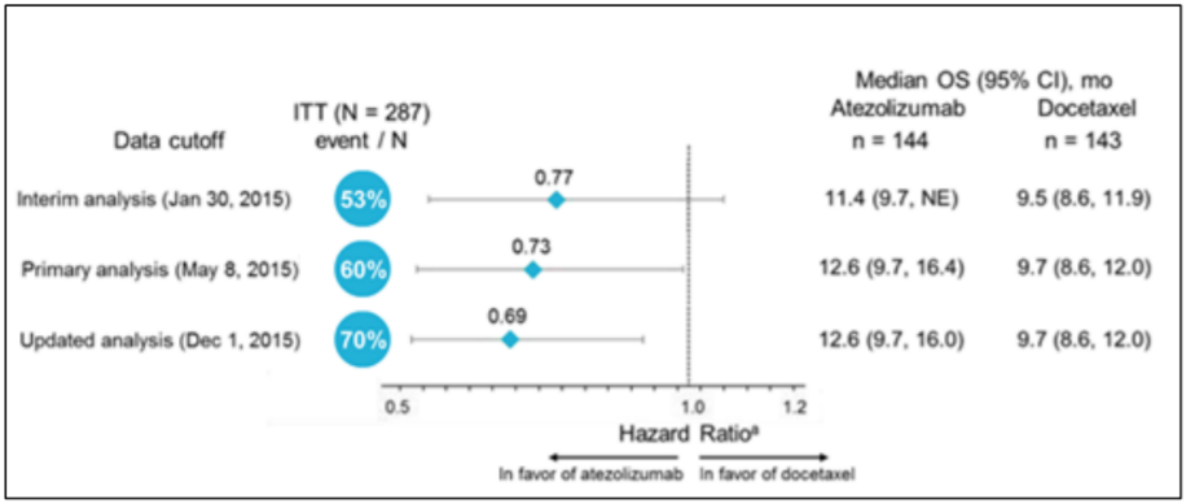


Parametric survival curves estimated using June 2016 data versus observed OS November 2017 follow-up data



Finally, this is consistent with data from immunotherapies approved in the advanced metastatic NSCLC setting (for example in the Phase II, open-label POPLAR study of atezolizumab 1200mg Q3W vs docetaxel 75mg/m^2 Q3W, as illustrated in the figure below from TA520).

OS in the POPLAR study with increasing data maturity (from the company submission; TA520)



[a]Stratified HR

ERG opinion on AZ response to provisional technical report

In their response to the provisional technical report (shared on 7 February 2019), the company stated to have identified one critical factual inaccuracy and one logical inconsistency. The ERG wishes to comment on these issues below.

1. The factual inaccuracy was in how the 10-25% PFS benefit was interpreted, i.e. as absolute PFS rate in the durvalumab arm, instead of percentage point benefit additional to SoC PFS. Indeed, in the provisional technical report this is misrepresented. This leaves unaffected though what the ERG stated before in response to the technical engagement document where these expert opinion estimates were first brought to the table: 'The company chose to maintain the generalized gamma for the PFS curve of durvalumab, using the same arguments that were used in the original company submission, complemented with additional clinical expert opinion. The ERG does not see any new evidence concerning PFS, and will therefore maintain their argumentation as stated in the ERG report.'

2. The 'logical inconsistency' was that when using the ERG and NICE technical team's preferred assumptions (lognormal PFS for durvalumab and generalised gamma for SoC), there is hardly any difference in the ICER for 3 and 5 yrs treatment effectiveness. This is indeed the case and is caused by the hazard curves crossing at 39 months (so just after 3 yrs), at which point the hazard cap comes into effect, lowering the hazard for durvalumab (making it equal to that of SoC). The company state this precludes a proper exploration of a 5 year treatment effect. The ERG feels it could also be seen as 'correcting' for a too optimistic 3 yr PFS benefit. The company proposed the NICE technical team to base the lower end of their ICER range on the generalized gamma PFS curve for durvalumab in combination with the 5 yr treatment effect – a scenario which is very close to the company base-case. The ERG does not consider switching back to generalized gamma PFS for durvalumab to be the designated way to explore a 5 yr treatment benefit.

