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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Karen Pickett critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor; Marcia Takahashi critically appraised the health economic systematic review and the economic evaluation, and drafted the report; Neelam Kalita critically appraised the health economic systematic review and the economic evaluation, and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review and drafted the report.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
CAV	Cyclophosphamide, doxorubicin and vincristine
cCRT	Concurrent chemoradiotherapy
CI	Confidence interval
CPI	Consumer Price Inflation
CRD	Centre for Reviews and Dissemination
CRT	Chemoradiation
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC-QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
FAS	Full analysis set
FPAS	Full PD-L1 analysis set
GP	General practitioner
Gy	Gray
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

IgG1κ	Immunoglobulin G1 kappa
IO	Immuno-oncology
ITT	Intention-to-treat
IVRS/IWRS	Interactive Voice/Web Response System
KM	Kaplan Meier
LS-SCLC	Limited-stage small-cell lung cancer
LYG	Life-year gained
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
OS	Overall survival
OS24	The proportion of patients alive at 24 months from randomisation
OS36	The proportion of patients alive at 36 months from randomisation
PAS	Patient access scheme
PCI	Prophylactic cranial irradiation
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PFS18	Progression-free survival at 18 months following randomisation
PFS24	Progression-free survival at 24 months following randomisation
PFS2	Time from randomisation to second progression or death
PGIS	Patient Global Impressions Severity
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event
SAS	Safety analysis set

SCLC	Small-cell lung cancer
sCRT	Sequential chemoradiotherapy
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TNM	Tumour, node, metastasis
TSD	Technical Support Document
UK	United Kingdom
VAS	Visual analogue scale
WHO	World Health Organisation
WTP	Willingness to pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID	Summary of issue	Report sections
1	Lack of evidence for durvalumab in patients whose disease has not progressed after sequential chemoradiotherapy (sCRT)	2.2.3, 2.3, 3.2.1, 3.4
2	Extrapolation of OS and PFS (and the cure assumption)	4.2.4.1, 4.2.4.2, 4.2.4.3, 6
3	Resource use and subsequent treatment	4.2.7.3, 4.2.7.4, 5.3.2 and 6
4	Treatment effect waning	4.2.5, 6.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are changes in the selection of survival distributions for extrapolating OS and PFS curves, cure assumption, resource use and subsequent treatment distribution (see section 1.6 below).

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Following their response to the clarification questions, the company updated their economic model. The EAG identified a few minor errors in the company's revised model, which we

corrected. The EAG corrected revised company model base case deterministic results [using updated commercial arrangement price for durvalumab] is shown in Table 2. The pairwise ICER for durvalumab versus 'watch and wait' is £19,160per QALY. The 'watch and wait' comparator is established clinical management without durvalumab (that is, active monitoring).

Table 2 EAG corrected company's revised base case results with updated commercial arrangement price for durvalumab

Technologies	Total costs (£)[a]	Total LYG[a]	Total QALYs[a]	ICER (£/QALY)[a]	NMB (£) for a WTP of £30,000
Watch and wait	£20,642	[redacted]	[redacted]	£19,160	£7,833
Durvalumab	[redacted]	[redacted]	[redacted]		
Increment	[redacted]	[redacted]	[redacted]		

Source: corrected company's economic model
Abbreviations: LYG, Life-year gained; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio ; NMB, Net Monetary Benefit; WTP, Willingness to pay.
[a] Discounted at 3.5% per year, with no severity modifier applied to QALYs

1.3 The decision problem: summary of the EAG's key issues

The EAG have not identified any key issues in relation to the company's decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Lack of evidence for durvalumab in patients whose disease has not progressed after sCRT

Report section	2.2.3, 2.3, 3.2.1, 3.4
Description of issue and why the EAG has identified it as important	The NICE scope for this appraisal states that the population of interest is people with limited-stage small-cell lung cancer (LS-SCLC) whose disease has not progressed after chemoradiotherapy. Furthermore, the scope states that subgroups of patients who have received concurrent chemoradiotherapy (cCRT) or sCRT are of interest. The company submission (CS) does not include any evidence on the clinical efficacy and safety of durvalumab maintenance therapy in people with LS-SCLC whose disease has not progressed after sCRT. One trial of durvalumab was included in the CS (ADRIATIC), which limited participant eligibility to those who had previously had cCRT and who had a World Health Organisation (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; people who had received sCRT, who are typically less fit, were excluded. A clinical expert advised us that when taking a strictly evidence-based approach, the results of the ADRIATIC trial cannot be generalised to people who

	have previously received sCRT. However, both the External Assessment Group's (EAG's) experts suggested that it may be reasonable to assume that patients who have previously received sCRT might benefit from durvalumab maintenance therapy. We received clinical expert advice that most patients with LS-SCLC who can have chemoradiation (CRT) will receive cCRT and the patient population who receive sCRT is small.
What alternative approach has the EAG suggested?	None; this is a limitation of the evidence base.
What is the expected effect on the cost-effectiveness estimates?	The parameters informing the model (e.g. clinical efficacy inputs, resource use, utilities) could potentially differ for populations who have previously received cCRT or sCRT, but the potential impact on the ICER is unknown. The EAG is not aware of any evidence that might inform assumptions about how the parameters might be affected, but it could be speculated that patients who have previously received sCRT might gain fewer QALYs from treatment, as these patients generally have a lower performance status.
What additional evidence or analyses might help to resolve this key issue?	Further discussion with clinical experts about the extent to which the ADRIATIC trial results are considered generalisable to the sCRT population.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 2 Extrapolation of OS and PFS (and the cure assumption)

Report section	4.2.4.1, 4.2.4.2, 4.2.4.3, 6
Description of issue and why the EAG has identified it as important	The company chose spline models to extrapolate progression-free survival (PFS) and overall survival (OS) for both the treatment arms and applied a cure assumption in modelling the PFS whereby a cure fraction of 90% is applied to those patients who are progression-free at 5 years. The EAG have the following concerns with the company's approach: • Based on Akaike Information Criterion (AIC)/ Bayesian Information Criterion (BIC) (goodness of fit) scores, the generalised gamma distribution provides a better fit to the PFS Kaplan Meier (KM)-curves, and 1-knot spline hazard for the OS KM-curves for the treatment arms. The company did not explore the impact of the latter in their scenario analyses. • While cure models may be suitable in the context of immunotherapies, if a proportion of patients is believed to not experience the event of interest and may be used to estimate the overall hazard functions with a complex shape by combining the hazard function of the cured fraction with that of the uncured fraction, the company argued that the spline models (that they chose for their

	base case) accommodated complex hazard functions. Therefore, we view that adding the cure assumption to the survival functions extrapolated using flexible spline models may overestimate the survival functions. • Secondly, the appraisal committee in the previous technology appraisal (TA) 638 preferred restricted spline models for extrapolating overall survival, after considering a mixture cure model that was conducted as part of additional analyses. • Finally, our clinical experts suggested that although a subset of patients with SCLC may not experience relapse within the first five years and are discharged on the presumption that they have been cured, some of them may experience long-term toxicities, particularly cardiac disease, due to radiotherapy. Therefore, this subgroup of patients may have additional needs, even if they are cured from their cancer, due to the long-term impact of radiotherapy.
What alternative approach has the EAG suggested?	Extrapolation of survival curves: • The EAG conducted several scenarios exploring the impact of different survival curves for both OS and PFS on the EAG corrected company's revised model (section 6.1). • For the EAG preferred assumptions, we applied 1-knot spline hazard model for the OS extrapolation and generalised gamma for the PFS extrapolation. (section 6.2) • We also conducted scenario analyses on the EAG preferred model with a set of distributions (section 6.3) Cure assumption: • We explored additional scenarios on the EAG corrected company's revised base case by varying the cure fraction and the cure timepoint (section 6.1) • We view it is appropriate to exclude a cure assumption and therefore explore the impact of this assumption in EAG preferred analyses (sections 4.2.4.3, 6.2) We also conducted scenario analysis on the EAG preferred model by applying company's cure assumption (section 6.3)
What is the expected effect on the cost-effectiveness estimates?	Applying 1-knot spline hazard model for the extrapolation of the OS curves for both treatment arms increase the ICER from £19,160 to £23,391 (Table 33). Using generalised gamma distribution to extrapolate PFS curves does not have significant impact on the ICER (CS Table 81). Similarly, excluding the cure assumption from the model or varying the cure fraction and the cure timepoint do not have a significant impact on the cost-effectiveness results (Table 33, Table 34).
What additional evidence or analyses might help to resolve this key issue?	Further discussion with clinical experts on the plausibility of cure assumption in patients with LS-SCLC.

Issue 3 Resource use and subsequent treatment

Report section	4.2.7.3, 4.2.7.4, 5.3.2 and 6
Description of issue and why the EAG has identified it as important	The EAG identified a few errors and inconsistencies in the company's estimation of resource use, costs and subsequent treatments. While the company corrected these as part of their response to clarification questions, we identified further minor errors (section 5.3.2). Consultation with our clinical experts also suggested some uncertainty in the company's resource use estimates (section 4.2.7.3). Finally, we have concerns about the company's base case estimates for the types and proportion patients receiving subsequent treatment (section 4.2.7.4)
What alternative approach has the EAG suggested?	The EAG corrected the errors identified in the company's revised base case that was submitted as part of their clarification response (section 5.3.2). To address the uncertainties associated with the resource use estimates and subsequent treatment distribution, we conducted EAG analyses (Table 33, section 6)
What is the expected effect on the cost-effectiveness estimates?	Incorporating the EAG corrections to the company's revised model increased the ICER slightly, from £18,743 per QALY to £19,160 per QALY (section 5.3.2). Applying the EAG estimates for resource use and subsequent treatment distribution (based on our experts' views) increase the ICER to £20,404 and £23,925, respectively (Table 33). In the EAG preferred base case, we applied the resource use estimates based on our clinical experts' opinions and the distribution for subsequent treatment from the ADRIATIC trial (Table 34) and conducted scenarios on our base case using the company's estimates (Table 36).
What additional evidence or analyses might help to resolve this key issue?	Further discussion on appropriate resource use and subsequent treatment distribution that is reflective of UK clinical practice.

Issue 4 Treatment effect waning

Report section	4.2.5, 6.3
Description of issue and why the EAG has identified it as important	No treatment effect waning was applied in the company's model. The company argued that there was no clinical evidence for treatment effect waning and that previous TAs (TA638 and TA184) did not incorporate this assumption in their base cases. We acknowledge that there is no established clinical evidence to indicate a treatment effect waning. From the previous appraisals, we note that: • In TA638, the appraisal committee was uncertain about the duration of treatment benefit. Therefore, additional scenario analyses were conducted to test the impact of treatment effect waning at 3 years, 4 years, 5 years, and maximum follow up of the relevant trial-Impower133. The committee acknowledged that varying the duration of treatment benefit had a minor impact on the cost-effectiveness results.

	• In TA798, after exploring additional analyses on varying the treatment effect waning at 3 years, 5 years, 7.5 years and 10 years, the committee concluded that both 3-year and 5-year treatment effect waning scenarios were appropriate for decision making. There is uncertainty over the company's assumptions of no treatment effect waning due to i) the appraisal committee's conclusion in TA798 which assessed durvalumab as maintenance treatment in unresectable NSCLC after platinum-based chemoradiation, and ii) median OS follow-up of durvalumab in the ADRIATIC trial (30.75 months) potentially not be a long enough follow-up to ascertain that there was no treatment effect waning.
What alternative approach has the EAG suggested?	We conducted three exploratory scenarios on the EAG preferred base case model varying the duration of treatment effect lasting between 3 and 5 years after stopping treatment. The exploratory scenarios were: • Treatment effect capped at 3 years • Treatment effect capped at 5 years • Treatment effect starts to wane at three years gradually over two years with the effect ceasing at five years
What is the expected effect on the cost-effectiveness estimates?	Assuming treatment waning has a significant impact on the ICER, resulting in an increase in the EAG preferred base case ICER. Varying the duration of treatment effect varies the ICER between £121,944 (treatment effect capped at 5 years) and £253,707 (treatment effect capped at 3 years) (Table 36)
What additional evidence or analyses might help to resolve this key issue?	Further committee discussion and expert clinical opinion on the appropriate assumption regarding treatment effect waning of durvalumab in the treatment of patients with LS-SCLC following CRT that is reflective of clinical practice.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Our preferred model assumptions are as follows:

- Overall survival curves for both the treatments: 1-knot spline hazard (section 4.2.4.2)
- Progression-free survival curves for both the treatments: generalised gamma (section 4.2.4.1)
- No cure assumption (section 4.2.4.3)
- Resource use based on EAG clinical expert advice (section 4.2.7.3)
- Subsequent treatment distribution based on the ADRIATIC trial (section 4.2.7.4)

Table 3 shows the cumulative cost-effectiveness results for durvalumab versus 'watch and wait' of adding the EAG's preferred model assumptions one at a time to the EAG corrected company's revised base case with the updated commercial arrangement price for durvalumab. Including all the EAG's preferred assumptions increases the ICER from £19,160 to £29,396 per QALY.

Table 3 EAG preferred assumptions (using updated commercial arrangement price for durvalumab)

Model	Section in EAG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
EAG corrected company revised base-case with updated commercial arrangement	5.3.2	[redacted]	[redacted]	£19,160
EAG preferred assumptions run on the above model version				
+ OS distribution for durvalumab and comparator: 1-knot spline hazard	4.2.4.2	[redacted]	[redacted]	£23,391
+ PFS distribution for durvalumab and comparator: generalised gamma	4.2.4.1	[redacted]	[redacted]	£23,298
+ No cure assumption	4.2.4.3	[redacted]	[redacted]	£23,181
+ Resource use suggested by the EAG clinical advice	4.2.7.3	[redacted]	[redacted]	£24,861
+ Subsequent treatment distribution from the ADRIATIC trial (based on CS Table 70)	4.2.7.4	[redacted]	[redacted]	£29,396
EAG preferred base case		[redacted]	[redacted]	**£29,396**

We performed a range of scenarios analyses on the EAG preferred base case to analyse the impact of changing some of the model assumptions (Table 36). The scenarios that have the most significant effect on the cost-effectiveness results are:

- **Selection of OS curve-** the ICER varied between £25,102 (2-knot spline normal, company assumption) and £42,533 (Gompertz, worst fit) per QALY
- **Distribution of subsequent treatment-** the ICER varied between £24,861 (key opinion leaders, company assumption) and £32,478 (clinical advice to the EAG) per QALY
- **Treatment effect waning-** the ICER varied between £121,944 (treatment effect capped at five years) and £253,707 (treatment effect capped at three years) per QALY

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to the National Institute for Health and Care Excellence (NICE) from AstraZeneca on the clinical effectiveness and cost effectiveness of durvalumab for treating limited-stage small-cell lung cancer (LS-SCLC) after chemoradiation (CRT). It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE in January 2025. A response from the company via NICE was received by the EAG on 13th February 2025, with an updated response received on 17th February 2025, and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

The company provide clear background information about lung cancer and small-cell lung cancer (SCLC) in particular in CS section B.1.3.1. CS section B.1.3.2 describes the impact of LS-SCLC on patients and its economic burden.

2.2.1 Background information on LS-SCLC

Lung cancer can be classified into three main types: SCLC, non-small-cell lung cancer (NSCLC) and neuroendocrine tumours.[1] SCLC is the rarer than NSCLC[2,3] and is an aggressive cancer with a poor prognosis, due to its high potential for metastasis.[1,4] Around two-thirds of patients present with distant metastasis.[4] SCLC is classified as either limited stage or extensive stage disease.[5,6] In LS-SCLC, the cancer is present in only one area of the chest (it is ipsilateral hemithorax) and the disease can be encompassed within a single radiotherapy field.[5,7] The LS-SCLC patient population includes those with early tumours [tumour, node, metastasis (TNM) stages I-II] and those with locally advanced disease (TNM stage III).[8] LS-SCLC is treated with curative intent.[5,7] Median survival of patients with LS-SCLC is estimated to be 16 to 22 months, and it is estimated that in around 20% of patients the disease will be cured.[5]

2.2.2 Background information on durvalumab

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that prevents the inhibition of immune responses in the tumour and leads to increased T-cell activation and anti-tumour activity (CS Table 2). It is a type of immunotherapy that may also be called an immune checkpoint inhibitor.[9] The company plans to make a regulatory

submission to the Medicines and Healthcare products Regulatory Agency (MHRA) for durvalumab for the LS-SCLC indication in [redacted] (CS Table 2). The marketing authorisation is expected in [redacted] (CS Table 2). The company provided the draft Summary of Product Characteristics (SmPC) with the CS.[10] Durvalumab monotherapy is indicated for adults who have LS-SCLC and whose disease has not progressed after platinum-based chemoradiation (CS Table 2). It is administered by intravenous infusion (CS Table 2). The [redacted] dose is 1,500 mg every four weeks until disease progression, unacceptable toxicity or up to a maximum treatment period of 24 months, whichever occurs first (CS Table 2).

2.2.3 The position of durvalumab in the treatment pathway

The company outlines the current clinical pathway of care for LS-SCLC in CS section B.1.3.3 and shows the treatment pathway in CS Figure 2 (reproduced here as Figure 1), including the proposed positioning of durvalumab. Our clinical experts thought that the company's depiction of the clinical pathway in CS Figure 2 was generally reasonable, with some minor exceptions, which we describe below in section 2.2.3.1. We discuss the company's proposed positioning of durvalumab in section 2.2.3.2.

2.2.3.1 Current clinical pathway

As CS Table 3 outlines, NICE guidance on the diagnosis and management of lung cancer (NG122)[11] recommends the following first-line treatment options for LS-SCLC:

- Four to six cycles of cisplatin-based combination chemotherapy. Carboplatin can be used instead of cisplatin in people with a World Health Organisation (WHO) score of ≥2 (indicating a poor performance status), impaired renal function or significant comorbidity.
- Radiotherapy delivered twice a day with concurrent chemotherapy in people with a WHO performance status of 0 or 1 and whose disease can be encompassed in a radical thoracic radiotherapy volume. This is referred to as concurrent chemoradiotherapy (cCRT) in this report. Radiotherapy is started during the first or second chemotherapy cycle.
- Once-daily radiotherapy for people who are unable to have twice-daily radiotherapy or who decline it.
- Sequential radical thoracic radiotherapy for people who are not fit enough to receive cCRT but who have a response to chemotherapy. This is referred to as sequential chemoradiotherapy (sCRT) in this report. One of our clinical experts informed us that patients receive four cycles of chemotherapy and then radiotherapy.

We received clinical expert advice that most patients with LS-SCLC who can have CRT will receive cCRT and the patient population who receive sCRT is small.

Surgical resection is recommended by NICE as an option for early-stage SCLC (T1-2a, N0, M0) (CS Table 3).[11] CS section B.1.3.3 states that a complete surgical resection (R0) followed by adjuvant chemotherapy is desirable in SCLC, but is not possible in most patients. One of our clinical experts advised us that a minority of patients have surgical resection. CS Figure 2 suggests that after surgical resection for Stage I-II disease is considered, CRT will follow. However, one of the EAG's experts stated that patients who have undergone surgery will only receive CRT if they have had an R1 resection. Otherwise, patients with a R0 resection receive adjuvant chemotherapy, as is outlined in CS section B.1.3.3, but this is not shown in the figure (this is a minor point).

NICE recommends that prophylactic cranial irradiation (PCI) is offered to people with LS-SCLC who have a WHO performance status of 0 to 2 and whose disease has not progressed on first-line treatment.[11] CS section B.1.3.3 states that PCI may help prevent brain metastases and prolong survival. We received clinical expert advice that PCI, if given, is delivered after CRT. We were informed by one of our clinical experts that use of PCI varies across centres. This expert estimated that between 20% to 50% of patients receive it. Our other expert estimated that half of patients receive PCI and half do not. One expert noted that there is supportive evidence for using PCI in younger people, but that it is generally not considered or recommended in people over the age of 75 or those with previous brain injuries, strokes, known epilepsy or subarachnoid haemorrhage or other problems. They commented that caution is exercised in using it in people aged 70+. Both experts noted that some patients may decline it. One expert was of the belief that PCI is being phased out, noting that some small trials suggest that magnetic resonance imaging (MRI) surveillance may be a better option and that there are also case series data that suggest stereotactic radiotherapy can be used for people with brain metastases and SCLC (but this is not currently recommended as an option in treatment guidelines).

The CS states that current treatment guidelines do not indicate any therapeutic maintenance options following first-line CRT (CS section B.1.3.4). Indeed, NICE guidance states that maintenance treatment can only be offered within a clinical trial.[11] The CS states that therefore, following CRT, patients usually receive routine monitoring involving repeat imaging to assess if disease recurrence has occurred and then second-line therapy may be considered if indicated. Both our experts advised that practice regarding monitoring can vary, and one commented that there are no standardised guidelines either nationally or

within Europe. We were told that imaging is generally carried out on a three- to six-monthly basis, depending on how long ago the patient received treatment. One expert advised that if it is near certain that a patient will not be fit for treatment should their disease relapse, then they may receive clinical monitoring, a clinical review or may be discharged back to their general practitioner (GP).

2.2.3.1.1 Subsequent therapy

As CS section B.1.3.3.1 outlines, NICE guidance states that if a person with SCLC experiences disease relapse after first-line treatment, they may be offered further treatment with a platinum-based chemotherapy regimen, or they may be offered an anthracycline-containing regimen[11] [e.g. cyclophosphamide, doxorubicin and vincristine (CAV)]. Palliative radiotherapy can be offered for symptom control.[11] Oral topotecan may be considered if re-treatment with the first-line therapy is not appropriate and if CAV is contraindicated.[11,12] One of our experts noted that the company has classed these treatments as 'second-line treatments' in Figure 1, but that clinicians refer to these as 'first-line palliative treatments' if patients have relapsed. Additionally, both experts observed that the company states in the figure that topotecan can be used in people who are 'unsuitable for chemotherapy' but that topotecan is a chemotherapy. We were advised that those who are unsuitable for chemotherapy would move onto best supportive care, with or without palliative radiotherapy. We received clinical expert advice that the subsequent treatment that may be used is partly dependent on how quickly a patient relapses. If relapse occurs within three months of completing chemotherapy, topotecan or CAV are likely to be used. If relapse occurs three or more months after chemotherapy, then patients tend to be re-challenged with platinum-based chemotherapy (e.g. etoposide + carboplatin or etoposide + cisplatin). More information about subsequent anti-cancer therapies and how these were considered in the company's economic model is available in section 4.2.7.4 of this report.

2.2.3.2 Company's proposed positioning of durvalumab in the clinical pathway

The company is positioning durvalumab as a maintenance treatment after CRT (either sCRT or cCRT) (see Figure 1 and clarification response A1). Both our clinical experts agreed with the company's proposed positioning of durvalumab, but noted that there is no evidence available for the use of durvalumab in people with LS-SCLC whose disease has not progressed after sCRT (see also sections 2.3 and 3.2.1). Durvalumab is expected to be given after completion of PCI in clinical practice (clarification response A2).

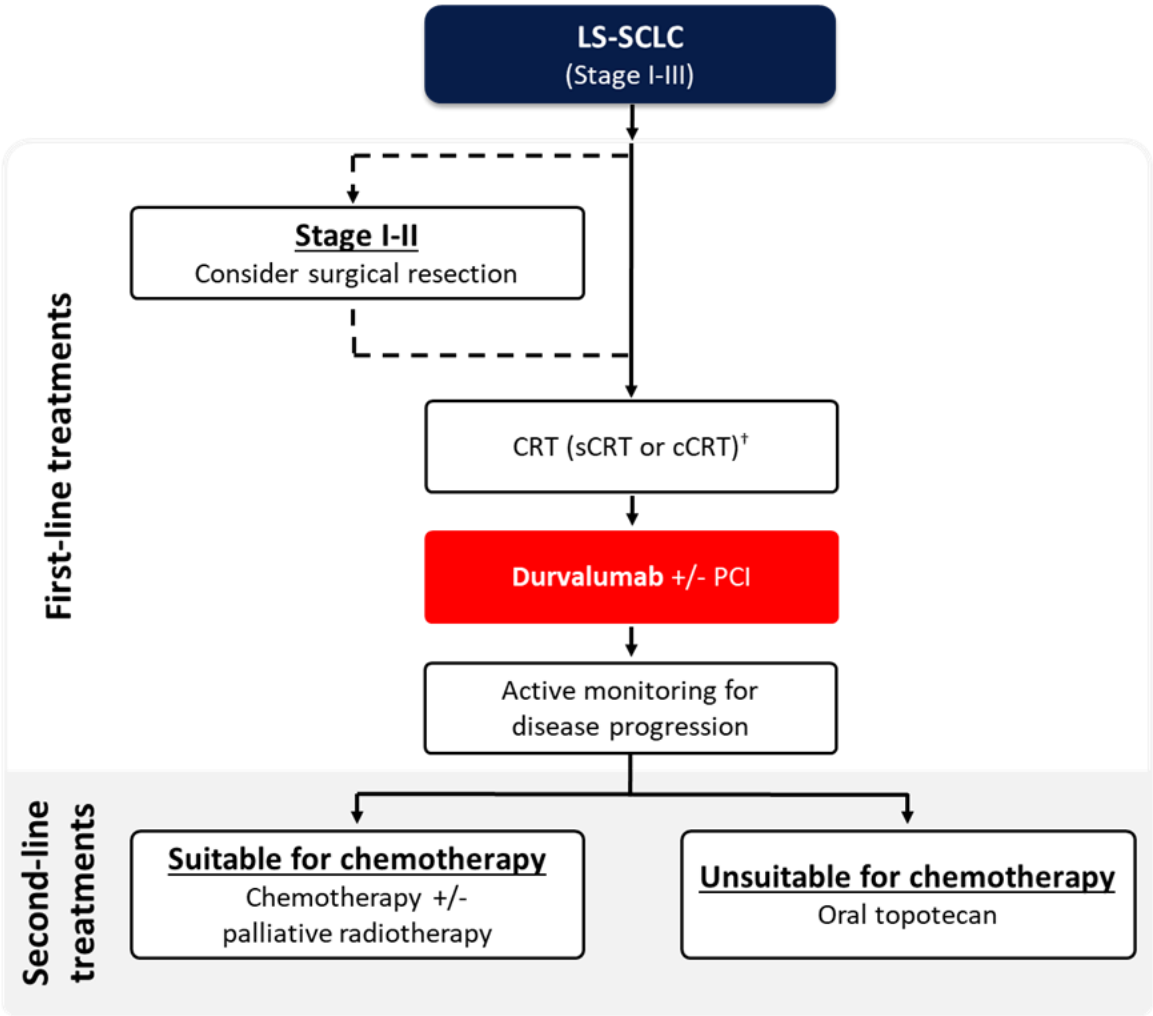

Figure 1 Company's proposed positioning of durvalumab in the LS-SCLC clinical pathway

Source: Reproduced from CS Figure 2.
†CRT is administered as sCRT or cCRT according to patients' ECOG PS score. Patients with a 'poor' PS score receive sCRT and those with a 'good' PS score receive cCRT.
CRT, chemoradiation therapy; cCRT, concurrent chemoradiation therapy; ECOG, Eastern Cooperative Oncology Group; LS-SCLC, limited-stage small-cell lung cancer; NHS, National Health Service; PCI, prophylactic cranial irradiation; PS, performance status; sCRT, sequential chemoradiation therapy

EAG comment

The company provides a clear overview of LS-SCLC and a generally accurate depiction of the treatment pathway for LS-SCLC in the CS. Our clinical experts agreed with the company's proposed positioning of durvalumab as a maintenance therapy after CRT, but it should be noted that no evidence is presented in the CS about the efficacy and safety of durvalumab in patients with LS-SCLC whose disease has not progressed after sCRT. The evidence presented is limited to patients whose disease has not progressed after cCRT.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the company's decision problem in relation to the final scope issued by NICE and the EAG's comments on this. The decision problem reflects the NICE scope with the exception that no clinical efficacy or safety evidence for durvalumab is presented in the CS for patients with LS-SCLC whose disease has not progressed following sCRT (see section 3.2.1) – a subgroup of interest specified in the scope.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	People with limited-stage SCLC whose disease has not progressed after chemoradiotherapy	As per Final scope	NA	In line with scope
Intervention	Durvalumab	As per Final scope	NA	In line with scope
Comparators	Established clinical management without durvalumab maintenance: • Active monitoring	As per Final scope	NA	In line with scope. The EAG's clinical experts confirmed that there are no other relevant comparators for durvalumab. In practice in the CS, the comparator is placebo and the participants included in the one trial of durvalumab in people with

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
				LS-SCLC included in the CS received tumour assessments at specified intervals. The EAG considers that this adequately represents active monitoring.
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Adverse effects of treatment • Health-related quality of life	As per Final scope	NA	In line with scope
Economic analysis	Reference case requirements (NICE scope wording abridged by EAG here for brevity): Costs to be assessed as	Not commented on	Not commented on	The company's economic model meets the reference case requirements (see section 4.2.1). Details of [redacted] are supplied in CS

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	cost per quality-adjusted life year (QALY), adequate time horizon, NHS and Personal Social Services perspective, commercial arrangements and managed access taken into account, and availability and cost of biosimilar and generic products taken into account.			Table 2 and this is applied in the company's base case model (CS section B.3.11.1).
Subgroups	If the evidence allows the following subgroups may be considered: • PD-L1 expression • Disease stage	Pre-planned subgroup analyses of OS and PFS were performed for disease status, receipt of prophylactic cranial irradiation, primary tumour location, time	There are no subgroups within the population that should be considered separately. Clinical data from the ADRIATIC trial demonstrates a	Subgroup analysis results by PD-L1 status (<1% or ≥1%) and disease stage (TNM stage I/II or III) are presented in the CS (CS Appendix E). The one trial of durvalumab in people with LS-SCLC included in

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	• Concurrent or sequential chemoradiation	from end date of cCRT to randomisation, time from last dose of radiotherapy to randomisation, prior platinum chemotherapy, prior radiotherapy regimen; best response to cCRT, sex, age, smoking status, race, region, World Health Organisation/ Eastern Cooperative Oncology Group Performance Status, and PD-L1 status. Pre-planned subgroup analysis of objective response rate was also	consistent treatment effect for durvalumab across the trial population.	the CS focused on people whose disease had not progressed after cCRT. There is no evidence in the CS for the efficacy and safety of durvalumab in people with LS-SCLC whose disease has not progressed after sCRT.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
		performed for PD-L1 status only.		
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per Final scope	NA	No equity or equality issues relevant to this appraisal were identified by either the EAG or our experts

Source: Partly reproduced from CS Table 1.
cCRT, concurrent chemoradiotherapy; CS, company submission; EAG, External Assessment Group; LS-SCLC, limited-stage small-cell lung cancer; NA, not applicable; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QALY, quality-adjusted life year; SCLC, small-cell lung cancer; sCRT, sequential chemoradiotherapy; TNM, tumour, node, metastasis.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a broad systematic literature review (SLR) to identify studies of the clinical efficacy and safety of durvalumab in the patient population of interest in this appraisal, to identify potential comparator treatments and to identify outcomes for patients receiving CRT (CS Appendix D.1). The review identified 30 studies (reported in 31 publications) that met the inclusion criteria (CS section B.2.1). Of these, a single publication reporting the effectiveness and safety of durvalumab in people with LS-SCLC whose disease had not progressed after CRT was identified: a conference abstract of the company sponsored ADRIATIC trial (Spiegel et al. 2024). Subsequent to the completion of the SLR the results of the trial were published in full in a journal publication (Cheng et al. 2024).

The EAG's critique of the company's SLR is summarised in Table 37 in Appendix 1. The review was generally well-conducted, but we note there is a theoretical risk that potentially relevant non-randomised studies (if any are available) may have been missed due to the search terms used (see Table 37 in Appendix 1). This is not a concern regarding identifying evidence in relation to the population who have previously received cCRT, as randomised controlled trial (RCT) evidence was identified, but it results in an uncertainty about whether relevant, non-RCT evidence in the sCRT population may be available (no RCT evidence was identified in this group).

Overall, it appears unlikely that the company's SLR would have missed relevant RCTs of the clinical efficacy and safety of durvalumab maintenance therapy after cCRT. There is uncertainty about whether there is any missing non-RCT evidence in the sCRT population.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

As mentioned above, the company's SLR identified one trial of durvalumab in people with LS-SCLC (ADRIATIC; NCT03703297) (CS section B.2.1).

3.2.1.1 Study characteristics

Table 5 provides an overview of the characteristics of the ADRIATIC trial. It is an ongoing, three-arm, double-blind, phase III, placebo-controlled, RCT comparing i) durvalumab monotherapy and ii) durvalumab in combination with tremelimumab versus placebo in adults with histologically and/or cytologically documented LS-SCLC (Stage I to III SCLC) who had previously received four cycles of first-line cCRT, had an Eastern Cooperative Oncology

Group (ECOG) performance status of 0 or 1 and had no disease progression after cCRT (CS section B.2.3.1.4 and CS Tables 4 and 5). [redacted][10] In the CS, the placebo arm of the trial is considered to reflect established clinical management without durvalumab maintenance (i.e. active monitoring) (B.2.12.2.2). As stated in section 2.3, we consider this to be an acceptable approach. One of our experts commented that the permitted and disallowed concomitant medications in ADRIATIC listed in CS Table 6 appear reasonable and are in line with what is used in clinical practice (the other expert did not comment on this).

The dual primary outcomes of the ADRIATIC trial were overall survival (OS) and progression-free survival (PFS) per Blinded Independent Central Review (BICR) assessed according to Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 criteria. The company confirmed in clarification response A9 that there was no cross-over (treatment switching) between the treatment arms in the trial, but that subsequent treatments were permitted. The classes of the subsequent treatments received are detailed in clarification responses A9 and A12. We received clinical expert advice that the classes of subsequent treatments received and the proportions of participants receiving them in each arm of the trial were a reasonable reflection of clinical practice. Clarification response A12 states that information about the specific therapies participants received is unavailable, so we were unable to ascertain the extent to which the specific subsequent therapies used are a part of standard practice.

The ADRIATIC trial was sponsored by the company.[13,14] Only the durvalumab monotherapy and placebo arms are relevant to this appraisal. [redacted][10] and was not stated to be the intervention of interest in the NICE scope. We therefore do not discuss the durvalumab in combination with tremelimumab trial arm further in this report.

OS, PFS and adverse events results are reported in the CS from the first interim analysis of ADRIATIC (dated 15th January 2024) (CS sections B.2.3.1.1, B.2.3.1.5, B.2.6.1.1, B.2.6.1.2, B.2.10, B.2.12.1.1 and B.3.4.1). The company supplied the interim clinical study report,[15] as well as the published journal paper[13] and the conference abstract identified by the company's SLR,[16] all reporting the interim results. At the time of the analysis, median OS follow-up in the durvalumab arm was 30.75 months, and median PFS follow-up in this arm was 9.07 months (CS section B.2.3.1.5).

The company confirmed in clarification response A6 that a second, event-driven interim analysis of OS [redacted]. No updated results were provided. The company

stated at the factual accuracy check stage of the appraisal that results were not provided as the analysis is ongoing.

Table 5 ADRIATIC study design and characteristics

Study characteristics	Details
Population	Adult patients with LS-SCLC whose disease has not progressed after concurrent chemoradiotherapy.
Interventions (number of patients randomised)	• **Durvalumab monotherapy (n = 264):** Durvalumab (1,500 mg IV) Q4W in combination with placebo tremelimumab (IV) Q4W for 4 doses/cycles each, followed by durvalumab 1,500 mg Q4W starting 4 weeks after the final dose of durvalumab in combination with placebo tremelimumab • **Durvalumab + tremelimumab (n = 200):** Durvalumab (1,500 mg IV) Q4W in combination with tremelimumab (75 mg IV) Q4W for 4 doses/cycles each, followed by durvalumab 1,500 mg Q4W starting 4 weeks after the final dose of durvalumab in combination with tremelimumab
Comparator (number of patients randomised)	• **Placebo (n = 266):** Durvalumab placebo (IV) Q4W in combination with tremelimumab placebo (IV) Q4W for 4 doses/cycles each, followed by durvalumab placebo Q4W starting 4 weeks after the final dose of the 2 placebos in combination.
Key participant inclusion criteria (abridged by EAG)	• Histologically and/or cytologically documented LS-SCLC (Stage I to III SCLC) • WHO/ECOG PS of 0 or 1 at enrolment and randomisation • Received four cycles of first-line cCRT consisting of platinum-based therapy plus etoposide • No progression after the receipt of definitive cCRT The full list of the key inclusion criteria is reproduced with added comments from the EAG's clinical experts in Table 38 in Appendix 1.
Study locations	19 countries, including the United Kingdom (1 site). One patient recruited from the UK study site was randomised into ADRIATIC and was allocated to durvalumab (clarification response A5).
Primary outcomes ***Bold text shows the outcomes that inform***	Dual primary efficacy endpoints: • **OS** • **PFS per BICR according to RECIST 1.1**

Study characteristics	Details
the company's economic model	
Other outcomes reported in the CS and / or used in the company's economic model ***Bold text shows the outcomes that inform the company's economic model***	• Adverse effects of treatment (specifically, **grade 3-4 pneumonia** is included in the model) • Health-related quality of life (specifically, **EQ-5D-5L** data inform the model) • **Time to treatment discontinuation** • Objective response rate (ORR) • Tumour shrinkage • Best objective response • Duration of response • PFS 2 • Time to death or distant metastases (TTDM)
Follow-up	• Median duration of OS follow-up for durvalumab: 30.75 months • Median duration of PFS follow-up for durvalumab: 9.07 months

Source: Partly reproduced from CS Tables 4 and 5, CS Appendix Figure 2, CS sections B.2.3.1.5, B.2.3.1.10, B.2.6 and B.3.3.2, and the company's economic model.
BICR, Blinded Independent Central Review; cCRT, concurrent chemoradiotherapy; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; LS-SCLC, limited-stage small-cell lung cancer; OS, overall survival; PFS, progression-free survival; Q4W, every four weeks; RECIST, Response Evaluation Criteria In Solid Tumours; SCLC, small-cell lung cancer; WHO, World Health Organisation

3.2.1.1.1 ADRIATIC trial eligibility criteria

Table 38 in Appendix 2 shows the full list of the key participant inclusion criteria presented in the CS for the ADRIATIC trial and the EAG's clinical experts' comments on these. An abridged list is shown in Table 5. Participant eligibility was limited to people whose disease had not progressed after cCRT; patients who had received sCRT were not eligible (CS Table 5). One of our experts commented that, when taking a strictly evidence-based approach, the ADRIATIC trial results cannot be generalised to people with LS-SCLC who have previously received sCRT and both our experts commented there is no evidence in the CS to support the use of durvalumab maintenance therapy after sCRT. One expert stated, however, that there are arguments from a biological point-of-view that patients who have received sCRT might benefit from receiving maintenance therapy. They stated that in the extensive-disease stage setting, where patients receive four cycles of chemotherapy, immunotherapy (a checkpoint inhibitor) and then maintenance treatment, there is some benefit from having

maintenance therapy. They also said that SCLC is a disease that often spreads further, so it may be assumed that patients would benefit from earlier maintenance treatment. Similarly, the other expert commented that if a patient has had sCRT and they have no evidence of disease on completion, it may be reasonable to assume that they will potentially derive benefit from adjuvant immunotherapy.

The EAG notes that NICE's recommendation of durvalumab maintenance treatment in locally advanced unresectable NSCLC in adults is restricted to those who previously had cCRT [Technology Appraisal (TA) 798].[17] This is because the clinical trial providing evidence in TA798 (the PACIFIC trial) restricted participant inclusion to those who had received cCRT, and the committee's view was the results were not generalisable to those who had previously received sCRT.[17]

To be included in the ADRIATIC trial, patients needed to have a cancer performance status of 0 or 1 (indicating no or little impairment to the patient's daily activity and functioning). However, one of our experts noted that patients who have previously received sCRT tend to have a higher (worse) performance status because they are not fit enough to receive cCRT. The expert noted, however, that it might be argued that if a patient has a good response to sCRT, then their performance status may improve. The EAG suggests that the performance status of the cCRT participants included in the trial may not be reflective of the population whose disease has not progressed after sCRT. Both experts informed us that other checkpoint inhibitors currently available have been recommended for use in people with a performance status of 0 or 1, because this was a requirement of the clinical trials. We note that in TA638 of atezolizumab with carboplatin and etoposide for untreated extensive-stage SCLC it was noted by clinical experts advising the committee that, in this disease stage setting, results from a trial of atezolizumab with carboplatin and etoposide in people with an ECOG performance status of 0 or 1 could not be extrapolated to people with a worse performance status because treatment effects may differ in people with a greater disease burden. The committee concluded that the results were not generalisable to people with a worse performance status and limited the recommendation of atezolizumab with carboplatin and etoposide to people with an ECOG performance status of 0 or 1.[18] The company point out in clarification response A17 that American Society of Clinical Oncology guidelines state that people with LS-SCLC who have an ECOG performance status of 3 or 4 who have received sCRT may be offered durvalumab for up to two years if they have no contraindications to immunotherapy and their performance status improved after sCRT.

The company argue that clinical experts expect people who have previously received sCRT to benefit from durvalumab. In support of this the company cite a trial of durvalumab in

people with non-small-cell lung cancer (NSCLC) who received durvalumab after sCRT (PACIFIC-6) which they state provides *"encouraging efficacy"* results (CS sections B.1.3.5 and B.2.12.1.2). More specific OS and PFS findings from this study are reported in clarification response A17. In PACIFIC-6, at 12 months, OS and PFS rates were proportionally higher in the durvalumab arm than in the placebo arm (clarification response A17). In their response, the company additionally cites evidence from a study called PACIFIC-R of durvalumab maintenance therapy in people with unresectable NSCLC, which provides OS and PFS results for subgroups of patients who had previously received cCRT or sCRT. PACIFIC-R found similar median PFS and 3-year OS rates in people who had received cCRT and sCRT (as reported in clarification response A17). The company argue that PACIFIC-R and the PACIFIC-6 provide findings that could be extrapolated to support use of durvalumab in people with SCLC after sCRT. With reference to PACIFIC-6, one of our experts did not consider that findings from a study of people with NSCLC are generalisable to a population of patients with SCLC whose disease has not progressed after sCRT. They stated that NSCLC and SCLC cannot be considered the same disease. The other expert did not comment on this.

Both the experts advising the EAG considered that the ADRIATIC trial inclusion criteria were otherwise generally representative of the patients expected to receive durvalumab in clinical practice.

3.2.1.2 Patients' baseline characteristics

The company presents the baseline characteristics of the participants in the ADRIATIC trial in CS Tables 8, 9 and 10. The characteristics were generally similar between the durvalumab and placebo arms. However, there were more patients with locally advanced disease involving the lymph nodes at study entry as assessed by the Investigator in the durvalumab group compared with placebo (63.6% vs 36.8%). The CS does not discuss what implications this may have for the study results and conclusions.