NICE National Institute for Health and Care Excellence

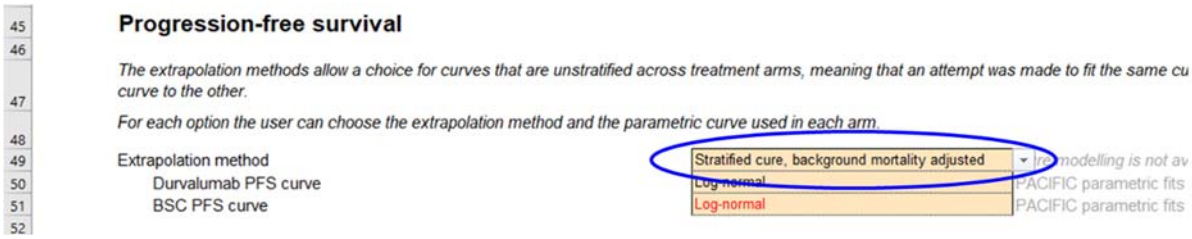
Reference: email received on 30.01.2019 regarding ID1175 (sent by: Lucy Beggs)

1. **NICE request:** we would like to provide the ERG with the mixture cure model. Please can you send this model, or instructions of how to implement the analysis in the existing model.

   AstraZeneca response: guidance on how to implement the mixture cure-rate model (MCM) function within the latest iteration of the economic model uploaded to NICE docs (file name: ID1175_Durvalumab_CEM_to_support_AZ_technical_engagement_response_210119) is as follows:

   To use the MCM survival functions within the model, please navigate to the "**Controls**" worksheet and select "**Stratified cure, background mortality adjusted**" within the dropdown menu in cell D49 (under the heading of "Progression-free survival"). A screenshot illustrating this is provided below:

   Screenshot ("Controls" worksheet):



   Please note that this selection will automatically update the same "extrapolation method" selection for the time-to-progression survival functions.

2. **NICE request:** please provide the proportion of patients progression free at 3, 5 and 10 years in durvalumab arm as predicted by the mixture cure model. Please provide these values under the assumptions of 3- and 5-year treatment effect duration.

   AstraZeneca response: The proportion of patients who are progression free at 1, 2, 3, 5, 10, 15 and 20 years using the MCM with 5-year and 3-year treatment effect durations for durvalumab are shown in Table 1 and Table 2 below, respectively.

   As mentioned in the cover note, we have also provided the corresponding half-cycle corrected values for the standard-of-care arm in Table 3. Please note that the estimates provided in the technical response document (Appendix E, table 12) are not half-cycle corrected. It is possible to validate both sets of numbers using the "PF_BSC" and "PF_Durvalumab" worksheets in the economic model. Column N provides the non-half-cycle corrected estimates and column U provides the half-cycle corrected estimates.

Table 1. Extrapolation of PFS outcomes for durvalumab using a 5-year treatment effect duration (MCM; half-cycle corrected)

PFS	Median (months)	1 year	2 years	3 years	5 years	10 years	15 years	20 years
Modelled								
Exponential	22.08	62.82%	48.69%	42.10%	36.62%	31.63%	26.50%	20.45%
Generalised-gamma	23.92	60.10%	50.49%	45.22%	38.80%	24.67%	17.20%	11.71%
Gompertz	22.08	62.86%	48.89%	41.91%	35.23%	27.93%	23.06%	17.75%
Log-logistic	21.16	60.33%	48.79%	44.34%	40.26%	33.94%	28.05%	21.51%
Log-normal	21.16	60.42%	48.72%	43.87%	39.38%	32.52%	26.80%	20.56%
Weibull	21.16	61.97%	47.97%	42.94%	39.76%	35.23%	29.53%	22.79%

Table 2. Extrapolation of PFS outcomes for durvalumab using a 3-year treatment effect duration (MCM; half-cycle corrected)

PFS	Median (months)	1 year	2 years	3 years	5 years	10 years	15 years	20 years
Modelled								
Exponential	22.08	62.82%	48.69%	42.10%	35.79%	30.91%	25.90%	19.99%
Generalised-gamma	23.92	60.10%	50.49%	45.22%	33.59%	21.31%	14.85%	10.11%
Gompertz	22.08	62.86%	48.89%	41.91%	33.20%	26.31%	21.72%	16.72%
Log-logistic	21.16	60.33%	48.79%	44.34%	39.33%	33.15%	27.39%	21.00%
Log-normal	21.16	60.42%	48.72%	43.87%	37.59%	31.02%	25.57%	19.62%
Weibull	21.16	61.97%	47.97%	42.94%	39.26%	34.79%	29.17%	22.51%