We received clinical expert advice that the characteristics of the participants included in the trial are generally representative of the patients seen in clinical practice who have limited-stage SCLC and whose disease has not progressed after CRT. However, it was noted:

- by both experts that the participants in the trial were slightly younger on average than the patients seen in practice (although it was acknowledged by one expert that patient age may vary by region). We were advised that the older a patient is, the more likely they are to have other health conditions and older people are potentially

less fit to tolerate treatment. However, if a patient is older and fit, then their age is unlikely to affect treatment outcomes.

- by one expert that, in clinical practice, around 50% of patients receive cisplatin and 50% receive carboplatin as part of their chemotherapy regimen (with potentially more patients than this receiving carboplatin), whereas across both arms of the trial, [redacted]% of patients received cisplatin and [redacted]% received carboplatin. We were advised that whether patients had received prior cisplatin or carboplatin was not expected to impact response to durvalumab. This expert further commented that in the trial, patients who had previously received carboplatin were able to move onto durvalumab more quickly, which is to be expected as there is less toxicity associated with carboplatin than cisplatin.
- by one expert that clinical practice has moved to a total radiotherapy dose of 45 gray (Gy) twice daily over three weeks, with some clinicians still using 60 or 66 Gy once daily. The EAG notes that only [redacted]% of the total trial population (percentage calculated by the EAG) previously received 45 Gy twice daily in the trial, while [redacted]% received ≥60 to ≤66 Gy once a day. The expert commented, however, that both the doses/fractionation regimes are acceptable and should not affect the efficacy of adjuvant durvalumab.

EAG comment on included studies

The CS included one company sponsored trial (ADRIATIC) of durvalumab maintenance therapy in people with LS-SCLC whose disease had not progressed following cCRT and who had an ECOG performance status of 0 or 1. The baseline characteristics of the participants included in the trial are generally representative of the patients seen in clinical practice, except that the trial participants were on average younger. The CS does not include any evidence on the efficacy and safety of durvalumab in people with LS-SCLC whose disease has not progressed after sCRT and the ADRIATIC trial's results may not be generalisable to this population.

3.2.2 Risk of bias assessment

CS Section B.2.5 reports the company's critical appraisal of the ADRIATIC trial, using a standard set of criteria adapted from the Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews in health care (CS Table 15). In the company's judgement the trial meets all the criteria necessary to be considered a well conducted study, with low risk of bias (NB. These criteria are not explicitly described as being a risk of bias assessment, but some of the items are indicators of potential bias in the design and

execution of the study methods). The EAG conducted an independent critical appraisal of the trial using the same CRD criteria and our judgements can be seen alongside the company's in Table 39, in Appendix 3. We agree with the company's judgments and conclude that the ADRIATIC trial is methodologically sound, with low risk of bias.

In addition to the CRD criteria, the CS reports that the Cochrane risk of bias criteria (version 2) were applied to the full texts of the 30 studies included in the company's systematic review which had been selected for data extraction. However, the EAG could not find any results from the Cochrane risk of bias assessment for these studies in the CS. In response to a clarification question (clarification question A18) the company provided a table showing the risk of bias judgements made for 23 of the 30 studies (Table 6, company's clarification question response). The EAG notes that there is no textual summary and interpretation of the judgements made nor discussion of any implications for clinical effectiveness or cost effectiveness. Importantly, the ADRIATIC trial is absent from the Cochrane risk of bias assessment. The company explained that, whilst the systematic review was being conducted, the only publication identified for the trial was a conference abstract, with limited detail. The journal article,[13] which reports the trial in greater detail was published subsequently. In the absence of a full trial publication the EAG would have expected the company to have used as yet unpublished data on file to inform the risk of bias assessment, and in time to update the risk of bias assessment accordingly when the journal article was available. However, this does not appear to have been considered.

The EAG considers the company's Cochrane risk of bias assessment (version 2), is of limited value, for the reasons stated above. However, the critical appraisal of the ADRIATIC trial based on the CRD criteria is sufficient in determining the risk of bias, which we judge to be low.

3.2.3 Outcomes assessment

The CS lists the outcomes measured in the ADRIATIC trial in CS Table 4. All the outcomes specified in the NICE scope and the company's decision problem are included in the CS: OS, PFS, adverse effects and HRQoL. All these outcomes also informed the company's economic model (see section 3.2.1.1). We focus on discussing these here, but information about how other trial outcomes were defined is available in CS section B.2.3.1.11.

3.2.3.1 Efficacy outcome(s)

OS and PFS per BICR according to RECIST 1.1 were the dual primary outcomes of the ADRIATIC trial (CS section B.2.3.1.10). The proportion of patients alive at 24 months from randomisation (OS24), the proportion of patients alive at 36 months from randomisation (OS36), progression-free survival at 18 months following randomisation (PFS18),

progression-free survival at 24 months following randomisation (PFS24) and time from randomisation to second progression or death (PFS2) were also measured as secondary efficacy endpoints (CS section B.2.3.1.11). Definitions of these outcomes are shown in Table 6. These measures are standard oncology outcomes and are appropriate.

Regarding the frequency of tumour follow-up as shown in Table 6, our experts commented that in clinical practice, tumours are assessed every 12 weeks during the first 72 weeks of follow-up rather than every eight weeks as in the ADRIATIC trial. The EAG suggests that this means that progression may have been identified sooner in the trial in some patients than it would necessarily have been in clinical practice. We understand that it is common for tumours to be more frequently assessed in trials than in clinical practice. We received clinical expert opinion that otherwise the way in which tumours were assessed in the trial reflects clinical practice.

Table 6 Definitions of the efficacy outcomes measured in the ADRIATIC trial

Outcome	Definition
OS	OS is a standard outcome measured in oncology trials that reflects time from randomisation to death.[19]
OS24 and OS36	Proportion of patients alive at 24 and 36 months from randomisation.
PFS per BICR according to RECIST 1.1	PFS is a standard oncology endpoint, which measures time from randomisation to the first of disease progression or death.[19] A summary of the RECIST 1.1 criteria are provided in CS Table 7. In ADRIATIC, tumour assessments were performed via CT or MRI conducted at screening, then every 8 weeks for the first 72 weeks (relative to the date of randomisation), followed by every 12 weeks until 96 weeks, and every 24 weeks thereafter until RECIST 1.1 defined radiological progression. After radiological progression, there was a follow-up scan no earlier than 4 weeks later, and no later than the next regularly scheduled imaging visit. Scans were evaluated according to RECIST 1.1.
PFS18 and PFS24	PFS at 18 and 24 months following randomisation (equivalent to the proportion of patients alive and progression free at 18 and 24 months following randomisation).
PFS2	The time from the date of randomisation to the occurrence of a second disease progression, as determined by the

Outcome	Definition
	investigator, or death (i.e. date of PFS2 event or censoring – date of randomisation + 1).

Source: Partly reproduced from CS sections B.2.3.1.11, B.2.3.1.10 and B.2.6.2.2.
BICR, Blinded Independent Central Review; CS, company submission; CT, computed tomography; MRI, magnetic resonance imaging; OS, overall survival; OS24, proportion of patients alive at 24 months from randomisation; OS36, proportion of patients alive at 36 months from randomisation; PFS, progression free survival; PFS18, progression-free survival at 18 months following randomisation; PFS2, time from randomisation to second progression or death; PFS24, progression-free survival at 24 months following randomisation; RECIST, Response Evaluation Criteria In Solid Tumours.

3.2.3.2 Patient-reported outcomes, including HRQoL outcomes

The following patient-reported outcome measures were used in ADRIATIC: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module (EORTC-QLQ-LC13), Patient Global Impressions Severity (PGIS), Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L). We describe these measures in Table 7. The selected measures are appropriate. The EQ-5D-5L results from the trial were used to inform utility estimates in the company's economic model.

Table 7 Description of the patient-reported outcome measures used in ADRIATIC

Measure	Description
EORTC-QLQ-C30	This is a measure of quality of life in cancer patients[20] and was a secondary outcome in the ADRIATIC trial (CS section B.2.6.4). The QLQ-C30 is the core EORTC measure that includes 30 items covering aspects of general quality of life in cancer patients.[20,21] Scores on the GHS/QoL scale of the measure can range from 0 to 100, with a higher score representing a better level of functioning or better global HRQoL (CS section B.2.6.4.1.2). A high score on a symptom scale or item reflects a high symptom burden (CS section B.2.6.4.1.4). The CS reports that a minimum clinically meaningful change on this measure on its scales/items is a change from baseline of ≥10 (CS section B.2.6.4.1.2). The company provided a reference and information to support the latter in response to clarification question A8. The EAG also identified a reference confirming that this threshold is appropriate.[22]

Measure	Description
EORTC-QLQ-LC13	The EORTC-QLQ-LC13 is a supplement to the core EORTC-QLQ-C30 measure and includes 13 items measuring aspects of quality of life that are specific to lung cancer.[21]. It was a secondary outcome in the ADRIATIC trial (CS section B.2.6.4). Scores on this measure can range from 0 to 100.[22] The CS reports that a minimum clinically meaningful change on this measure on its scales/items is a change from baseline of ≥10 (CS section B.2.6.4.1.2).
PGIS	This measure assessed patients' overall impression of the severity of their cancer symptoms (CS section B.2.3.1.3 and clarification response A7). It was an exploratory endpoint in ADRIATIC (CS sections B.2.3.1.3 and B.2.6.4.2). Clarification response A7 states that the PGIS measure is a validated global rating-of-change scale in advanced cancer. In the CS, the proportion of participants in different symptom categories as measured by the PGIS is reported (CS section B.2.6.4.2.2).
PRO-CTCAE	This measures treatment-related AEs and was an exploratory outcome in ADRIATIC (CS section B.2.3.1.3). This measure was developed specifically for cancer trials and is used to evaluate the presence or absence of symptoms, and symptom frequency, severity, amount, and burden in the last seven days.[23]
EQ-5D-5L	The EQ-5D-5L is a global measure of HRQoL. It was an exploratory outcome in ADRIATIC (CS section B.2.3.1.3). It measures five dimensions of QoL: mobility, self-care, usual activities, pain/discomfort and anxiety and depression.[24] An index score can be derived from the EQ-5D-5L where a score of 0 represents a health state equivalent to dead, while a score of 1 represents the value of full health.[25] The measure also includes a VAS scale on which patients can rate their health from the best health imaginable to the worst health imaginable on a 0 to 100 scale.[20,25] The company reports results for the EQ-5D-5L index and VAS scores in the CS (section B.2.3.1.12 B.2.6.4.2.3). The measure was used to generate the utility estimates in the company's economic model (EQ-5D-5L results were mapped to EQ-5D-3L values) (CS section B.3.5.1).

Source: EAG created table using information sourced from various CS sections and other references (as detailed within the table).

AEs, adverse events; CS, company submission; EAG, External Assessment Group; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC-QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module; EQ-5D-5L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; EQ-5D-3L, European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels; GHS, Global Health Score; HRQoL, health-related quality of life; PGIS, Patient Global Impressions Severity; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QoL, quality of life; VAS, visual analogue scale.

3.2.3.3 Safety outcomes

The safety endpoints assessed in ADRIATIC are shown in Table 8. The CS states that adverse events were categorised according to system organ class and preferred term using MedDRA version 26.1 (CS section B.2.3.1.13). The Common Terminology Criteria for Adverse Events (CTCAE) v4.03 was used to grade the adverse events (CS section B.2.3.1.13).

Table 8 Safety endpoints assessed in ADRIATIC

Endpoint / Description
Frequency and severity of all AEs and treatment-related adverse events.
AEs of special interest, potential interest, immune-mediated adverse events
AEs in anti-drug antibody positive patients
Frequency of serious AEs, discontinuations, and deaths due to AEs

Source: Reproduced from CS section B.2.3.1.13.
AEs, adverse events.

EAG comment on outcomes assessment

The outcomes assessed in the ADRIATIC trial are standard oncology endpoints. The EAG has not identified any key concerns about how the outcomes were assessed.

3.2.4 Statistical methods of the included studies

The CS (section B.2.4) reports the statistical methods used in the ADRIATIC trial, with further detail available in the statistical analysis plan (SAP).[26] Below we summarise and critique the main aspects of the company's statistical approach, with a focus on the dual primary outcomes OS and PFS (Table 9).

Table 9 Statistical methods of the ADRIATIC trial

Analysis populations
Several analyses populations are described in the CS, of which two are most relevant to this appraisal (CS Table 11): *Full analysis set (FAS),* all randomised participants who received any amount of the investigational product. [redacted][27] FAS was used for all efficacy analyses. Includes all **530** patients randomised to durvalumab (n=**264**) or placebo (n=**266**); includes 2 randomised patients who did not receive treatment (1 patient in each arm). *Safety analysis set (SAS),* all patients receiving at least one dose of study treatment (n=**527**; durvalumab **n=262** and placebo **n=265**). This represents **99.4**% of the randomised study population. CS Table 14 reports that only two patients did not receive treatment (one in each arm), so one patient appears to be missing from the SAS (this is a minor discrepancy). [redacted].[27]
EAG comment: The analyses sets are clearly defined and align with methodological standards for clinical trials. The company liken the FAS set to an intention-to-treat (ITT) population, defined as *"all patients randomised to treatment"* (CS Table 15). The EAG concurs.
Sample size calculations
The study was powered to demonstrate the superiority of durvalumab versus placebo for OS and PFS outcomes. The target total sample size of approximately **724** randomised patients across the three trial arms (the 'global cohort') was marginally exceeded (total of **730** randomised patients). Likewise, the initial target sample sizes for the durvalumab arm and placebo arms (**262** randomised patients in both arms) were exceeded (durvalumab arm **n=264** randomised patients, placebo arm **n=266** randomised patients). The trial allows for two data cuts for PFS (one interim and one primary) and up to three data cuts for OS (two interim and one primary). The first **interim data-cuts for OS and PFS** were done on 15/01/24 and these results are the focus of the CS and the trial journal publication.[13] [redacted][26]

Event-driven statistical power calculations are provided for both OS (CS Section B.2.4.4.1) and PFS (CS Section B.2.4.4.2). See Table 10 and Table 11 below for details. In response to clarification question A6 the company reported that the **second interim OS analysis** [redacted], and that *"the data cut is event-driven to imply improved survival rates among participants, with the durvalumab and placebo treatment arms both having the required number of events for the planned OS IA2 (i.e. approximately 299 deaths across the two treatment arms"*). The company did not indicate when the results will be made publicly available.

EAG comment: The sample size calculation is clearly defined. The required number of patients randomised was achieved, and likewise the number of expected events was sufficient for the first planned interim analysis of PFS and OS. This indicates that statistical power was sufficient to detect the expected treatment effects (as summarised below in Table 10 and Table 11).

Methods to account for multiplicity

[redacted]

There doesn't appear to be any hierarchical multiple testing protocol in place for the key secondary outcomes (e.g. ORR, best objective response, duration of response, PFS2, time to death or distant metastases).

EAG comment: the hierarchical multiple testing procedures for the dual primary outcomes OS and PFS are explicitly described, and appropriate for event-driven statistical analysis.

Analysis of outcomes

Below is a brief summary of statistical tests used in the analysis of the dual primary outcomes and some of the key secondary outcomes:

- OS and PFS: stratified log-rank test (stratified by disease status and receipt of PCI); Cox proportional hazard model (also stratified).
- PFS 2: stratified log-rank tests with similar methods to PFS
- ORR: stratified Cochran-Mantel-Haenszel (CMH) test with adjustments as per PFS
- TTDM similar methods to PFS using stratified log-rank tests

EAG comment: The statistical analyses used are appropriate and generally consistent across the outcomes.

Handling of missing data

- Censoring rules for OS and PFS as part of RECIST assessment are reported in the CS (as footnotes to CS Tables 16 and 17) but are too detailed to summarise here. In general, the censoring rules appear similar to standard rules applied in cancer treatment trials.
- The EAG notes a discrepancy in the description of the PFS censoring scheme, whereby in response to clarification question A9 the company state that participants were censored from the PFS analysis before progression or death if they received a subsequent therapy.

  [redacted]

  The EAG considers PFS censoring for subsequent treatment to be more appropriate as an exploratory sensitivity analysis, and the main analysis assessing patients "as is" without adjustments. We also note that censoring for subsequent treatment pre-progression is not listed as reason for censoring in CS Table 17. Our assumption, therefore, is that the wording of the company's response to clarification question A9 inadvertently omitted to state this was a sensitivity analysis.
- CS section B.3.6.4.1 appears to suggest that participants receiving subsequent therapies were not censored from the OS analyses for this reason. Given that the EAG's clinical experts think that the classes of subsequent therapies used in the trial are a reasonable reflection of clinical practice, we contend that there would have been no reason to adjust OS for the effects of subsequent therapies. This accords with a recommendation from a NICE Decision Support Unit (DSU) Technical Support Document (TSD) (No. 24)[28] on adjusting survival estimates due to treatment switching. The recommendation states that *"if the treatment switched to is available at the relevant line of care in standard clinical practice in England and Wales, adjustment would not be required to address the HTA decision problem*" (page 15).

EAG comment: The company's censoring procedures are similar to standard censoring protocols used in cancer treatment trials.

Sensitivity & post-hoc analyses

OS Sensitivity analyses

- **Attrition bias**, using a Kaplan-Meier (KM) plot of time to censoring where the censoring indicator of the primary OS analysis is reversed (CS section B.2.6.1.1.1 and CS Appendix N.3.1.1).

OS other analyses

- OS exploratory sub-group analyses to assess **consistency of treatment effect** across expected prognostic factors (CS Appendix E).
- OS Cox proportional hazards models to assess **impact of covariates** on the HR, and to assess **consistency of treatment effects** (an overall global interaction test for plausible subgroups).

PFS sensitivity analysis

- **Evaluation-time bias assessment** for scans [redacted]
- **Attrition bias assessment**, [redacted]

  Similarly to OS, a sensitivity analysis in which the censoring indicator was reversed was also carried out for PFS, to also assess attrition bias.
- **Ascertainment bias** assessment comparing site investigator versus BICR estimates of progression or death.

[redacted] Results of the evaluation-time bias, attrition bias and ascertainment bias sensitivity analyses are reported in CS Appendix N and CS section B.2.6.1.2.1.

As far as the EAG can determine there are no post hoc analyses reported in the CS.

EAG comment: The exploratory sub-group analyses include a number of relevant prognostic and demographic factors and can be considered comprehensive. Due caution is advised in the interpretation of the results as the trial was not statistically powered to detect effects in subgroups. The sensitivity analyses are appropriate, but the EAG notes that the CS does not report the results of [redacted] (which we assume the company chose not to carry out).

Source: Partly reproduced from the CS Document B and the Statistical analysis plan
CS, company submission; FAS, full analysis set; HR, hazard ratio; IA, interim analysis; ORR, objective response rate; OS, overall survival; TTDM, time to death or distant metastasis.

Table 10 ADRIATIC trial statistical sample size calculation for co-primary outcome measure OS

Analysis time-point	Alpha level (2-sided)	Events		Power (%)	HR		Data Maturity (%)		Median duration [redacted]	DCO
		Exp	Rec		Exp	Rec	Exp	Rec		
OS IA 1[a]	4.5%[b]	242	261	48	0.73	0.73	46.2	49.2	[redacted]	15/01/24
OS IA 2		299	tbd	68	0.73	tbd	57.1	tbd	tbd	20/01/25[c]
OS primary		348	tbd	80	0.73	tbd	66.4	tbd	tbd	tbd

Source: Partly reproduced from the CS Document B
DCO, data cut-off; Exp, expected; HR, hazard ratio; IA, interim analysis; OS, overall survival; Rec, recorded; Tbd, to be determined (when data-cut is triggered)
[a] This data-cut was done simultaneously with PFS interim analysis 1
[b] The 2 sided alpha level (4.5%) was split between the interim and primary analyses; 0.01% (2 sided) was allocated for an OS assessment at the time of PFS primary analysis if OS-IA2 did not coincide with the PFS primary analysis, and the remaining alpha was split using the Lan-DeMets spending function that approximates an O'Brien Fleming approach. The actual boundaries were calculated at the time of each IA, based on the number of events available at the time of analysis, and assuming 348 death events being observed at the primary OS analysis.
[c] Clarification response A6 (OS IA 2 results have not yet been made available).

Table 11 ADRIATIC trial statistical sample size calculation for co-primary outcome measure PFS

Analysis time-point	Alpha level (2-sided)	Events		Power (%)	HR		Data Maturity (%)		Median duration [redacted]	DCO
		Exp	Rec		Exp	Rec	Exp	Rec		
PFS IA 1[a]	0.5%[b]	308	308	75%	0.65	0.76	58.8	58.1	[redacted]	15/01/24
PFS primary		370	tbd	90%	0.65	tbd	[redacted]	tbd	tbd	tbd

Source: Partly reproduced from the CS Document B and the statistical analysis plan
DCO, data cut off; Exp, expected; HR, hazard ratio, IA, interim analysis; PFS, progression-free survival; Rec, recorded; Tbd, to be determined (when data-cut is triggered)
[a] This data-cut was done simultaneously with OS interim analysis 1
[b] The 2 sided alpha level (0.5%) was split between the interim and primary analyses using the Lan DeMets spending function that approximates an O'Brien Fleming approach. The actual boundary was to be calculated at the time of the IA, based on the number of events available at the time of analysis and assuming 370 PFS BICR events at the primary PFS analysis

EAG comment on study statistical methods

The statistical methods used in the ADRIATIC trial are clearly described, and are appropriate for a cancer treatment trial. The EAG has no major concerns with the methods used.