Table 3. Extrapolation of PFS outcomes on standard-of-care (MCM; half-cycle corrected)

PFS	Median (months)	1 year	2 years	3 years	5 years	10 years	15 years	20 years
Modelled								
Exponential	6.44	35.10%	21.88%	17.53%	14.89%	12.86%	10.77%	8.31%
Generalised-gamma	5.98	34.11%	22.99%	18.15%	13.43%	8.52%	5.94%	4.04%
Gompertz	6.44	35.38%	22.28%	17.45%	13.79%	10.93%	9.02%	6.94%
Log-logistic	5.98	32.39%	23.17%	20.31%	17.99%	15.17%	12.53%	9.61%
Log-normal	5.98	32.87%	22.68%	19.20%	16.42%	13.55%	11.17%	8.57%
Weibull	6.44	33.71%	21.31%	18.10%	16.53%	14.65%	12.28%	9.48%

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Cancer Drugs Fund Clinical Lead statement

Durvalumab after chemoradiotherapy for locally advanced and unresectable non small cell lung cancer which has a ≥1% PD-L1 expression and which has not progressed following platinum-based chemoradiotherapy [ID1175]

Background

1. The aims of treatment for locally advanced and unresectable stage III non small cell lung cancer (NSCLC) are to maximise the long term cure rate and in those that cannot be cured to delay disease progression and maintain quality of life for as long as possible at the expense of as few side effects as possible.

2. Any new treatment or any combination therapy which increases the efficacy of standard treatment is welcome as this is likely to increase the cure rate or delay the consideration of further active treatment. A strategy that does this using a fixed duration of systemic treatment with modest toxicity offers additional advantages.

The treatment pathway

3. The term concurrent chemo-radiotherapy describes the use of both chemotherapy and radiotherapy together at the same time ie there are days during the whole treatment period in which patients receive both chemotherapy and radiotherapy on the same days. In concurrent treatment, chemotherapy is being used to treat the cancer in its own right and is also acting as a sensitising agent to radiation therapy. This concurrent approach is commonly used in other cancers such as those originating in the head and neck, bladder, cervix and rectum.

4. The term sequential chemotherapy-radiotherapy is used to describe initial chemotherapy on its own and when after chemotherapy has been completed, this is followed by radiotherapy on its own. Chemotherapy is being used to shrink the cancer prior to the start of radiotherapy.

5. These two concurrent and sequential ways of combining chemotherapy and radiotherapy are used in different groups of patients with unresectable stage III NSCLC. Fit patients with lung cancers which can be encompassed within a radical radiotherapy treatment field have concurrent chemo-radiotherapy. Less fit patients and/or those with lung cancers which are initially too large to be encompassed in a radiotherapy treatment field have sequential chemotherapy followed by radiotherapy. These two different treatments are used in different patients who have different longer term outcomes.

6. For unresectable locally advanced stage IIIA and IIIB NSCLC, concurrent chemo-radiotherapy is the preferred treatment for patients who are fit as it leads to higher 5 year rates of overall survival albeit with higher rates of initial oesophageal and lung toxicity. The optimal chemotherapy to be combined with concurrent chemoradiotherapy is a platinum-based combination of drugs.

7. Several trials have shown the superiority of the concurrent approach when directly compared to sequential chemotherapy-radiotherapy. The largest (JNCI 2011; 103: 1452, the RTOG 9410 trial) showed that 5 year survival was 16% with concurrent treatment versus 10% with sequential therapy. This trial had a median duration of follow-up of 11 years when last reported and showed increased short term side-effects but no difference in late toxic effects. It used an old cisplatin-based combination which has been replaced with better combination therapy. A smaller concurrent vs sequential Japanese trial which also used an old chemotherapy combination regimen found the 5 year

survival rate of 16% with concurrent treatment to be superior to that of 9% with sequential therapy (J Clin Oncol 1999; 17: 2692). A Cochrane meta-analysis in 2010 concluded that overall survival was superior with concurrent vs sequential treatment (Cochrane Database Syst Rev 2010; 16: CD002140).