3.2.5 Efficacy results of the intervention studies

The outcomes specified in the NICE scope and the company's decision problem were OS, PFS, adverse effects and HRQoL. All these outcomes from the ADRIATIC trial informed the company's economic model (see section 3.2.1.1). We therefore focus on reporting the results for these here and do not report results for the other outcomes presented in the CS. Observed time-to-treatment discontinuation from ADRIATIC also informed the company's economic model. The results are reported in CS section B.3.4.4 and this outcome is discussed further in section 4.2.4.5 of this report.

OS, PFS and HRQoL results are reported in the CS for the FAS population.[27]

3.2.5.1 Overall survival

OS was a dual primary outcome, along with PFS, in the ADRIATIC trial. OS results in the FAS population from the first interim analysis of ADRIATIC are shown in Table 12. Overall data maturity for OS at this point was 49.2% (CS section B.2.6.1.1) (that is, 49.2% of the trial population had died). At this data cut-off, there was a statistically significant 27% reduction in the risk of death with durvalumab compared to placebo (HR: 0.73; 98.321% CI: 0.54, 0.98; p=0.01). Kaplan Meier (KM)-estimated median OS was 55.9 months (95% CI: 37.3, not reached) in the durvalumab arm and 33.4 months (95% CI: 25.5, 39.9) in the placebo arm. We received clinical expert advice that the improvement in median OS seen with durvalumab is clinically meaningful.

The KM plot of the OS results from the ADRIATIC trial (FAS population) is shown in Figure 2. The KM plot is used to inform the estimates of OS used in the company's economic model (see section 4.2.4.2). In line with what is reported in the CS, the durvalumab and placebo curves appear to begin to separate at around eight months, with the durvalumab arm showing consistently better OS rates over time than the placebo arm.

The EAG observed that CS section B.2.4.3 states that OS analyses were stratified by both disease status and receipt of PCI, yet the OS results presented in the CS were from a stratified Cox proportional hazards model that adjusted for receipt of PCI (yes vs no) only. The company explained in clarification response A10 that there were too few deaths in the placebo group stratum of patients with Stage I/II disease and who had received PCI, so, as

per the statistical analysis plan, disease stage was not used as an adjustment factor in the analyses. When adjusting for both disease stage and PCI use, OS results were similar to those when just adjusting for PCI use (HR when adjusting for both stratification factors, with treatment as the only covariate: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]).

Table 12 OS results from ADRIATIC (FAS population, first interim analysis)

Outcome	Durvalumab (n=264)	Placebo (n=266)
Number of deaths, n (%)	115 (43.6)	146 (54.9)
Median OS follow-up, months	30.75 months	28.63 months
Median OS months (95% CI) [a]	55.9 (37.3, NR)	33.4 (25.5, 39.9)
Survival rate at 24 months, % (95% CI) [a]	68.0 (61.9, 73.3)	58.5 (52.3, 64.3)
Survival rate at 36 months, % (95% CI) [a]	56.5 (50.0, 62.5)	47.6 (41.3, 53.7)
HR [b c]	0.73	
98.321% CI [b d]	0.54, 0.98	
95% CI [b]	[redacted]	
p-value [e]	0.01	

Source: Reproduced from CS Table 16, with the addition of median OS follow-up months sourced from CS section B.2.6.1.1.
CI, confidence interval; FAS, full analysis set; HR, hazard ratio; NR, not reached; OS, overall survival
[a] Calculated using the KM technique. CI for median OS is derived based on Brookmeyer-Crowley method with log-log transformation. CI for OS24 and OS36 are derived based on a log(-log(.)) transformation.
[b] The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for receipt of PCI (yes vs no), with treatment as only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach.
[c] A HR <1 favours durvalumab to be associated with a longer survival than placebo.
[d] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed, the boundaries for declaring statistical significance are 1.679% for a 4.5% overall alpha for OS. The Lan-DeMets spending function that approximates the O'Brien Fleming approach was used to derive the adjusted alpha level.
[e] The analysis was performed using the stratified log-rank test, adjusting for receipt of PCI (yes vs no).

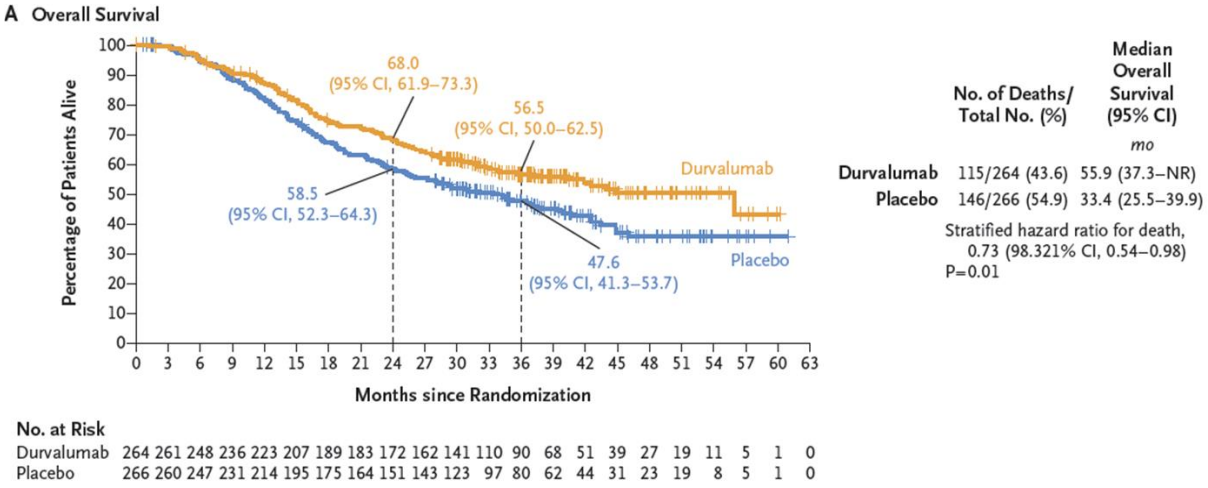

Figure 2 KM plot of OS results from ADRIATIC (FAS population, first interim analysis)

Source: Reproduced from CS Figure 4.
CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival

Clarification response A11 confirms that one sensitivity analysis of OS was conducted. In this analysis, the censoring indicator of OS was reversed in a KM plot; that is, this was an analysis of time to censoring which showed the probability of participants in each trial arm being censored from the OS analysis (CS Appendix N.3.1.1). The results of the analysis showed there was no difference in censoring patterns between the two treatment arms (CS section B.2.6.1.1.1. and CS Appendix N.3.1.1).

Furthermore, the CS reports results of Cox proportional hazards model analyses of OS (stratified by PCI use only), with and without adjustment for covariates. The EAG summarises the analyses and results in Table 13, along with the results of the main OS analysis and the analysis of OS presented in clarification response A10, which was stratified by both PCI use and TNM stage. The company state that the findings were similar to those of the main analysis both when covariates were included and when they were excluded (CS section B.2.6.1.1.1). The EAG concurs.

Table 13 Results of main and other analyses of OS from the ADRIATIC trial, including different stratification factors and including or excluding covariates

Cox proportional hazards model analysis	HR (95% CI, unless otherwise indicated)
Main analysis, stratified by PCI use only. Covariate: Treatment	0.73 (98.321% CI: 0.54, 0.98)
Clarification response A10 analysis, stratified by both TNM stage and PCI use Covariate: Treatment	[redacted]

Cox proportional hazards model analysis	HR (95% CI, unless otherwise indicated)
Analysis including covariates and stratified by PCI use only Covariates: treatment, sex, age at randomisation, smoking status, baseline WHO/ECOG PS, region, race, time from final administration of cCRT to randomisation, previous platinum chemotherapy, previous radiotherapy regimen and best response to cCRT	[redacted]
Analysis excluding covariates and stratified by PCI use only	[redacted]

Source: EAG created table using information sourced from CS section B.2.6.1.1.1 and CS Appendix N.3.1.1.1.
cCRT, concurrent chemoradiotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PCI, prophylactic cranial irradiation; PS, performance status; TNM, Tumour, Node, Metastasis; WHO, World Health Organisation

3.2.5.2 Progression-free survival

PFS was a dual primary outcome, along with OS, in the ADRIATIC trial. At the first interim analysis data cut-off, the overall maturity of the PFS data was 58.1% (CS section B.2.6.1.2). At this cut-off, there was a statistically significant 24% reduction in the risk of PFS as assessed by BICR with durvalumab compared to with placebo (HR: 0.76; 97.195% CI: 0.59, 0.98; p=0.02) in the FAS population. KM-estimated median PFS was 16.6 months (95% CI: 10.2, 28.2) in the durvalumab arm and 9.2 months (95% CI: 7.4, 12.9) in the placebo arm. We received clinical expert advice that the improvement in median PFS seen with durvalumab is clinically meaningful.

The KM plot of the PFS results from the ADRIATIC trial (FAS population) is shown in Figure 2. The KM plot informs the estimates of PFS used in the company's economic model (see section 4.2.4.1). As reported in the CS, the durvalumab and placebo curves appear to begin to separate after around six months, with the durvalumab arm showing consistently better PFS rates over time than the placebo arm. The company and the EAG observe that there appears to be a plateauing of treatment effect in both arms in the latter months of the trial between around three to five years, which the company state aligns with clinical expert opinion that functional cure may occur in patients who remain progression-free around this time. Both our experts advised us that if a person with LS-SCLC remains progression-free at five years, then it is reasonable to assume they are cured. The EAG notes that the number of patients at risk shown in the ADRIATIC trial PFS KM plot between around three to five years is small (ranging from 4 to 34 patients between 36 and 54 months, with no participants

at risk at 57 and at 60 months) and thus the results at this timepoint may be subject to uncertainty.

Table 14 PFS results as assessed by BICR from ADRIATIC (FAS population, first interim analysis)

Outcome	Durvalumab (n=264)	Placebo (n=266)
Total events, n (%) [a]	139 (52.7)	169 (63.5)
RECIST progression	126 (47.7)	158 (59.4)
Death in absence of progression	[redacted]	[redacted]
Median PFS follow-up	9.07 months	7.39 months
Median PFS months [b]	16.6 (10.2, 28.2)	9.2 (7.4, 12.9)
PFS at 18 months, % (95% CIs) [b]	48.8 (42.2, 55.0)	36.1 (29.9, 42.2)
PFS at 24 months, % (95% CIs) [b]	46.2 (39.6, 52.5)	34.2 (28.2, 40.3)
HR [c d]	0.76	
98.816% CI [e f]	0.53, 1.08	
97.195% CI [c f]	0.59, 0.98	
95% CI [c]	0.61, 0.95	
p-value [g]	0.02	

Source: Reproduced from CS Table 17, with minor modifications made by the EAG and with the addition of median PFS follow-up months sourced from CS section B.2.6.1.2.
BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours
[a] Patients who had not progressed or died, or who progressed or died after two or more missed visits were censored at the latest evaluable RECIST assessment, or Day 1 if there were no evaluable visits. Patients with RECIST progression within two visits of baseline who did not have any evaluable visits or did not have a baseline assessment were censored at Day 1.
[b] Calculated using the KM technique. CI for median PFS is derived based on Brookmeyer-Crowley method with log-log transformation. CI for PFS18 and PFS24 are derived based on a log(-log(.)) transformation.
[c] The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for TNM stage (Stage I/II vs III) and receipt of PCI (yes vs no), with treatment as only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach.
[d] A HR < 1 favours durvalumab to be associated with a longer event-free survival than placebo.
[e] Death occurred after two or more missed visits in the absence of RECIST progression.
[f] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed, the boundaries for declaring statistical significance for PFS are 0.184% for a 0.5% overall alpha and 2.805% for a 5% overall alpha. The Lan-DeMets spending function that approximates the O'Brien Fleming approach was used to derive the adjusted alpha level.
[g] The analysis was performed using the stratified log-rank test, adjusting for TNM stage (Stage I/II vs III) and receipt of PCI (yes vs no).

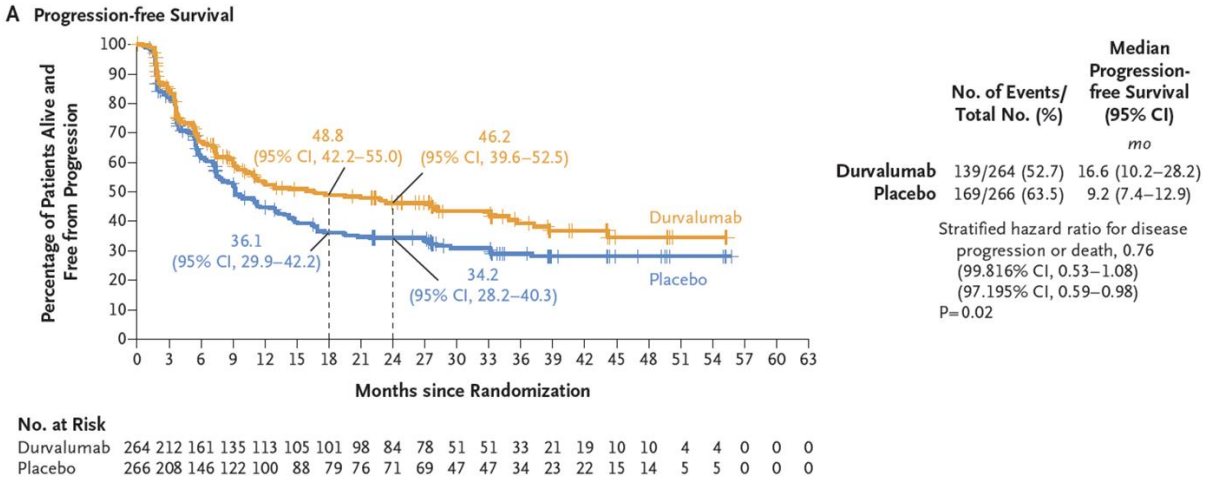

Figure 3 KM plot of PFS as assessed by BICR (FAS population, first interim analysis)

Source: Reproduced from CS Figure 6.
BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival

Three sensitivity analyses were conducted to assess evaluation-time, attrition and ascertainment bias. Results of these analyses were consistent with those of the main analyses (CS section B.2.6.1.2.1 and Table 15 below).

Table 15 Results of sensitivity analyses of PFS as assessed by BICR (ADRIATIC trial)

Analysis / sensitivity analysis	HR (95% CI, unless otherwise indicated)
Main PFS analysis	0.76 (97.195% CI: 0.59, 0.98)
Interval censored analysis of PFS by BICR to assess evaluation time bias	[redacted]
Analysis of PFS per BICR using alternative censoring rules to assess attrition bias	[redacted]
Analysis of PFS per Investigator assessments to assess ascertainment bias	[redacted]

Source: Partly reproduced from CS section B.2.6.1.2.1 and CS Table 17
BICR, Blinded Independent Central Review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

An additional sensitivity analysis in which the censoring indicator of PFS as assessed by BICR was reversed showed that participants in the durvalumab arm were potentially censored earlier for PFS than those in the placebo arm (CS section B.2.6.1.2.1). The reasons for this are not clear, but this raises a possibility that attrition bias may affect the PFS results.

The CS reports that the PFS results from Cox proportional hazards model analyses (stratified by TNM disease stage and PCI) adjusted and not adjusted for covariates were

similar (CS section B.2.6.1.1.1) (HR: [redacted] and HR: [redacted], respectively). The EAG notes that these results were [redacted] the main PFS analysis findings (HR: 0.76; 97.195% CI: 0.59, 0.98).

3.2.5.3 Progression-free survival 2

PFS2 results are presented in CS section B.2.6.2.2. PFS 2 events were defined in the trial as investigator-determined second disease progression or death. This outcome does not inform the economic model. At the first interim analysis, more patients in the placebo arm had a PFS 2 event (n = [redacted], [redacted]%) than in the durvalumab arm (n = [redacted], [redacted]%). The durvalumab arm had a 34% reduction in risk for PFS 2 events (HR: [redacted]). The associated KM plot is shown in CS Figure 11. PFS 2 results were not used in the company's economic model.

3.2.5.4 HRQoL outcomes

The patient reported outcome measures used in ADRIATIC were: the EORTC QLQ-C30, EORTC-QLQ-LC13, PGIS, PRO-CTCAE and EQ-5D-5L. The EQ-5D-5L measure informs the utility estimates in the company's economic model (see section 4.2.6.2), so we focus on summarising the results of this here. We summarise the results from the other measures briefly in section 3.2.5.4.2.

3.2.5.4.1 EQ-5D-5L results

Up to Week 96, the overall completion rate of the EQ-5D-5L was reported in the CS as [redacted]% in the durvalumab arm (overall completion is not reported for the placebo arm). Rates of missing data were similar between the trial arms at selected timepoints (baseline, Week 8 and Week 272; clarification response A15). Reasons for missing data were not collected during the trial (clarification response A15). The company provides the mean (SD) EQ-5D-5L index scores and VAS scores over time for both trial arms in Tables 4 and 5 in clarification response A16, respectively. We agree with the company's summary in CS section B.2.6.4.2.3 that both these scores were similar between trial arms and remained stable over time. As might be expected, fewer patients contribute data to the results at the later timepoints of the trial, which may lead to some uncertainty in the findings at those points.

3.2.5.4.2 Results of other patient reported outcomes

The CS reports improvement and deterioration rates in EORTC QLQ-C30 and QLQ-LC13 subscales or items over the ADRIATIC trial (CS sections B.2.6.4.1.4 and B.2.6.4.1.5). Only two statistically significant differences were found between the durvalumab and placebo arms: i) statistically significantly proportionally more participants randomised to durvalumab experienced an improvement in chest pain compared to those randomised to placebo ([redacted]% versus [redacted]%; OR [redacted], 95% CIs [redacted]) (CS Table 24), ii) [redacted] participants in the

durvalumab arm than in the placebo arm experienced deterioration in arm / shoulder pain ([redacted]% versus [redacted]%), with CS Figure 15 showing that the [redacted]

The CS reports that PRO-CTCAE and PGIS results were similar between the trial groups (reported in CS sections B.2.6.4.2.1 and B.2.6.4.2.2, respectively). Missing data rates for these outcomes were not reported in the CS but were provided for the PGIS in response to clarification question A13. Compliance with completing this measure was similar to that reported for other patient reported outcome measures. Missing data rates for PRO-CTCAE were not collected in the trial (clarification response A13).

3.2.5.5 Subgroup analyses

The NICE scope stated that the following subgroups were of interest in this appraisal: PD-L1 expression, disease stage and previous receipt of cCRT and sCRT. As already noted in this report, the ADRIATIC trial provides data for the cCRT subgroup, but no data are available for the sCRT subgroup (see sections 2.3 and 3.2.1.1.1). The CS reports the results of subgroup analyses of OS and PFS as assessed by BICR in the FAS population by various characteristics, including disease stage (TNM I or II, and TNM III) and PD-L1 status (< 1% and ≥ 1%) (CS sections B.2.6.1.1.2 and B.2.6.1.2.2, and CS Appendix E). The CS reports that the OS and PFS results were broadly consistent across the subgroups, and we concur. However, there was a small number of OS and PFS events among people with TNM stage I/II disease (ranging from 11 to 14 across the arms for the subgroup analyses of TNM stage based on IVRS and based on eCRF) and the 95% confidence intervals around the hazard ratio were wide (CS Appendix Figures 3 and 4), suggesting uncertainty in the results and thus limiting the conclusions that may be drawn.

More detailed PD-L1 status subgroup results from the full PD-L1 analysis set (FPAS) are reported in CS Appendix N.3.2.1 and shown in Table 16 below. The FPAS included all patients in the FAS who had evaluable PD-L1 data. This analysis set included [redacted] participants in the durvalumab arm ([redacted] with high expression and [redacted] with low expression) and [redacted] participants in the placebo arm ([redacted] with high expression and [redacted] with low expression). PD-L1 data were unevaluable in [redacted] participants ([redacted]% of the trial participants; CS Table 9). Similar OS results were obtained for people with evaluable PD-L1 status (i.e. the whole FPAS population regardless of low or high expression) and for the FAS population, which additionally included people with unevaluable PD-L1 status. In the high PD-L1 subgroup, in the durvalumab arm there was a [redacted]% reduction in the risk of death compared to in the placebo group [redacted]. In the low PD-L1 group, the reduction in the risk of death with durvalumab was [redacted]% [redacted] compared to placebo. The OS HRs for the FPAS population and high and low PD-L1 subgroups fell within the confidence interval range

for the HR from the FAS population analysis, suggesting no heterogeneity of findings across the populations. Similarly, there was no evidence of heterogeneity of PFS findings across the FAS and FPAS populations and high and low PD-L1 subgroups.

We were advised by one of our clinical experts that PD-L1 is not tested in SCLC and that they do not expect that there will be a need to start doing this in clinical practice.

Table 16 ADRIATIC trial OS and PFS results by PD-L1 status

Subgroup (population)	Durvalumab, median OS or PFS, months (95% CI)	Placebo, median OS or PFS, months (95% CI)	HR, Durv vs Placebo (95% CI, unless otherwise indicated)
OS			
Main analysis (FAS population)	55.9 (37.3, NR)	33.4 (25.5, 39.9)	0.73; (98.321% CI: 0.54, 0.98)
All participants with evaluable PD-L1 data (FPAS population)	[redacted]	[redacted]	[redacted]
High PD-L1 participants (FPAS population)	[redacted]	[redacted]	[redacted]
Low PD-L1 participants (FPAS population)	[redacted]	[redacted]	[redacted]
PFS			
Main analysis (FAS population)	16.6 (10.2, 28.2)	9.2 (7.4, 12.9)	0.76 (97.195% CI: 0.59, 0.98)
All participants with evaluable PD-L1 data (FPAS population)	[redacted]	[redacted]	[redacted]
High PD-L1 participants (FPAS population)	[redacted]	[redacted]	[redacted]
Low PD-L1 participants (FPAS population)	[redacted]	[redacted]	[redacted]

Source: EAG created table, using data sourced from CS Tables 16 and 17, and CS Appendix Figures 5 to 10.
CI, confidence interval; Durv, durvalumab; FAS, full analysis set; FPAS, full PD-L1 analysis set; NR, not reached; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

3.2.5.6 Safety outcomes

Adverse event data are presented in the CS from the first interim analysis of the ADRIATIC trial (dated 15th January 2024) for the safety analysis set (SAS) population, which was defined as all patients who had received at least one dose of the study treatment (CS Table 11). [redacted].[27] This population included 262 patients who had received durvalumab and 265 who had received placebo (CS section B.2.10). Median total duration of treatment at this point was [redacted]weeks (min [redacted], max [redacted]) in the durvalumab group and [redacted]weeks (min [redacted], max [redacted]) in the placebo group (CS Table 26).

3.2.5.6.1 Any adverse events

In the durvalumab group, 94.3% of the participants experienced a documented adverse event, compared to 88.3% in the placebo group (CS Table 27). Proportionally more participants in the durvalumab group were considered to have had an adverse event possibly related to treatment than in the placebo group (67.2% versus 48.7%, respectively; CS Table 27). Of the adverse events occurring in >5% of the trial participants, the most common ones with durvalumab were radiation pneumonitis (reported for 22.9% of the participants in the durvalumab group versus 23.4% in the placebo group), decreased appetite (16.8% versus 12.8%) and hypothyroidism (16% versus 3.8%) (CS Table 28). We received clinical expert advice that pneumonitis is usually treated in outpatients and tends to be treated with a high dose of prednisolone or another steroid. Occasionally, drugs like infliximab may be used if the pneumonitis is considered to be due to durvalumab rather than radiation. We were advised that pneumonitis is also experienced by patients who receive active monitoring, because it is related to radiotherapy. Hypothyroidism is treated with medication (hormones).

Radiation pneumonitis and pneumonitis were the most common adverse events leading to dose interruption during the trial (radiation pneumonitis led to dose interruption in [redacted]% of the participants in the durvalumab group versus [redacted]% in the placebo group; pneumonitis leading to dose interruption: [redacted]% versus [redacted]%, respectively) (CS section B.2.10.1.5).

3.2.5.6.2 Any adverse events leading to discontinuation of the study treatment

Adverse events leading to discontinuation of the study treatment were reported in 16.4% of the participants in the durvalumab group, compared to in 10.6% of the participants in the placebo group (CS Table 27). Proportionally more participants in the durvalumab group discontinued treatment due to an adverse event possibly related to treatment than in the placebo group ([redacted]% versus [redacted]%) (CS Table 27). CS section B.2.10.1.9 reports that rates of reported Grade 3 or 4 Common Terminology Criteria for Adverse Events (CTCAE) adverse events leading to discontinuation were similar between the treatment groups, but

proportionally more participants treated with durvalumab had Grade 2 events leading to discontinuation than participants treated with placebo ([redacted]% versus [redacted]%). The most common adverse events leading to discontinuation (reported in ≥1% of patients) were radiation pneumonitis, pneumonitis, immune-mediated lung disease and pneumonia, all of which were reported more frequently with durvalumab than with placebo (CS Table 34).

3.2.5.6.3 Deaths

In the SAS population, seven of the participants in the durvalumab group had an adverse event with an outcome of death (CS Table 27). In two cases, the adverse events were classed as possibly related to treatment (as assessed by the investigator and defined as related if considered to be related to the allocated study treatment or if there was a missing response). Five participants in the placebo group had an adverse event with an outcome of death, but none of the adverse events were assessed as being possibly related to the treatment (CS Table 27). Deaths in the FAS population are reported in CS Table 35.

3.2.5.6.4 Grade 3 or higher adverse events

A similar proportion of participants in both the durvalumab and placebo groups had a documented adverse event classed as Grade 3 or higher in severity ([redacted]% versus [redacted]%, respectively; CS Table 29). The most common of these was pneumonia (2.7% of participants in the durvalumab group versus 3.4% in the placebo group) (CS Table 29). Grade 3 to 4 pneumonia is the only adverse event included in the company's economic model (CS section B.3.6.3 and section 4.2.4.6 of this report). CS section B.2.10.1.11.1 reports that maximum CTCAE Grade 3 or 4 pneumonitis or radiation pneumonitis occurred in proportionally more participants treated with durvalumab than placebo (3.1% versus 2.6%).

3.2.5.6.5 Immune-mediated adverse events

Immune-related adverse events were reported for proportionally more participants in the durvalumab group than in the placebo group (32.1% versus 10.2%) (CS section B.2.10.1.6). The CS states that this was driven by hypothyroid ([redacted]% versus [redacted]%) and pneumonitis events ([redacted]% versus [redacted]%) (CS section B.2.10.1.6).

3.2.5.6.6 Serious adverse events

In the durvalumab group, 29.8% of participants were documented as having had a serious adverse event, versus 24.2% in the placebo group. The most commonly reported serious adverse events were radiation pneumonitis, pneumonia and pneumonitis (see Table 17).

Table 17 Most common serious adverse events reported in ≥1% of patients

Adverse event, n (%)	Durvalumab (n=262)	Placebo (n=265)
Any SAE reported	**78 (29.8)**	**64 (24.2)**
Radiation pneumonitis	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]

Source: Reproduced from CS Table 33 (but only the three most commonly reported serious adverse events listed in that table are presented).
SAE, serious adverse event.

3.2.6 Pairwise meta-analysis of intervention studies

As the CS only identified one relevant trial, a meta-analysis was not needed (CS section B.2.8).

3.3 Critique of the indirect treatment comparison

The CS states that the ADRIATIC RCT provides comparative evidence relevant to the NICE scope. As no other studies were identified that were considered relevant to the decision problem, the company did not carry out an indirect treatment comparison (CS section B.2.9). The EAG agrees that an indirect treatment comparison was not needed.

3.4 Conclusions on the clinical effectiveness evidence

The company's decision problem adequately addresses the NICE scope, except that no evidence is presented in the CS for the subgroup of patients with LS-SCLC whose disease has not progressed after sCRT (**Key Issue 1**). The company's SLR was generally well-conducted, but the EAG are concerned that, due to the search terms used, there is a theoretical risk that if there is non-RCT evidence available in the sCRT population this could potentially have been missed.

The CS included one RCT of durvalumab maintenance therapy in people with LS-SCLC whose disease had not progressed after cCRT: the ongoing ADRIATIC trial. The EAG considers the trial to be of a low risk of bias. Results from the first planned interim analysis dated 15th January 2024 showed an estimated improvement in median OS of 22.5 months and an estimated improvement in median PFS of 7.4 months with durvalumab compared to placebo (which was considered to represent active monitoring without durvalumab). The greater OS and PFS benefits that were observed with durvalumab compared to placebo were statistically significant (OS: HR: 0.73; 98.321% CI: 0.54, 0.98; p=0.01; PFS per BICR: HR: 0.76; 97.195% CI: 0.59, 0.98; p=0.02). Our clinical experts considered the gains in OS and PFS to be clinically meaningful. We note that the PFS results may be subject to attrition

bias, as participants in the durvalumab arm were potentially censored earlier for PFS than those in the placebo arm.

There were few apparent differences in HRQoL between the durvalumab and placebo arms over the course of the trial. Common adverse events experienced in the durvalumab group were radiation pneumonitis (22.9% of patients), which occurred at a similar rate to that in the placebo group (23.4% of patients), and decreased appetite and hypothyroidism, which occurred more frequently with durvalumab than with placebo (decreased appetite: 16.8% versus 12.8%; hypothyroidism: 16% versus 3.8%). The most common grade 3 or higher adverse event in the trial was pneumonia, which occurred in a similar frequency in both groups (2.7% of participants in the durvalumab group versus 3.4% in the placebo group).

The only concern the EAG has about the clinical effectiveness estimates presented in the CS is that it is uncertain whether the treatment effects found among the patients who had previously received cCRT in the ADRIATIC trial are generalisable to a population of patients with LS-SCLC whose disease has not progressed after sCRT (**Key Issue 1**).

4 COST EFFECTIVENESS

4.1 The company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify published economic evaluations for patients with LS-SCLC. The search, reported in CS Appendix G, was conducted between May and June 2024. Results are presented in CS Section B.3.2. Only two studies were identified, neither of which were conducted from a UK perspective or evaluated the cost-effectiveness of systemic consolidation therapy following CRT. Therefore, they were excluded from consideration for the current appraisal. The company, however, conducted a targeted literature review of previous NICE TA submissions assessing treatment for extensive-stage SCLC or relapsed SCLC. They reported that five previous NICE TAs were identified, of which three were chosen to inform the current appraisal. These were:

- TA638[18]: Atezolizumab + carboplatin and etoposide for adult patents with untreated extensive-stage SCLC
- TA184[12]: Topotecan for adult patients with relapsed SCLC
- TA798[17]: Durvalumab for adult patients with locally advanced unresectable NSCLC after platinum-based chemotherapy

The company reported that the above appraisals were used to inform their choice of model structure, assumptions and inputs, which we discuss in the following sections. The EAG also conducted a targeted search in PubMed to identify any further relevant economic evaluations on LS-SCLC published in the last six months, but did not identify any.

EAG comment on company's review of the cost-effectiveness evidence

The reporting of the search strategies and results of the company's systematic literature review were clear. The date coverage of the searches was appropriate, although the searches were about six months out of date. The EAG did not identify any relevant economic evaluations on LS-SCLC published in the last six months. Therefore, we believe the company's review has identified all the relevant economic evaluations on LS-SCLC for the current appraisal.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The EAG assessed the company's economic evaluation against NICE reference case requirements, as shown in Table 18. We identified no deviations from the reference case.

Table 18 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, direct patient effects are included.
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes (lifetime, 39 years)
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes (severity modifier CS Section B.3.7)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: EAG assessment based on the company submission

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company's model structure is described in CS Section B.3.2.2, the model assumptions in CS Table 76 and the parameters in CS Sections B.3.4 to B.3.6. It is a mixture cure partitioned-survival model, programmed in Microsoft Excel with a time horizon of 39 years and a cycle length of four weeks with a half-cycle correction applied. The model structure comprises three health states: progression-free, progressed disease, and death. It is assumed that a proportion of patients (the cure fraction) will not experience disease progression after a certain timepoint (we discuss this further in Section 4.2.4.3 of this report). The company's model structure is illustrated in CS Figure 16 (reproduced in Figure 4 below).

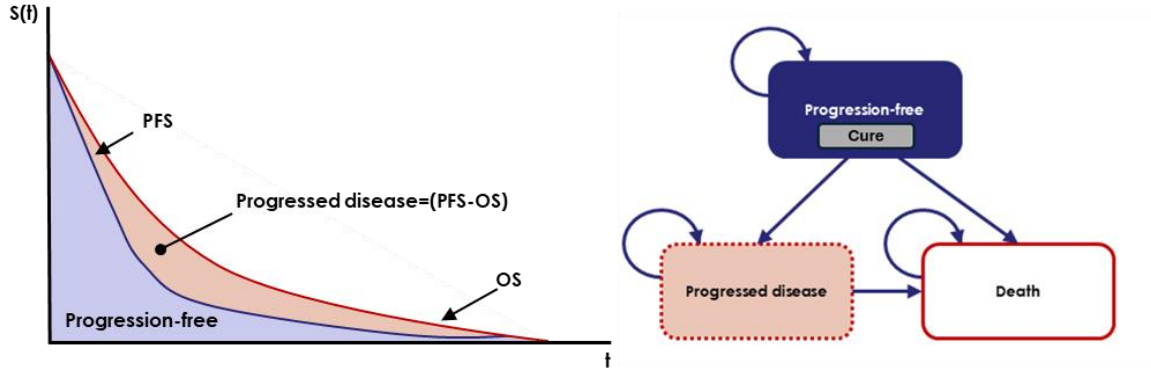

Figure 4 Company's economic model structure

Source: Reproduced from CS Figure 16

Patients enter the model in the progression-free health state (where they receive first-line treatment of durvalumab or 'watch and wait') and can transition to the progressed disease or death health states. Patients in the progressed disease health state are only able to remain in the progressed disease state or transition to the death state. The proportion of patients in the progression-free state is estimated directly from the modelled PFS curves; that in the death state is calculated as one minus OS curve; and that in the progressed disease state as OS minus PFS. Within the progression-free health state, a proportion of patients are assumed to achieve a functional cure, i.e., these patients are assumed to be cured at a certain time point (see Section 4.2.4.3 for further discussion). These cured patients are assumed to experience the same mortality risk as the general population and no longer experience progression for the remainder of the model. Time to treatment discontinuation (obtained from the ADRIATIC trial) was used to estimate durvalumab-related treatment costs.

EAG comment on model structure

The three-state partitioned survival model structure is appropriate. It follows the same structure as that used in the previous NICE technology appraisals for lung cancer, including TA638, TA184 and TA798. With respect to the cure assumption, in TA638, a mixture model was explored as part of additional analyses to extrapolate the long-term survival (OS curve). The committee of that appraisal, however, concluded that restricted spline models (and not mixture models) provided the best approach to model overall survival. In TA184 and TA798, the economic models did not incorporate a cure fraction. We discuss the cure assumption further in Section 4.2.4.3.

4.2.3 Decision problem for the model

4.2.3.1 Population

The base case population for the company's economic analysis is patients with LS-SCLC who have not progressed following CRT. The ITT population of the ADRIATIC trial informed the patient characteristics: [redacted] female with a mean age of 61.50 years, mean body weight of [redacted] kgs, and a mean height of [redacted] cm (shown in CS Table 38). The company did not report any results for sub-groups of patients as part of their cost-effectiveness analyses. Furthermore, they did not explicitly state that the modelled population includes both the cCRT and sCRT subgroups of patients. For a detailed critique of the patient population, see sections 2.2.3.1, 2.3 and 3.2.1 of this report.

4.2.3.2 Interventions and comparators

The modelled intervention is durvalumab monotherapy, administered intravenously at a dose of 1,500mg every 4 weeks until disease progression, intolerable toxicity, or a maximum of 24 months, whichever occurs first. The comparator 'watch and wait' matches the specified comparator in the NICE scope, which is active monitoring. This arm in the model is represented by the placebo arm of the ADRIATIC trial and includes only the costs associated with the resource use (discussed in Section 4.2.7).

4.2.3.3 Perspective, time horizon and discounting

The company's model adopts a UK National Health Service (NHS) and personal social services healthcare payer perspective, includes a lifetime model horizon and applies an annual discount rate of 3.5% to both costs and health outcomes, as per NICE guidelines.

EAG comment on the decision problem

The EAG notes that the population included in the economic model is based on the characteristics of the patients with LS-SCLC who were included in the ADRIATIC trial, who had all previously received cCRT (patients who had previously received sCRT were excluded from the trial). We acknowledge that in clinical practice, most patients with LS-SCLC who can have CRT will receive cCRT and that the patient population receiving sCRT is small. The company does not explicitly model patients who have previously received sCRT. We are, therefore, unable to comment if costs and effects in patients who have had sCRT will be similar to those assumed for patients who have received cCRT and the potential impact on the cost-effectiveness results is unknown. The intervention and comparator meet the decision problem criteria as outlined in the NICE scope.

4.2.4 Treatment effectiveness and extrapolation

The company uses parametric curves fitted to OS and PFS data from the ITT population of the durvalumab monotherapy and placebo arm in the ADRIATIC trial to model the durvalumab and 'watch and wait' arms, respectively. They have not implemented treatment waning but applied a cure assumption to both the OS and PFS curves (discussed in Section 4.2.4.3).

Survival analyses were conducted and assessed by the company as per the guidelines in NICE DSU TSDs 14 and 21, which included: assessing the assumption of proportional hazards; statistical goodness of fit; visual fit to Kaplan-Meier plots; assessment of hazard functions; and external validation of the fitted curves.

4.2.4.1 Progression-free survival

The KM estimates of PFS for durvalumab and the placebo arm from the ADRIATIC trial are presented in CS Figures 6 and 20. Proportional hazard assumptions are tested through Schoenfeld residuals and log cumulative hazard plots (CS Figures 18,19, 22 and 23). The company assume that proportional hazards do not hold and fit models independently for each arm. The parametric curves fitted to each arm are presented in CS Figures 21 and 26. Apart from the standard parametric distributions (exponential, Weibull, Gompertz, lognormal, log-logistic, and generalised gamma), the company also fitted spline models (1 spline hazard, 2-knot spline hazard, 3-knot spline hazard, 1 spline odds, 2 spline odds, 3 spline odds, 1 spline normal, 2-spline normal and 3-knot spline normal). Goodness of the curve fit was provided by Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics, presented in CS Tables 41 and 44. Visual fit to KM plots were presented in CS Figures 21 and 26. Based on their assessment of the hazard function for the ADRIATIC trial

data (CS Figures 22 and 23), the company argued that the spline models were flexible to accommodate complex hazard functions (an initial decrease followed by a small increase before decreasing again) (CS Figures 22 and 23). The PFS hazard plots for all parametric curves were extrapolated over a 10-year period (shown in CS Figures 24 and 25). Finally, 10- and 15-year PFS predictions associated with the parametric distributions were presented in CS Tables 42 and 43 for the durvalumab arm. For the 'watch and wait' arm, 5-year PFS predictions from the parametric curves and the 5-year predictions reported in two published literature – CONVERT[29,30] and CAL GB 3061[31] were presented in CS Table 45 and 10-year predictions in CS Table 46. The EAG identified an error in the PFS estimates which the company addressed in their response to clarification questions B1. The company clarified that they sought clinical expert opinion to validate the PFS predictions projected by the standard parametric curves, but not for the estimates predicted by the spline model.

For their base case, the company chose the 1-knot spline normal model for both the durvalumab and 'watch and wait' arm and conducted scenario analyses using the generalised gamma distribution. We note that the model includes an adjustment to prevent PFS exceeding OS. Furthermore, they apply a cure assumption whereby a cure fraction of 90% is applied to those patients who are progression-free at 5 years in both the treatment arms. We discuss the cure assumption in Section 4.2.4.3.

From the company's revised base case, we have reproduced the PFS estimates at 10 years and 20 years in Table 19, and the survival extrapolations in Figure 5 and Figure 6 respectively.

Table 19 Estimated PFS for the treatment arms at 10 years and 20 years

Distributions	Durvalumab		Watch and wait	
	10-year	20-year	10-year	20-year
Exponential	1.99%	0.04%	0.56%	0.00%
Weibull	8.04%	1.50%	3.23%	0.30%
Gompertz	35.54%	35.53%	26.24%	26.23%
Log-logistic	13.60%	7.47%	7.28%	3.56%
Log-normal	13.29%	6.37%	6.73%	2.52%
Gen gamma	26.38%	21.03%	16.64%	12.12%
Gamma	5.47%	0.46%	1.77%	0.05%
1-knot spline hazard	29.43%	23.75%	19.46%	14.26%
2-knot spline hazard	25.50%	17.89%	18.33%	12.68%
3-knot spline hazard	26.55%	19.37%	20.17%	15.32%
1-knot spline odds	30.00%	25.06%	19.39%	14.77%

Distributions	Durvalumab		Watch and wait	
	10-year	20-year	10-year	20-year
2-knot spline odds	26.89%	20.70%	18.55%	13.73%
3-knot spline odds	27.91%	22.04%	20.52%	16.31%
1-knot spline normal (company base case)	29.20%	23.72%	18.22%	13.03%
2-knot spline normal	26.83%	20.35%	18.32%	13.15%
3-knot spline normal	27.55%	21.33%	20.27%	15.77%

Source: EAG produced from the Company revised model submitted as part of the clarification response
[a] These estimates are obtained without applying the cure assumption and the PFS adjustment to ensure PFS<OS

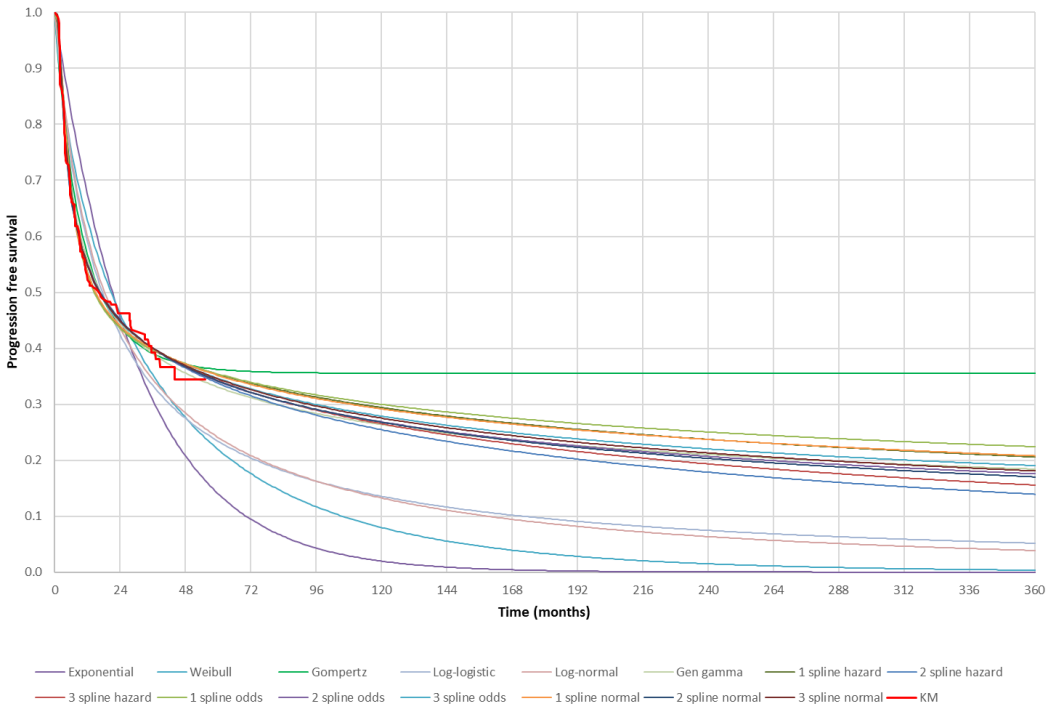

Figure 5: PFS KM curve and extrapolations from the company's revised base case for durvalumab (curves are not bounded by OS)