8. These older chemotherapy regimens in these 2 RCTs have been replaced by better systemic therapies and both more efficacious and less toxic radiotherapy techniques. More recent phase III trials in unresectable NSCLC and with mature follow-up have shown 5 year overall survival rates of 20-30% with concurrent chemo-radiotherapy. Part of this increase in long term survival has been probably due to the increased use of PET scanning in the staging of such NSCLC patients.

9. NHS England notes that the Roy Castle Lung Cancer Foundation quotes a real world 5 year survival rate after concurrent chemo-radiotherapy as being 15%. Professional consultees indicated a 25-30% 5 year survival rate in selected patients and a range of 15-20% 5 year survival in less selected patients. Since all the longer term modelling of the durvalumab versus placebo arms is based on PACIFIC clinical trial data, NHS England considers that clinical trial data has to be used for examination of all parts of the overall survival curves for both durvalumab and placebo.

10. PET scanning is routine practice in England for all stage III patients fit for potentially radical treatment.

Comparator for durvalumab post chemo-radiotherapy for unresectable stage III NSCLC

11. The correct comparator in NHS England practice for durvalumab is routine surveillance as chosen in the PACIFIC trial and by the company in this NICE submission.

12. Since the marketing authorisation for durvalumab restricts use to those patients with PD-L1 expression of ≥1%, the NICE-recommended and routinely commissioned comparator treatment options after disease progression on routine surveillance are pembrolizumab monotherapy or atezolizumab monotherapy or combination chemotherapy usually with either platinum-based chemotherapy with pemetrexed with maintenance pemetrexed (non-squamous NSCLC) or gemcitabine (squamous NSCLC). For those patients with EGFR or ALK mutations, targeted therapy would be the next line of therapy after disease progression on routine surveillance. Nivolumab is not a comparator as it is not routinely commissioned for NSCLC.

13. For patients relapsing during treatment with durvalumab, then the next line of treatment would be with chemotherapy or targeted therapy as outlined above but not with further immunotherapy. For patients relapsing after completion of 12 months of durvalumab therapy, the time at which relapse occurs and the mutation status are likely to determine whether targeted therapy and further immunotherapy is next used or not. Those patients with mutations will have targeted therapy. If patients relapse shortly after completing durvalumab, then it is unlikely that there will much benefit from further immunotherapy. If patients relapse a substantial time after completing durvalumab, then further immunotherapy could be of benefit and thus treatment options would be as outlined above in paragraph 12.

Clinical trial data for the use of durvalumab post chemoradiotherapy

14. NHS England considers that there is great immaturity of outcome data in the PACIFIC trial as so far it has a median duration of follow-up of 25.8 months and a maximum follow up duration of only 41 months. NHS England notes that a data cut is planned in [redacted] but that

further data cuts will provide the necessary clarity as to longer term survival durations.

15. The addition of post-chemoradiotherapy durvalumab yields a clinically noteworthy and worthwhile difference in progression free survival (PFS) in PD-L1≥1% patients of 23.9 for durvalumab versus 5.6 months for placebo. NHS England notes that there are few patients at risk of disease progression after 27 months and that PFS maturity in the company's submission is 55%.

16. The addition of post-chemoradiotherapy durvalumab results in a significant improvement in overall survival (OS) in the PD-L1 ≥1% group, the median duration of OS being not reached in the durvalumab arm versus 29.1 months in the placebo arm. There are few patients at risk after 30 months of follow-up and the data used in the company submission has an OS maturity of 33% for durvalumab and 50% for the placebo arm.

17. NHS England welcomes the company's analyses of the times to first and especially second treatments given the sequence of potential treatments now in routine commissioning for NSCLC. However, the data for subsequent treatment also needs to be mature to be meaningful. Such maturity would also offer the opportunity to examine the rates of treatment at 1st and 2nd subsequent treatments when compared with the starting population. This is important in a disease such as NSCLC in which the rates of subsequent therapies can fall rapidly from line to line of therapy. NHS England notes that in the AZ submission the treatment rate at disease progression with immunotherapy was 8.5% in the durvalumab arm versus 24% in the placebo arm. These rates appear low and one reason for this and the current difference is likely to be the immaturity of follow up data.