Source: EAG reproduced the graph from the company's revised base case model
Abbreviation: PFS, progression-free survival; KM, Kaplan-Meier; OS, overall survival

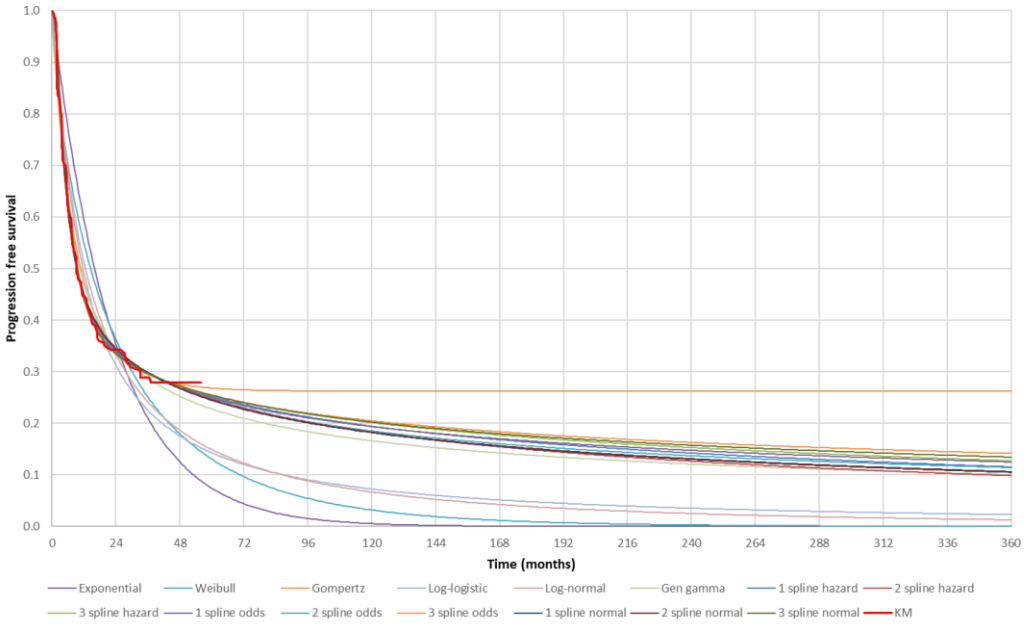

Figure 6: PFS KM curve and extrapolations from the company's revised base case for 'watch and wait' (curves are not bounded by OS)

Source: EAG reproduced the graph from the company's revised base case model
Abbreviation: PFS, progression-free survival; KM, Kaplan-Meier; OS, overall survival

EAG comment on company's PFS extrapolation

We agree with the company that the spline models, in general, provide a similarly good fit to the KM curves, compared to the standard distributions and provide similar long-term extrapolations. However, we note that based on their AIC/Bayesian Information Criterion (BIC) scores, the generalised gamma distribution provides a better fit to the KM curves for both the treatment arms compared to the company's chosen 1-knot spline normal distribution. There was limited exploration of the impact of different survival curves on the cost-effectiveness analysis in the CS. We conducted an exhaustive list of PFS scenarios in section 6 of this report using different survival curves. Finally, we agree with the company's adjustment of the PFS curves to not exceed OS; however we have reservations about their cure assumption, which we discuss in section 4.2.4.3.

4.2.4.2 Overall survival

The KM estimates of OS for durvalumab and the placebo arm from the ADRIATIC trial are presented in CS Figure 4 (and reproduced as Figure 2 in section 3.2.5.1). Proportional

hazard assumptions are tested through Schoenfeld residuals and log cumulative hazard plots (CS Figures 27 and 28). The company assumes that proportional hazards do not hold and fits models independently for each arm. Goodness of the curve fit was provided by AIC and BIC statistics, presented in CS Tables 49 and 52. Like PFS, standard parametric distributions as well as spline model were fitted to the KM curves. Visual fits to KM plots were presented in CS Figures 29 and 34. The company assessed the hazard function for the ADRIATIC trial data, which showed [redacted] (CS Figures 30 and 31). The OS hazard plots for all parametric curves were extrapolated over a 10-year period (shown in CS Figures 32 and 33). Finally, 10- and 15-year OS predictions associated with the parametric distributions were presented in CS Tables 50 and 51 for the durvalumab arm. For the 'watch and wait' arm, 5-year OS predictions from the parametric curves and the 5-year OS predictions from two published literature - CONVERT and CALGB 3061 were presented in CS Table 53 and 10-year and 15- year predictions in CS Tables 54 and 55.

For their base case, the company chose the 2-knot spline normal model for both the durvalumab and 'watch and wait' arm and conducted scenario analyses using the 2-knot spline odds model. We have reproduced the OS estimates at 5 years, 10 years and 20 years in Table 19, and the survival extrapolations in Figure 7 and Figure 8 respectively.

Table 20 Estimated OS for the treatment arms at 10 years and 20 years

Distributions	Durvalumab			Watch and wait		
	5-year	10-year	20-year	5-year	10-year	20-year
Exponential	41%	17%	3%	30%	9%	1%
Weibull	37%	10%	0%	24%	3%	0%
Gompertz	40%	14%	1%	28%	5%	0%
Log-logistic	39%	19%	8%	27%	11%	4%
Log-normal	41%	21%	8%	28%	11%	3%
Gen gamma	43%	27%	15%	32%	18%	10%
Gamma	36%	10%	1%	24%	4%	0%
1-knot spline hazard	45%	27%	11%	33%	15%	4%
2-knot spline hazard	46%	30%	16%	32%	15%	4%
3-knot spline hazard	46%	30%	15%	32%	14%	3%
1-knot spline odds	45%	29%	17%	33%	19%	10%
2-knot spline odds	46%	32%	21%	33%	19%	10%

Distributions	Durvalumab			Watch and wait		
	5-year	10-year	20-year	5-year	10-year	20-year
3-knot spline odds	46%	32%	20%	33%	18%	9%
1-knot spline normal	43%	26%	13%	32%	16%	7%
2-knot spline normal (company base case)	46%	32%	20%	33%	18%	8%
3-knot spline normal	46%	31%	19%	32%	17%	7%

Source: EAG produced from the Company revised model submitted as part of the clarification response
[a] These estimates are obtained without applying the cure assumption

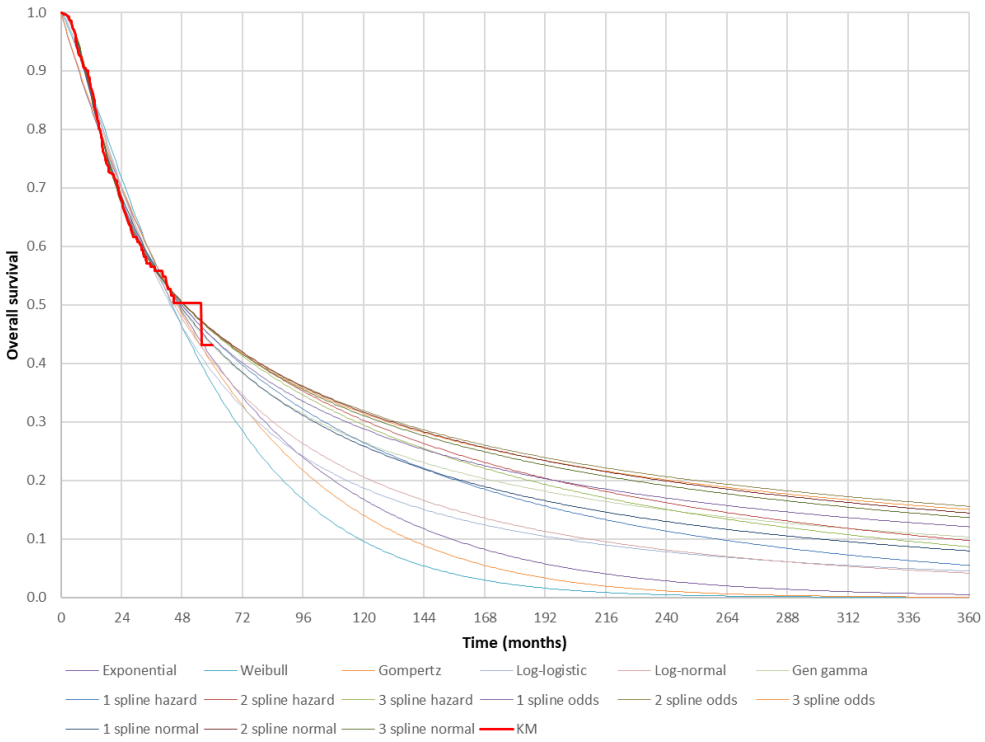

Figure 7: OS KM curve and extrapolations from the company's revised base case for durvalumab

Source: EAG reproduced the graph from the company's revised base case model
Abbreviation: KM, Kaplan-Meier; OS, overall survival

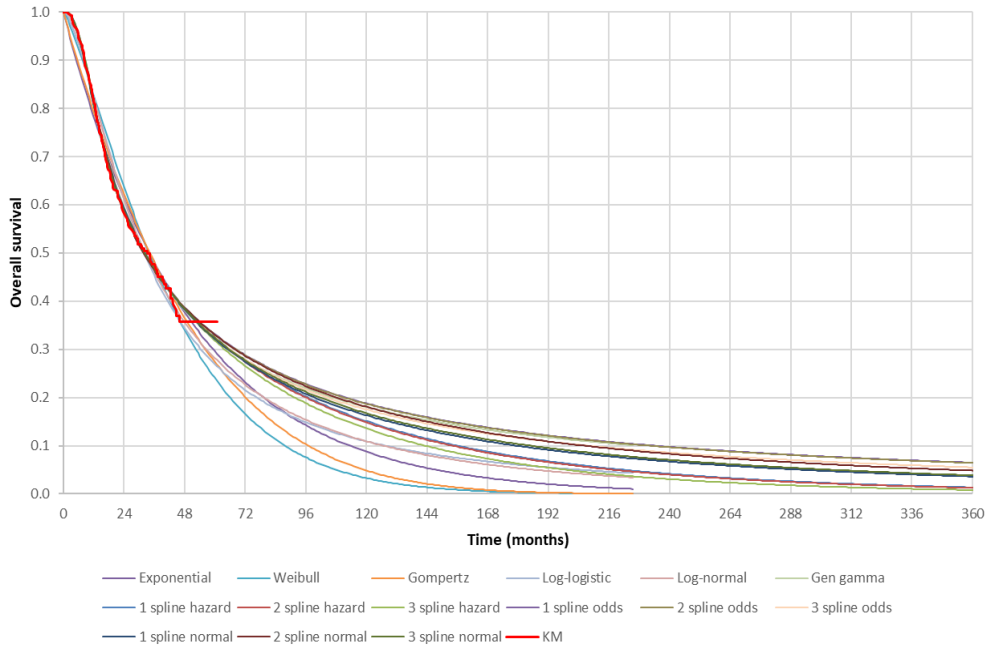

Figure 8: OS KM curve and extrapolations from the company's revised base case for durvalumab

Source: EAG reproduced the graph from the company's revised base case model
Abbreviation: KM, Kaplan-Meier; OS, overall survival

EAG comment on company's OS extrapolation

The EAG notes that the best fitting curves according to AIC/BIC scores are log-normal, followed by 1-knot spline hazard, 1-knot spline odds and 1-knot spline normal. These curves provide a better fit than the company's chosen 2-knot spline normal curve for OS extrapolations of the two treatment arms. Like for PFS, the CS did not explore the impact of different survival curves, except 2-knot spline odds, on the cost-effectiveness results. We report OS scenarios in section 6 of this report.

4.2.4.3 Cure assumption

The company applied a cure assumption to the OS and PFS curves of both the treatment arms. The CS stated this assumption was based on their clinical experts' opinions and plateauing of the PFS KM curves in both the durvalumab and placebo arms of the ADRIATIC trial. After the cure timepoint, the 'cured' patients were assumed to follow the survival rates of general population. In terms of the impact on costs and utilities, the cured patients did not incur treatment-related or health state costs, only end of life costs. Additionally, the cured patients were assumed to have general population utilities, adjusted for age and sex.

In their base case, the company assumed that 90% of patients who are progression-free at 5 years achieve functional cure. They conducted two scenario analyses assuming i) a 3-year cure timepoint, and ii) a cure fraction of 80% in both the treatment arms. Neither of these scenarios had a significant impact on the overall cost-effectiveness results, as discussed later in section 5.2.2.

Generally, cure models may be suitable in the context of immunotherapies if a proportion of patients is believed to not experience the event of interest (for example, disease-progression or death). In such cases, the cure models may be able to estimate the overall hazard functions with a complex shape by combining the hazard function of the cured fraction with that of the uncured fraction.[32] However, in the current appraisal, the company argued that the spline models accommodated complex hazard functions. Therefore, we view that adding the cure assumption to the survival functions extrapolated using flexible spline models may overestimate the survival functions. Secondly, as pointed out in section 4.2.2.1, in the previous appraisal TA638, a mixture cure model was explored in scenario analyses to extrapolate the long-term survival, but the appraisal committee preferred restricted spline models for extrapolating overall survival. Finally, our experts considered that the chance of cure in stage I to III SCLC is about 20%. Although there may be a subset of patients with SCLC who do not experience relapse within the first five years and are discharged on the presumption that they have been cured, some of them may experience long-term toxicities, particularly cardiac disease, due to radiotherapy. Therefore, this subgroup of patients may have additional needs, even if they are cured from their cancer, due to the long-term impact of radiotherapy.

EAG comment on the cure assumption

Based on the reasons cited above, we view that it is not appropriate to include a cure assumption. We explore the impact of this assumption in EAG analyses in section 6.

4.2.4.4 General population mortality

General population mortality, adjusted by age and sex, was obtained from the ONS life tables for England and Wales, as per NICE recommendations. In the economic model, the OS and PFS were capped by applying the background mortality across the two treatment arms in each cycle. This was to ensure that the hazard of progression or death in each cycle would not be lower than the hazard of age- and gender- adjusted death of general population.

4.2.4.5 Time to Treatment Discontinuation

The company used the observed Time to Treatment Discontinuation (TTD) curve from the ADRIATIC trial to estimate the proportion of patients receiving durvalumab (and who therefore incurred durvalumab treatment-related costs), in each cycle. They did not extrapolate the TTD curve from the trial due to the availability of fully mature data. The CS stated that at the time of ADRIATIC interim analysis all patients received the maximum of 24 months of treatment and no patients were receiving ongoing treatment. Figure 9 (reproduced from CS Figure 35) shows the company's TTD data for durvalumab arm. The TTD data for the placebo arm of ADRIATIC was not used in the model as there were no treatment-related costs for the 'watch-and-wait' arm.

Figure 9: TTD Kaplan-Meier curve for durvalumab (reproduced from CS Figure 35)

Source: Reproduced from CS Figure 35
Abbreviation: TTD, Time to treatment discontinuation; KM, Kaplan-Meier

EAG comment on time to treatment discontinuation

The company's approach is appropriate as all the patients discontinued durvalumab at the time of data cut-off at 2 years.

4.2.4.6 Adverse events

The economic model included only one adverse event - pneumonia for both the treatment arms (CS Table 56). The company cited that this was the only AE that was Grade 3 or 4 and occurred in ≥2% of patients in either of the treatment arms in the ADRIATIC trial. Advice from our clinical experts suggests that in addition to pneumonitis, the other common AEs seen in clinical practice include skin rashes, arthritis, muscular pains, diarrhoea, hypothyroidism and hepatitis. While most of the immunotherapy-related AEs are managed as outpatients, patients experiencing adverse events require regular and closer monitoring (such as conducting blood tests).

EAG comment on adverse events

Based on our experts' advice, we view that besides pneumonia, patients may experience other adverse events requiring regular and closer monitoring. While this is likely to impact resource use, the associated costs may not be significant enough to influence the overall cost-effectiveness results.

4.2.5 Treatment effect waning

No treatment effect waning was applied in the company's model. In their response to clarification question B7, the company argued that there was no clinical evidence for treatment effect waning and that previous TAs (TA638 and TA184) did not incorporate this assumption in their base cases.

Based on our clinical experts' advice, the EAG acknowledge that there is no established clinical evidence to indicate a treatment effect waning. However, assessing the two previous relevant appraisals, we note that:

- In TA638 (atezolizumab with carboplatin and etoposide for untreated extensive-stage SCLC), the NICE appraisal committee was uncertain about the duration of treatment benefit from the start of treatment. After exploring scenario analyses by the company (which included scenarios for no treatment effect cut-off and treatment effect cut-off for 36, 48 and 60 months from the start of treatment) and the EAG (which included an illustrative scenario of 30 months - the maximum follow up in the IMpower133 trial), the committee acknowledged that varying the duration of treatment benefit had a minor impact on the cost-effectiveness results.

- In TA798 (durvalumab for maintenance treatment for unresectable NSCLC after platinum-based chemoradiation), the company did not model any treatment effect waning as they argued that risk of disease progression or death was based on 5-year long data from PACIFIC trial. However, as part of additional analyses, both the company and the EAG explored several assumptions varying the treatment effect waning at different time points (i.e., 3, 5, 7.5 and 10 years). The committee pointed out that other appraisals of fixed duration immunotherapies in NSCLC had assumed treatment effect durations lasting between 3 and 5 years after stopping treatment. They concluded that both 3- and 5-year treatment effect waning scenarios were appropriate for decision making.

EAG comment on treatment waning

There is uncertainty over the company's assumption of no treatment effect waning due to two factors: i) the appraisal committee's conclusion in TA798 which assessed durvalumab as maintenance treatment of unresectable NSCLC after platinum-based chemoradiation, and ii) median OS follow-up of durvalumab in the ADRIATIC trial (30.75 months) may not be long enough follow-up to ascertain that there was no treatment effect waning. We therefore explore scenarios varying the duration of treatment effect lasting between 3 and 5 years from the start of the treatment, in section 6.

4.2.6 Health related quality of life

The company describe their approach to estimating HRQoL for the cost-effectiveness analysis in CS section B.3.4. They used utilities estimated from the ADRIATIC trial for the progression-free and progressed health states in the cost-effectiveness analyses (see section 4.2.6.2). Results are also reported for scenarios: with an alternative assumption for progression-free utility value, and with utilities from previous published literature. Age-adjustment of utilities is applied (see section 4.2.6.4 below). A disutility for the one adverse event included in the model was used. See the subsections below for further discussion.

4.2.6.1 Systematic literature review for utilities

The company's systematic literature review of utility studies identified 22 studies, of which three reported EQ-5D data. None of these studies were included for the reasons provided by the company in a tabulated summary of these studies in CS Table 61.

4.2.6.2 Utility estimates from trial data

The methods used to analyse the HRQoL outcomes from the ADRIATIC trial are described in CS Sections B.3.5.1 and B.3.5.2.

EQ-5D-5L data were collected at week 0 (i.e. first study treatment visit) and then every 8 weeks until second disease progression (PFS2) or death. 503 patients from the ITT population were included. The company stated that the questionnaire data were mapped to EQ-5D-3L utility values *"using the mapping function developed by the NICE DSU"*, to align their approach to the reference case recommended in the NICE health technology evaluations manual.[33-35] No information on missing utility observations was provided. Therefore, we are unclear how missing observations were treated and whether any imputation was necessary and therefore, undertaken. CS Table 60 provides a summary of the EQ-5D-5L mapped to EQ-5D-3L values.

Mixed models for repeated measures (MMRM) were applied after mapping the EQ-5D-5L to EQ-5D-3L data to estimate the statistical relationship between utilities and health states. The company stated that this was used to account for correlation in utility scores across repeated measurements for each subject and provide valid results where utility data are missing at random. The MMRM analysis excluded any observations recorded after the time of censoring for progression. The EQ-5D-5L observations that had an unknown/missing health status were also omitted from the MMRM analysis. The company reported that univariate as well as multivariate analyses were conducted by fitting a range of covariates (such as, treatment, progression status, the interaction of treatment and progression status). The clinical model parameters and variables used in four MMRM models are presented in CS Table 58 (reproduced below in Table 21); the coefficients and standard errors along with the AIC/BIC for statistical model fit of each of the models are presented in CS Table 59. Based on the best model fit, the company chose the equation with progression status as a covariate (equation 2 in CS Table 58) to inform the utilities in the economic model. We agree with the company's model selection.

Table 21 Clinical model parameters and variables used in MMRM models

MMRM model name	Equation
Equation 1	$Utility = \beta_0 + \beta_1 \cdot Treatment$
Equation 2	$Utility = \beta_0 + \beta_1 \cdot Progression\ Status$
Equation 3	$Utility = \beta_0 + \beta_1 \cdot Treatment + \beta_2 \cdot Progression\ Status$
Equation 4	$Utility = \beta_0 + \beta_1 \cdot Treatment + \beta_2 \cdot Progression\ Status + \beta_3 \cdot \text{Treatment} * Progression\ Status$

Source: Reproduced from company's CS Table 58

For clarity, we have reproduced below the company's equations (from CS Section B.3.5.1 Pg 174) used for the estimation of the health state utilities.

$$Utility = \beta_0 + \beta_1 \cdot Progression\ Status = [redacted] - [redacted] \cdot Progression\ Status$$

$$Utility_{\mathrm{PFS}} = [redacted]$$

$$Utility_{\mathrm{PD}} = [redacted]$$

Where progression status = 0 for the PFS health state and 1 for the PD health state

The same utility values were used for both the durvalumab and placebo arms. The impact of AEs is modelled through AE disutility, as discussed below.