18. NHS England notes that the PD-L1 tumour cell expression was not a stratification factor in the trial design and that this was tested

retrospectively. There is an imbalance in the proportions of each arm that had PD-L1 status of ≥1%, 44.5% in the durvalumab arm versus 38.4% in the placebo arm. A large proportion (37%) of patients were of unknown PD-L1 status although NHS England notes that this group gained survival benefit from durvalumab of a broadly similar order to that of the PD-L1 ≥1% group.

19. Given the very substantial difference in PFS, NHS England is surprised that there was no difference in quality of life observed between the durvalumab and placebo arms in the PACIFIC trial.

20. NHS England notes that there was increased toxicity in the durvalumab arm of the PACIFIC trial (as expected). Whilst most side-effects of PD-L1 directed immunotherapy are relatively mild, there are small but definite percentages of patients who develop serious toxicities such as colitis, pneumonitis, nephritis, hepatitis and endocrinopathies.

Generalisability of the PACIFIC study to NHS practice

21. The evidence from the PACIFIC study can be broadly translated to resulting in similar outcomes in NHS England for the use of durvalumab following concurrent chemoradiotherapy. The main reason for this is that concurrent chemoradiotherapy stage III NSCLC patients are highly selected already on account of PET imaging and performance status, just as patient in clinical trials are highly selected too. NHS England therefore is confident that outcomes from the PACIFIC trial will be broadly seen in clinical practice in England.

22. NHS England wishes to make it very clear that the only evidence for the use of durvalumab after chemo-radiotherapy for stage III NSCLC is seen with its use after patients treated with concurrent chemo-radiotherapy. A NICE recommendation for durvalumab would now be based on both the clinical and cost effectiveness of durvalumab in

concurrent chemoradiotherapy patients. Outcomes are inferior with sequential chemotherapy-radiotherapy and the clinical and cost effectiveness of durvalumab with such treatment is unknown. If the durvalumab results could be directly translated from concurrent to sequential treatment, why then is the company doing studies of durvalumab in sequential chemotherapy-radiotherapy? NHS England also notes that the FDA license is based on the results of the PACIFIC study and the FDA marketing authorisation is only for durvalumab after concurrent chemo-radiotherapy (albeit without any PD-L1 restriction). NHS England regrets the vague wording of the EMA marketing authorisation but would only wish for the clinical and cost effectiveness of durvalumab to be considered by NICE for the population of patients with unresectable stage III NSCLC treated with concurrent chemoradiotherapy.

23. IF NICE recommends durvalumab within its marketing authorisation, NHS England is confident in the commissioning of a maximum durvalumab treatment duration of 12 months so that the clinical and cost effectiveness evidence base for durvalumab is directly translated into NHS practice.

Specific issues in this appraisal of clinical and cost effectiveness of durvalumab post chemo-RT

24. NHS England notes that in its model the company after a maximum of 1 year of treatment with durvalumab assumed that the treatment waning effect of durvalumab would not begin until after 10 years. NICE and in particular committee D has generally preferred analyses of 3-5 year treatment waning effects but these have all been after a maximum of two year and not one year treatment durations.

NHS England notes that the company's model assumes a 12% 5 year OS in the placebo arm. This is too low for two reasons. The first is that concurrent chemo-radiotherapy for unresectable stage III NSCLC would be expected to deliver a 5 year rate of OS of considerably in excess of 15% ie 20-30% (see above). The second is that immunotherapy has produced a modest but definite tail on the OS curve in NSCLC and the figures quotes above do not reflect the additional impact of subsequent immunotherapy. Of course, the PACIFIC data is immature and the 3, 4 and 5 year survival figures with further follow-up will give much greater certainty to the analysis of clinical and cost effectiveness of durvalumab after concurrent chemo-radiotherapy.

25. NHS England notes the uncertainty as to subsequent treatments given the immaturity of the PACIFIC trial data. NHS England also notes the importance of subsequent treatments to both the clinical outcomes and costs of the durvalumab and placebo arms. Drugs in the CDF cannot be considered as standard therapies and hence the drugs used after durvalumab or placebo must be in line with the current treatment pathway for routine recommended options as set out in paragraph 12 above. NHS England notes that the company's economic model assumed that 32% received nivolumab and 7% received pembrolizumab in the placebo arm and the corresponding figures for the durvalumab arm are 15% and 5%, respectively. These figures are highly uncertain and nivolumab should not have been used as it is not in routine commissioning for the treatment of NSCLC. NHS England also queries the differential use of docetaxel between treatment arms (22% in the durvalumab arm versus 7% in the placebo arm; 21% pemetrexed in the durvalumab arm and 12% in the placebo arm.