4.2.6.3 Adverse events

Disutility related to the adverse event of pneumonia was applied as a one-off decrement in the first model cycle as it was assumed to last for 28 days. The disutility of -0.0735, obtained from Mehra et al.[36] was applied. This estimate is consistent with the value used in TA798.

4.2.6.4 General population utilities and age adjustment

The model applied age-based utility multipliers in the base case to reflect declining quality of life with age in the general population. Age-specific utilities were based on data from the 2014 wave of the Health Survey for England.[37] The company appropriately applied the age-adjustment in the model by ensuring that the general population utility was applied in the model if the utilities associated with each health state were greater than the general population utility.

4.2.6.5 Summary of utility estimates

Table 22 summarises the utility values used in the company's base case model which are obtained from the ADRIATIC trial. The company acknowledged that the base case utility values derived from the trial may be relatively higher compared to clinical practice. To investigate the impact of this, they conducted scenario analyses shown in CS Section B.3.12.3 and discussed in Section 5.2.2. None of these scenarios had any significant impact on the overall cost-effectiveness results.

Table 22: Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)	95% CI	Source
PF	[redacted]	[redacted]	Based on MMRM using data derived from ADRIATIC trial
PD	[redacted]	[redacted]	

Source: Partially reproduced from CS Table 63
Abbreviations: CI, confidence interval; MMRM, mixed models for repeated measures; PD, progressed disease; PF, progression-free.

EAG comment on HRQoL

The methods used to estimate health state utilities in the ADRIATIC trial are consistent with NICE's preferred methods.[33] To investigate the impact of using utility estimates reflective of clinical practice, the company conducted scenario analyses based on i) published literature by Kuehne et al.[38] and ii) EQ-5D data from the durvalumab CASPIAN trial indication (first-line treatment of extensive stage-SCLC).[39] Overall, we agree with the company's approach and do not report further scenario results with utilities.

4.2.7 Resources and costs

4.2.7.1 Drug acquisition

The company presented the drug acquisition cost in CS section B.3.6.1.1. CS Table 64 summarises the unit drug costs for the intervention and the comparator.

Durvalumab is administered via intravenous infusion. Patients receive a 1,500 mg fixed dose every four weeks with a relative dose intensity (RDI) of 100%. Durvalumab is available in packages of one vial with a list price of £2,466 for a 500 mg vial and £592 for a 120 mg vial [British National Formulary (BNF) 2024][40]. The CS presented [redacted]. However, NICE informed the EAG on 24/01/2025 [redacted] for durvalumab [redacted] For the comparator 'watch and wait', the company assumed no treatment-related costs.

4.2.7.2 Drug administration

The cost of intravenous infusions required for durvalumab, and some subsequent treatment therapies is taken from the National Health Service (NHS) Cost Collection 2022/2023 (SB12Z – Deliver simple parenteral chemotherapy at first attendance) and is shown in CS Table 66. The EAG notes, after response to clarification question B5, that the reference in CS Table 66 is incorrect, and the price refers to the total cost, not to the outpatient cost. Oral treatments are assumed to have no administration cost.

4.2.7.3 Resource use

Health state costs include consultations with health and social services care professionals, hospital resource use, and treatment follow-up. The frequency of resource use was taken from TA798[17] which is based on the PACIFIC trial data. CS Table 67 shows the per year

resource use for the progression-free health state, and CS Table 68 for the progressed disease health state. We validated these estimates with our experts, who noted some differences in the estimates reported in the CS from those in UK clinical practice. Our experts advised that patients would see an oncologist or nurse to have their treatment prescribed. In practice, patients would see an oncologist or nurse practitioner every two to four weeks when receiving durvalumab treatment on treatment (i.e., at least twelve visits per year for two years); less frequently in Year 3 to 5. For durvalumab off-treatment, patients' visits to the oncologist would vary between 4 and 6 annually in the first two years; and six-monthly in year 3 to 5 (i.e., 2 visits per year) . Our experts agreed with the company estimates for the 'watch and wait' arm. For the durvalumab arm, our experts also viewed that patients would have one blood test per oncologist visit (twelve blood tests each year, i.e. twenty-four in the first two years); four blood tests during durvalumab off-treatment. We were advised that these blood tests would not be done for 'watch and wait'. Our experts also suggested that patients in the durvalumab arm would have four CT scans (on average) per year (i.e. eight in the two years of durvalumab treatment), and in the following years (Year 3-5), at least one CT-scan per year. Regarding chest X-ray, our experts stated that most centres use CT scans for surveillance, not X-rays. Therefore, patients, in both the arms, are unlikely to have any X-rays. Our experts agree with the company that there would be no blood tests for the 'watch and wait' arm.

For progressed disease (i.e., after disease progression), our experts stated that patients will have four to six cycles of chemotherapy every three weeks, thereby, requiring between nine to twelve oncologist visits. Patients are likely to have CT scans, instead of Chest X-rays. Our experts also suggested that patients might need more support and more GP surgery contact.

Based on the above observations, the EAG has added alternative estimates to those provided by the company, and these are shown in Table 23 and Table 24, for progression-free and progressed health states, respectively.

Table 23 Progression-free health state resource use

Item cost	Resource use per year					
	Company submission			EAG clinical experts		
	Durvalumab on treat.	Durvalumab off-treat.	Watch and Wait	Durvalumab on treat.	Durvalumab off-treat.	Watch and Wait
Outpatient oncologist visit: Year 1	0.00	5.00	5.00	12	4-6	5.00
Outpatient oncologist visit: Year 2	0.00	3.00	3.00	12	4-6	3.00
Outpatient oncologist visit: Year 3–5	0.00	2.00	2.00	0	2	2.00
Chest X-ray: Year 1	0.00	2.00	2.00	0.00	0	0
Chest X-ray: Year 2	0.00	0.00	0.00	0.00	0	0.00
Chest X-ray: Year 3–5	0.00	2.00	2.00	0.00	0	0
CT scan (chest): Year 1	6.00	3.00	3.00	4	4	3.00
CT scan (chest): Year 2	6.00	3.00	3.00	4	4	3.00
CT scan (chest): Year 3–5	6.00	0.00	0.00	1	1	1
Blood tests	24.00	0	0	12	4	0

Source: Partially reproduced from CS Table 67 and based on EAG clinical expert opinions
Abbreviation: EAG, External Assessment Group; CT scan, Computed Tomography scan.

Table 24 Progressed disease health state resource use – expert opinions

Cost Item	Resource per year	
	Company submission	EAG clinical experts
Outpatient oncologist visit	9.61	9- 12
Chest X-ray	6.79	0
CT scan (chest)	0.62	6.79
CT scan (other)[a]	0.36	6.79
ECG	1.04	1.04
Community nurse visit	8.70	8.70
Clinical nurse specialist	12.00	12.00
GP surgery	12.00	12.00
Blood test	0.00	9-12

Source: Partially reproduced from CS Table 68 and based on EAG clinical expert opinion
Abbreviation: EAG, External Assessment Group; CT scan, Computed Tomography scan; ECG, Electrocardiogram; GP, General Practitioner
[a] As per clinical advice, follow-up include CT chest and CT abdomen.

Healthcare unit costs were taken from the NHS Cost Collection 2022/23[41] data. In response to clarification questions B4 and B5, the company updated the unit cost for "Outpatient oncologist visits" (from £233.95 to £199.08) and ECG (from £296.02 to £370.94) in the CS and the economic model, and the frequency of CT scans (from 2 to 6) in the CS for the durvalumab on-treatment health state. With these corrections, the total healthcare cost per cycle is given in Table 25 below. The EAG assessed a scenario with these modifications, see section 6.1.

Table 25 Revised disease management costs per year

Health State	Year of the treatment	Company submission	Revised cost (£)
Durvalumab on treatment	Year 1 cost per cycle	£84.29	£84.29
	Year 2 cost per cycle	£84.29	£84.29
	Year 3-5 cost per cycle	£84.29	£84.29
Durvalumab off treatment	Year 1 cost per cycle	£135.61	£122.25
	Year 2 cost per cycle	£93.42	£85.40
	Year 3-5 cost per cycle	£42.19	£36.84

Health State	Year of the treatment	Company submission	Revised cost (£)
Watch and wait	Year 1 cost per cycle	£135.61	£122.25
	Year 2 cost per cycle	£93.42	£85.40
	Year 3-5 cost per cycle	£42.19	£36.84
Progressed disease	Cost per cycle	£399.11	£379.40

Source: Company's revised economic model

4.2.7.4 Subsequent treatment costs

Patients who progress to the progressed disease (PD) health state are modelled to receive subsequent treatments. They may commence chemotherapy (with or without immunotherapy) or receive best supportive care (BSC, which is assumed to be equivalent to the 'watch and wait' comparator).

- *Associated costs and effects*

The economic model only accounts for costs associated with the subsequent treatments, and not effects. The CS justified this by stating that the clinical effects are already captured in the post-progression survival data from the ADRIATIC trial and used in the model.

The unit costs for the subsequent treatments included in the company's model are shown in CS Appendix K Table 20, the regimens and the total cost per model cycle in CS Table 72, and the administration cost per regimen and per treatment cycle in CS Table 73. The EAG notes that the list price of carboplatin 150 mg/15 ml should consider the eMIT 2024 (£12.18)[42] price instead of the BNF 2024[43] price (£60.59). The company amended this in response to clarification question B3 and updated the economic model (see section 5.3.1). In addition, the company amended the topotecan price in CS Appendix K Table 20 to represent the price per package, not per capsule, in response to clarification question B4. The total subsequent treatment cost per intervention and comparator are shown in Table 27 below.

Finally, we identified an error in the calculation of subsequent treatment cost at year 5 (60 months) in the cure fraction of the progression-free health state. This is corrected and discussed in the section 5.3.2.

- *Proportion of patients receiving subsequent treatments*

The company obtained the types and proportions of subsequent treatments from the ADRIATIC trial (shown in CS Table 70). The CS stated that these estimates were validated and adjusted with their clinical experts to reflect clinical practice (shown in CS Table 71). The CS described the company's approach to estimate these proportions in CS section B.3.6.4.1

and in their response to clarification question B4. A total of [redacted] and [redacted] of patients in the durvalumab and "watch and wait" arms, respectively, were assumed to receive subsequent treatment. For their base case, they use the proportions in CS Table 71 (estimates based on the company's clinical experts) and conduct a scenario with the estimates in CS Table 70 (estimates obtained from ADRIATIC). We validated the company's base case estimates with our clinical experts. Below is a summary of our experts' advice:

- One of the key therapies, anthracycline (CAV) regimen is excluded from the basket of subsequent treatment. CAV is used in fit patients who relapse within three months of finishing their chemotherapy and have a platinum-resistant disease. Some centres might prefer either CAV or topotecan and in this case, CAV would share the proportion with topotecan.
- The choice of subsequent treatment depends on how quickly a patient relapses. If the patient relapses within three months of finishing the chemotherapy, they will probably receive topotecan or CAV. If they relapse more than six months after finishing the chemotherapy, the patient would be re-challenged and probably receive carboplatin + etoposide.
- Regarding the proportions of patients across subsequent treatments, it was noted that a lower proportion of patients would receive BSC. As most patients will receive "atezolizumab + etoposide + carboplatin" therefore, the proportion of "etoposide + carboplatin" would be smaller. Moreover, patients receiving "etoposide + cisplatin" would be fit enough to receive atezolizumab. Therefore, the "etoposide + cisplatin" proportion should be close to zero, transferring the proportion to "atezolizumab + etoposide + carboplatin".
- "Durvalumab + etoposide + platinum" has been approved and could displace the "atezolizumab + etoposide + carboplatin" therapy. Although it is expected that the proportion of "durvalumab + etoposide + platinum" therapy will be higher in the future, it is unclear if clinicians will change their treatment choice due to the differences in treatment administration as "atezolizumab + etoposide + carboplatin" treatment has faster administration.

We note that our experts' advice [redacted] We note from GID-TA11423[45] (Tarlatamab) that the topotecan shortage was temporary. Furthermore, in TA798,[17] we note that subsequent treatments were modelled based on their distribution and duration in the PACIFIC trial. Patients in the PACIFIC trial had immunotherapy after stopping

durvalumab, which is not the current practice in the NHS in the context of NSCLC. The committee acknowledged the uncertainty about the use of immunotherapy after durvalumab treatment but concluded that *"subsequent treatment assumptions should be based on the PACIFIC data to align costs and effects in the model" (committee discussion point 3.9 in the guidance document).*

Based on the above observations from our experts, we explored two scenarios in section 6.1

- Use of CAV and "atezolizumab + etoposide + carboplatin" for both arms.
- Use of CAV for both arms, "atezolizumab + etoposide + carboplatin" for watch and wait arm and "durvalumab + etoposide + carboplatin" for the durvalumab arm.

Table 26 shows the costs and regimen included in the economic model for the CAV treatment.

Table 26 CAV treatment – acquisition costs and regimen

	Dose per admin	Formulation per vial (mg)	Vials per package	Cost per package (£)	Cost per treatment[a] (£)
Cyclophophamide	1.4 mg/m^2	1000	1	£13.11	£78.64
Doxorubicin	750 mg/m^2	200	1	£17.67	£742.11
Vincristine	50 mg/m^2	1	5	£38.42	£2,305.40
Total cost of CAV treatment					£3,126.15

Source: eMIT 2024[42], cyclophosphamide SmPC, doxorubicin SmPC, and vincristine SmPC
[a] Assuming RDI of 100% and six cycles of treatment, and assumes wastage

We have summarised the proportions of subsequent treatment and the associated costs included by the company and the estimates based on the EAG clinical advice in Table 27.

Table 27 Subsequent treatment distributions and associated costs

Treatments	Total cost of the treatment (£)	Proportions based on ADRIATIC (CS Table 70)		Proportions revised by the advisory board (used in company's base case) (CS Table 71)		Estimates based on EAG clinical advice	
		Durvalumab	Watch and wait	Durvalumab	Watch and wait	Durvalumab	Watch and wait
Topotecan (oral)	£3,000	31.1%	32.5%	10.0%	10.0%	5.0%	5.0%
Etoposide + cisplatin	£15,462	8.9%	8.0%	5.0%	5.0%	0.0%	5.0%
Etoposide + carboplatin	£5,418	26.8%	23.9%	56.5%	23.9%	20.0%	23.9%
Durvalumab + etoposide + cisplatin	[redacted]	0.3%	0.5%	0.0%	0.0%	0.0%	0.0%
Durvalumab + etoposide + carboplatin	[redacted]	0.9%	1.6%	0.0%	0.0%	0.0%	0.0%
Atezolizumab + etoposide + carboplatin	£28,206	7.5%	13.9%	0.0%	38.5%	50.0%	38.5%
Cyclophosphamide + doxorubicin + vincristine (CAV)	£3,126					5.0%	5.0%
BSC	£0	24.6%	19.6%	28.5%	22.6%	20%	22.6%
Total cost		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IO, immune-oncology; BSC, best supportive care.
Source: Reproduced from CS Tables 70 and 71 and based on the EAG clinical advice

- *Vial sharing*

The company assumed vial sharing in their base case analysis for the subsequent treatment with a RDI of 100% for all medicaments. This is consistent with the assumption in TA798. The company provided a scenario analysis with no vial sharing per cycle for each treatment, and it had a negligible impact on the ICER. The EAG corrected an error in modelling the vial sharing control (see section 5.3.2).

4.2.7.5 Adverse event costs

The adverse event cost is calculated by multiplying the total frequency of the selected adverse event by its unit cost. This cost is applied as a one-off cost in the first treatment cycle only. The company stated that only pneumonia had more than 2% frequency of Grades 3 or 4 adverse events for both arms and was considered in the modelling (see CS B.3.4.5).

CS Table 69 shows the unit cost of treating pneumonia. This cost was taken from the NHS Cost Collection 2022/2023.[41] The adverse event frequencies for pneumonia are 2.7% for durvalumab and 3.4% for 'watch and wait' arm, respectively as shown in CS Table 56.

As discussed earlier in section 4.2.6.3, our clinical experts suggested that most of the immunotherapy-related adverse events (such as pneumonia, skin rashes, arthritis, muscular pains, diarrhoea, hypothyroidism and hepatitis) are managed as outpatients and require regular monitoring and use of health resources and medications. Overall, we view that the costs associated with managing these AEs are unlikely to have any significant impact on the cost-effectiveness results.

4.2.7.6 End of life costs

The company's model includes a cost of £4,703.66 for end-of-life care for deaths related to LS-SCLC. This estimate was taken from TA638[18] and was updated to 2024 costs using the Consumer Price Inflation (CPI) for health from the Office for National Statistics. The end-of-life cost is applied to the population considered functionally cured as a one-off cost. The EAG observed that TA638 based its costs on TA484 (Table 70)[46] from 2016 as suggested by an Advisory Board.[18]

The EAG observed that:

- Adjusting the prices using the CPI is in line with the NICE health technology evaluation manual, section 4.4.12.[33]
- The PSSRU Unit Costs for Health and Social Care 2023 manual [47] reports end-of-life health and social care costs based on the Nuffield Trust report by Georghiou et al.

(2012)[48], with hospital and social care costs of £13,314 for cancer patients (Table 7.2.2).

- Round et al 2015 [49] assessed the end-of-life cost for terminal patients, with a cost of £5,432 for lung cancer patients (inflated to a PSSRU 2022/23 price).

Table 28 shows the original and adjusted prices of each source. We note that the costs reported by Georghious et al.[48] is significantly higher compared to those reported in previous TAs and by Round et al. The EAG ran an exploratory scenario using Georghiou et al. 2012 using the higher price limit, see section 6.1.

Table 28 End of life cost for health and social care

Source	Cost £ per person in the final year of life		
	Original prices	PSSRU 2022/2023 prices	CPI 2024 prices
TA638 (Atezolizumab) / TA484 (Nivolumab)	£3,739, inflated to 2015 prices using PSSRU	£4,530	£5,010
TA184 (Topotecan)	£4,977 at 2007/08 prices	£7,031	£8,054
Round et al. 2015	£4,515, 2013/14 prices	£5,432	£6,167
Georghiou et al. 2012	£10,844, 2010/11 prices	£13,314	£16,115

Source: Produced by EAG
Abbreviations: PSSRU, Personal Social Services Research Unit; CPI, Consumer Price Inflation; TA, Technology Appraisal.

EAG comment on resources and costs

Overall, the company's approach to estimating resources and costs in the economic model is consistent with the NICE reference case and previous technology appraisals for LS-SCLC. We identified a few minor errors in resource use ("outpatient oncology visit cost" and ECG costs) and subsequent treatment (carboplatin price) and noted inconsistencies in the company submission related to drug administration cost (reference should be SB12Z total cost), resource use (CT scans in CS Table 67), and subsequent treatment (topotecan price in CS Appendix Table 20). The company corrected these errors in their responses to clarification questions B3, B4, and B5. In addition to these, we identified a few errors in the company's revised model (submitted as part of their response to clarification questions) relating to subsequent treatment cost calculation per cycle, updating the cost of 'outpatient oncologist visit' in the progressed disease health state, and control for the vial sharing assumption. We address these as part of EAG corrections, discussed in section 5.3.2 of this report. Lastly, we noted some uncertainty in the company's resource use estimates (discussed in section 4.2.7.3),

which we assessed in EAG additional analyses based on Table 23 and Table 24 (see section 6.1).

With respect to the types and proportion of patients receiving subsequent treatment, we prefer to use the ADRIATIC trial data. This is based on the committee conclusion in TA798 where the committee preferred the distribution of subsequent treatment to be informed by the relevant pivotal trial. While it may be common to adjust the distribution of subsequent treatments for costing to reflect current NHS practice, we view that such an approach may introduce a potential bias as the assumed costs aren't necessarily consistent with the effectiveness results from the trial. Therefore, we conduct EAG scenarios based on our expert advice which includes, including CAV in the subsequent treatment basket and varying the proportions of the subsequent therapies (see section 6.1).

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

CS Tables 77 and 78 report the base case results for durvalumab versus the 'watch and wait' arms for treating LS-SCLC after chemoradiation. On 24th January 2025, NICE informed the EAG [redacted]. On 10th April 2025, NICE made a correction to [redacted] We re-ran the company's original model with the updated commercial arrangementand obtained the base case results as reported in Table 29 below.

Table 29 Company's original base case results with the updated commercial arrangement price for durvalumab

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER (£/QALY)	NMB (£) for a WTP of £30,000
Watch and wait	[redacted]	[redacted]	[redacted]	£18,704	£18,583
Durvalumab	[redacted]	[redacted]	[redacted]		
Increment	[redacted]	[redacted]	[redacted]		

Source: Partially reproduced from CS Tables 77 and 78 as we re-ran the company's original model with the updated commercial arrangement for durvalumab that was received from NICE on 24th January 2025
Abbreviations: LYG, Life-year gained; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio; NMB, Net Monetary Benefit; WTP, Willingness to pay.
[a] Discounted at 3.5% per year, with no severity modifier applied to QALYs

The company's base case results do not include confidential discounts for medications besides durvalumab. Therefore, the ICERs do not reflect the actual prices that would be paid by the NHS. Results, including all available NHS price discounts for subsequent medications in addition to the proposed commercial arrangement for durvalumab, are presented in a separate confidential addendum to this report.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

CS section B.3.12.2 reports the deterministic sensitivity analyses (DSA) results for durvalumab versus 'watch and wait' arms. The economic model considered 42 input parameters varying by 20% instead of the 10% reported in the CS. The company notes that parametric survival model coefficients were only varied in the probabilistic sensitivity analysis (PSA), not in the DSA, because these coefficients are correlated. The EAG observed that in

the DSA, the company varied the disease management total costs for the progression-free and progressed disease states in both arms, whereas, in the PSA they varied the frequencies of the resource use parameters which informed the estimation of the disease management total costs. The EAG considers that this is reasonable for testing the sensitivity of individual parameters.