26. The company's model included the costs of PD-L1 testing. There is no need for PD-L1 testing costs to be included as these are already routinely funded.

27. The company's model did not include drug wastage. Whilst NHS Trusts do all they can to minimise waste and can schedule patients on durvalumab to be treated on certain days of the week, the number of patients treated with durvalumab will not be very high. Although it is reasonable to use the mean weight in the PACIFIC trial of 71.4Kg, it is better to analysis the impact on drug wastage when the whole population in the trial is analysed according to their weights. In the PACIFIC trial, 36% had a weight between 70 and 90Kg and 11% had a weight above 90Kg. There are two vial sizes (120mg and 500mg) and hence it is possible that drug wastage could be lesser or greater than that suggested by just considering a mean weight and a treatment dose of durvalumab10mg/Kg.

Commissioning perspective

28. As has been stated above, NHS England interprets the evidence base and the marketing authorisation of durvalumab as durvalumab being used after concurrent chemo-radiotherapy and not being used after sequential chemotherapy-radiotherapy. The latter awaits a robust evidence base and sequential chemotherapy-radiotherapy with durvalumab is being investigated in the PACIFIC-5 and -6 trials. NHS England notes that the company stated in clarification that the effectiveness of durvalumab when following sequential chemotherapy-radiotherapy is unknown.

29. NHS England expects the treatment numbers to be modest for durvalumab use in patients who do not progress following concurrent chemo-radiotherapy for unresectable stage III NSCLC. A recent British Thoracic Oncology Group audit recorded about 200 patients in 2016 treated with concurrent chemo-radiotherapy for unresectable

stage III NSCLC. It is not known how complete this audit was in terms of capturing all patients treated in this way. Some of these patients may have been outside England and some would have been ineligible for durvalumab as they would have progressed during concurrent chemo-radiotherapy.

30. NHS England would welcome any application for durvalumab in this indication to the CDF. The PACIFIC trial results are very promising but uncertain. Further follow-up is planned and will give information on overall survival and subsequent treatments and thus be of great help in giving greater certainty to the clinical and cost effectiveness of durvalumab after concurrent chemo-radiotherapy for unresectable stage III NSCLC.

Implementing a positive NICE recommendation

NICE recognises that in the event of a positive recommendation, more prescriptive clinical commissioning criteria for treatments commissioned via Specialised Services will be implemented by NHS England to ensure appropriate use within the NHS.

NHS England is responsible for ensuring that the final clinical commissioning criteria are aligned with final guidance (section 1 – recommendation and section 3 – committee discussion).

Draft commissioning criteria

31. If durvalumab for treating patients with unresectable stage III PD-L1 ≥1% NSCLC who have not progressed following concurrent platinum-based chemoradiotherapy is recommended for use within its marketing authorisation, NHS England proposes to use the following commissioning treatment criteria:

- Patients must have confirmed NSCLC which has a PD-L1 tumour cell expression of at least 1%

- Unresectable stage IIIA or IIIB NSCLC
- Treated with platinum-based concurrent chemo-radiotherapy
- Not progressed after such concurrent chemo-radiotherapy
- Patients must have an ECOG performance status of 0 or 1
- No prior treatment with any immunotherapy for NSCLC
- Maximum of 12 months treatment duration with durvalumab
- Patients will continue treatment until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment or a treatment duration of 12 months, whichever is the sooner

If this technology is recommended for routine commissioning in a subpopulation or with certain specifications the final commissioning criteria will reflect these conditions.

Issues for discussion

32. These have all been mentioned above

Equality

33. The issue of equality of access to patients who have insufficient tissue for PD-L1 testing or whose PD-L1 test fails will need to be addressed as to whether any access to durvalumab is recommended by NICE. It is NHS England's intention for all patients to have PD-L1 testing but occasionally the availability of results can defy commissioning intention.

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The indication as approved by the CHMP doesn't make explicit reference to "concurrent" chemoradiation therapy, but this was the understanding of the term "chemoradiation". The data on the basis of which the MA of durvalumab was granted is indeed in patients who did not progress following definitive, platinum-based, concurrent chemoradiation therapy.

Best wishes

[redacted]
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