The company has shown ten results from parameters with the most impact in the ICER in CS Table 80 and a tornado diagram in CS Figure 39. Only four parameters presented more than 5% difference between the low and upper bounds: proportion from 'watch and wait' to receive atezolizumab + etoposide + carboplatin at second-line (2L), cost of subsequent treatment atezolizumab + etoposide + carboplatin, cost of administration – durvalumab, and proportion from durvalumab to receive etoposide + carboplatin 2L. These four parameters were the main drivers for the model.

In Figure 10 below, we present an updated tornado diagram with the updated commercial arrangement for durvalumab, maintaining the 20% variation. The EAG assessment remains the same.

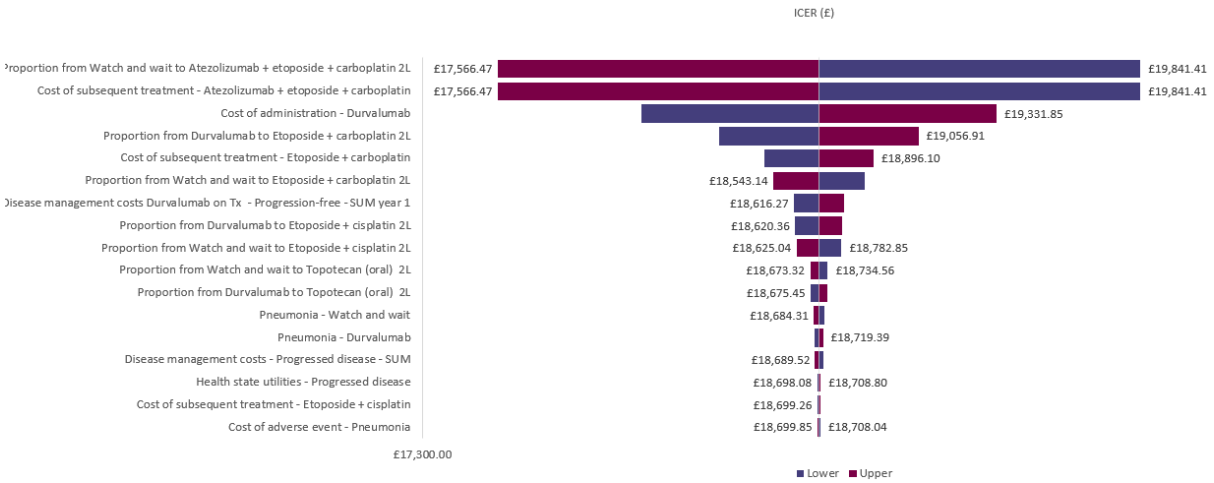

Figure 10 Tornado diagram for the company's base case using updated commercial arrangement for durvalumab

Source: revised company's economic model
Abbreviation: ICER, Incremental cost-effectiveness ratio

5.2.2 Scenario analysis

The company set up 17 scenarios to test structural and methodological uncertainties in its economic model and reported the results in CS Table 81. We observed modelling errors in two scenarios (relating to cure assumption and vial sharing) when we ran these scenarios manually (see section 5.3.2). The EAG requested additional scenarios in clarification question B7 to explore a treatment effect waning as in TA638[18] and TA798[17]. The company

argued that treatment effect waning is not applicable in this modelling and therefore did not conduct any scenario (see section 4.2.5). The EAG re-ran all the company's scenarios in the EAG corrected company's revised base case with the revised commercial arrangement for durvalumab arm (see section 5.3.2). We also assessed additional scenarios on the clinical effectiveness, resource use, and subsequent treatment, as discussed in section 6.1.

5.2.3 Probabilistic sensitivity analysis

The company's probabilistic sensitivity analysis results were estimated for 5,000 simulations, illustrated in a scatterplot (CS Figure 36) and a cost-effectiveness acceptability curve (CEAC, CS Figure 38). Mean probabilistic results for the company's base case are reported in CS Table 79. The probabilistic results are stable and have a 3.5% difference from the deterministic results. The EAG ran the PSA with the updated commercial arrangement. The scatterplot with an updated commercial arrangement is in Figure 11 and the CEAC is in Figure 12. The results indicate that there is a 75.1% probability of durvalumab being cost-effective for a willingness to pay of £30,000.

The distributions used for the parameters included in the PSA analysis are summarised in CS Table 75. The EAG considers the distributions adequate for the economic modelling.

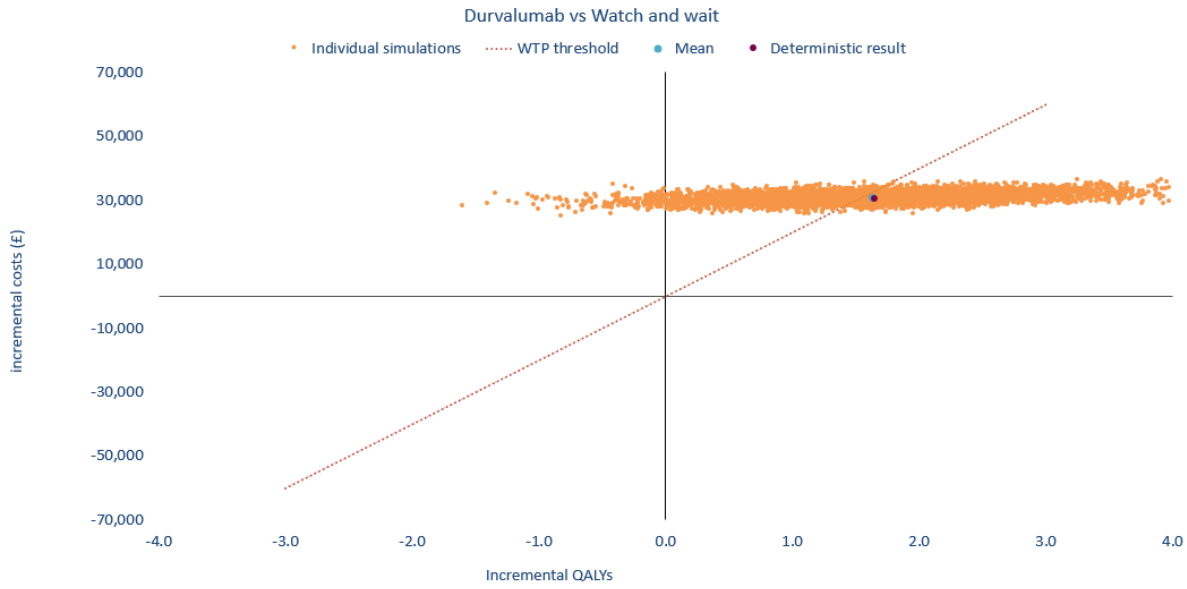

Figure 11 Scatterplot graph for durvalumab vs watch and wait using the company's base case and updated commercial arrangement

Source: revised company's economic model
Abbreviation: WTP, willingness to pay; QALY, Quality-adjusted life year

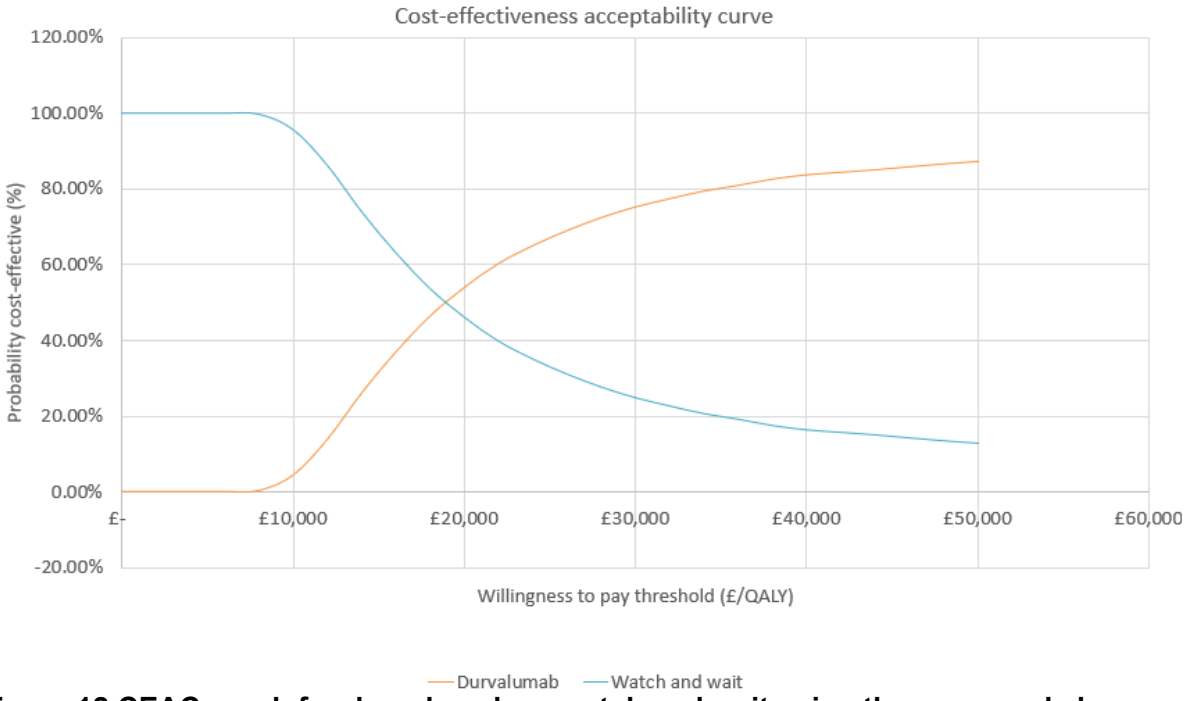

Figure 12 CEAC graph for durvalumab vs watch and wait using the company's base case and updated commercial arrangement

Source: revised company's economic model
Abbreviation: QALY, Quality-adjusted life year

5.3 Model validation and face validity check

We conducted a range of checks on the company's model using an EAG checklist:

- **Input checks:** comparison of all parameter values in the model against the values stated in the company submission and cited sources.
- **Output checks:** replication of results reported in the CS using the company model. Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses.
- **'White box' checks:** checking individual equations within the model.
- **'Black box' checks:** applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed.

The model is generally well-implemented, although we spotted discrepancies between the company submission and the initial (original) version of the model, which were corrected in a revised version submitted with the company's clarification response, as described below.

5.3.1 Company corrections to the company model

In their response to the EAG clarification questions, the company amended some parameter values listed below:

- The price of carboplatin 150 mg/15 ml from £60.59 to £12.18 (clarification question B3)
- Outpatient oncology visits cost (CS Table 67 and 68) from £233.95 to £199.08 (clarification question B4)
- ECG costs (CS Table 68) from £296.02 to £370.94 (clarification question B4)

Applying the above corrections, the company has provided revised results in section B of their clarification response. Their revised model included the original commercial arrangement. The revised base case results are in Table 7, deterministic sensitivity analysis in Table 9 and Figure 2, probabilistic sensitivity analysis in Table 8 and Figure 1, and scenarios in Table 10 respectively of the clarification response. The company's revised results (with [redacted]) were slightly higher than their original results, resulting in a slight increase of £41 in ICER per QALY gained. We re-ran the company's revised model (received as part of the clarification response) with [redacted] for durvalumab; this resulted in an increase in the ICER from £18,704 to £18,745 per QALY gained.

In addition, the company updated the model to address some divergences between the economic model and the company submission pointed out by the EAG in the clarification questions. These corrections did not affect the outcome, only the presentation of the parameters:

- PSM extrapolation spline curves were modelled referring to incorrect parameters in sheet "Extrapolation Data", columns BQ16:BY525 and CH15:CP525 (clarification question B1)
- AIC /BIC tables in the economic model "Survival (PSM)!F24:I32, U24:X32, F76:I84, and U76:X84" were incorrectly associated to sheet "Clinical Data (PSM + TTD)" (clarification question B6)

5.3.2 EAG corrections to the company model

The EAG identified four additional issues in the company's revised economic model:

- Subsequent treatment cost calculation per cycle is incorrect when considering the cure fraction of the progression-free health state due to the half cycle modelling. We amended in sheet "Flow!AO13:AO521" and "Flow!BG13:BG521".
- The company updated the "outpatient oncologist visit" cost for the progression-free health state, but not for the progressed disease health state (cell "Country_data!E82")

- The controls for the cure assumption were not modelled. The EAG amended the formula in sheet Parameters!E649:653 to allow the model to use different time points and cure fractions.
- The control for the vial sharing assumption was mismatched. It used the "include subsequent treatment cost?" control (Settings!E57) instead of the "include wastage?" one (Settings!E59). We amended it in the sheet "Costs_SubTx!AA48:AA62".

We incorporated the above corrections in the company's revised model and applied the updated commercial arrangement for durvalumab. The results obtained are presented in Table 30 below. We note these changes has resulted in a slight increase in ICER, from £18,743 (obtained in the company's revised model submitted as part of the clarification response with updated commercial arrangement for durvalumab) to £19,160.

Table 30 EAG corrected company's revised base case results with updated commercial arrangement for durvalumab

Technologies	Total costs (£)[a]	Total LYG[a]	Total QALYs[a]	ICER (£/QALY)[a]	NMB (£) for a WTP of £30,000
Watch and wait	£20,642	[redacted]	[redacted]	£19,160	£17,833
Durvalumab	[redacted]	[redacted]	[redacted]		
Increment	[redacted]	[redacted]	[redacted]		

Source: corrected company's economic model
Abbreviations: LYG, Life-year gained; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio; NMB, Net Monetary Benefit; WTP, Willingness to pay.
[a] Discounted at 3.5% per year, with no severity modifier applied to QALYs

The probabilistic results remained stable and have a 2.9% difference from the deterministic results and a 73.5% probability of being cost-effective (see Figure 13 below).

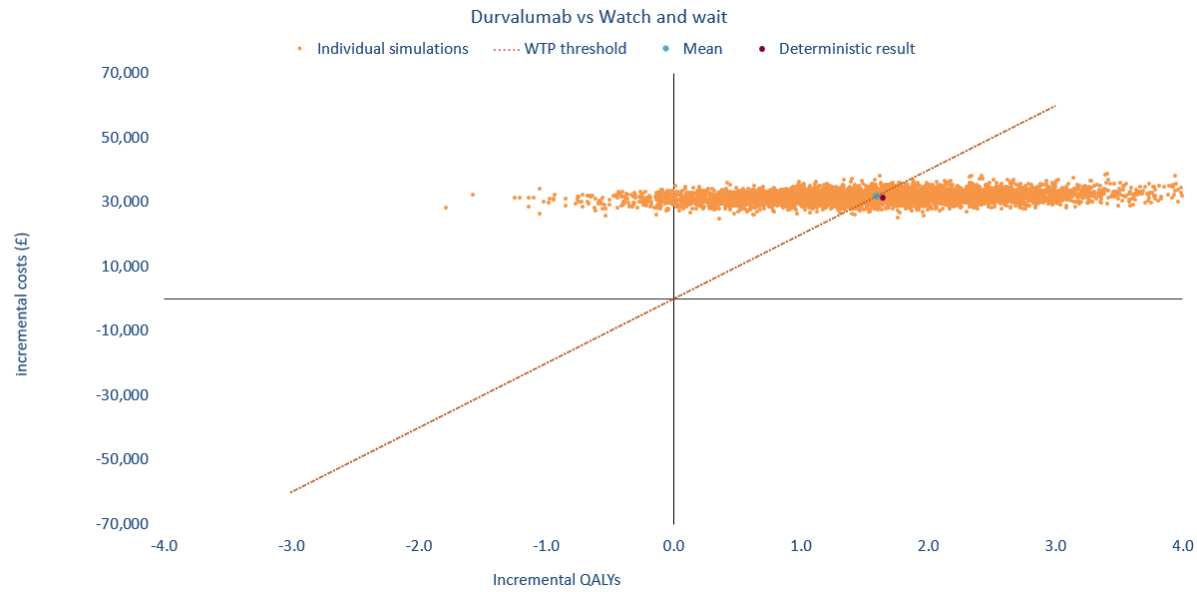

Figure 13 Scatterplot graph for durvalumab vs watch and wait using the corrected company's base case and updated commercial arrangement

Source: corrected company's economic model
Abbreviation: WTP, willingness to pay; QALY, Quality-adjusted life year

Figure 14 shows the tornado diagram associated to the deterministic sensitivity analysis obtained from the EAG corrected company's revised model with the updated commercial arrangement for durvalumab.

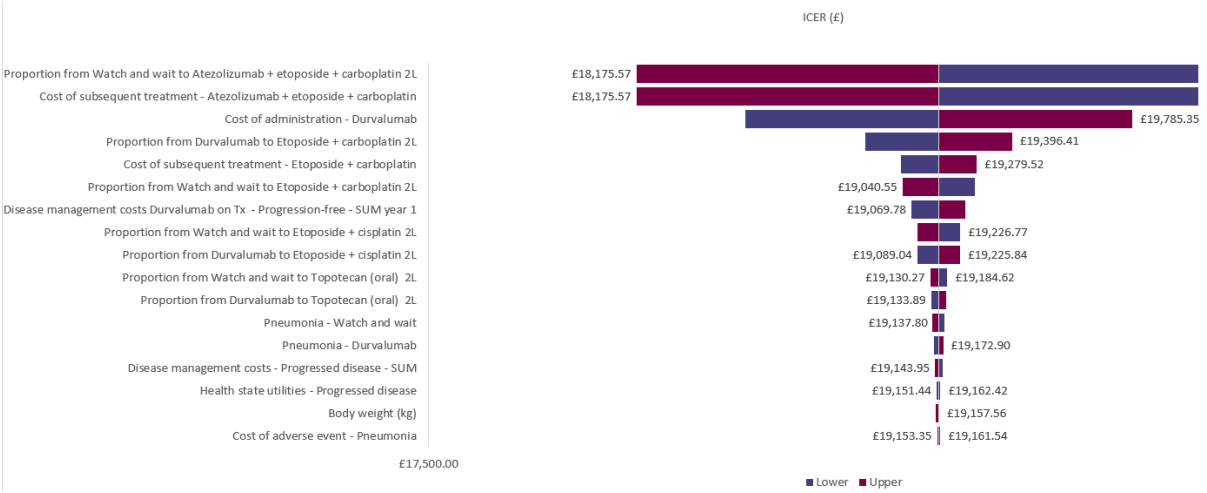

Figure 14 Tornado diagram for the corrected company's base case using updated commercial arrangement for durvalumab

Source: corrected company's economic model
Abbreviation: ICER, Incremental cost-effectiveness ratio

Table 31 below shows the company scenarios conducted on the EAG corrected version of the company's revised base case model that includes the updated commercial arrangement

for durvalumab (described in section 5.3.1). The scenarios that have the most impact on the ICER are alternate distributions for subsequent treatment and OS extrapolation.

Table 31 Company scenario analysis conducted on the EAG corrected company's revised model with an updated commercial arrangement for durvalumab and list price for the remaining drugs

	Scenario	Increm. cost (£)	Increm. QALYs	ICER (£/QALY)
EAG corrected company revised base case with updated commercial arrangement		[redacted]	[redacted]	£19,160
Company scenarios conducted on the above model				
PFS Durvalumab: 1-knot spline normal	Generalised gamma	[redacted]	[redacted]	£19,313
PFS 'Watch and wait': 1-knot spline normal	Generalised gamma	[redacted]	[redacted]	£18,974
PFS both arms: 1-knot spline normal	Generalised gamma	[redacted]	[redacted]	£19,127
OS Durvalumab: 2-knot spline normal	2-knot spline odds	[redacted]	[redacted]	£18,740
OS 'Watch and wait': 2-knot spline normal	2-knot spline odds	[redacted]	[redacted]	£20,330
OS both arms: 2-knot spline normal	2-knot spline odds	[redacted]	[redacted]	£19,858
Cure timepoint – 60 months	36 months	[redacted]	[redacted]	£19,304
Cure fraction – 90%	80%	[redacted]	[redacted]	£19,172
Discount rates (costs and health outcomes): 3.5%	1.5%	[redacted]	[redacted]	£15,533
Health state utility values; PF: [redacted], PD: [redacted]	PF: [redacted] PD: [redacted]	[redacted]	[redacted]	£19,142
	PF: [redacted] PD: [redacted]	[redacted]	[redacted]	£19,144
	PF: [redacted] PD: [redacted]	[redacted]	[redacted]	£19,156

AE disutility: included	Excluded	[redacted]	[redacted]	£19,160
Age-adjusted utility	Excluded	[redacted]	[redacted]	£19,155
Time horizon (years)	20 years	[redacted]	[redacted]	£22,909
Vial sharing: include	Excluded	[redacted]	[redacted]	£19,159
Subsequent treatment distribution: key opinion leaders (based on CS Table 70)	ADRIATIC trial	[redacted]	[redacted]	£22,200

Source: Partially reproduced from the CS Table 81, updated using the EAG corrections to the revised company's economic model
Abbreviation: QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio; PFS, Progression-free survival; OS, Overall survival; PF, progression-free disease; PD, progressed disease; AE, adverse event

5.3.3 EAG summary of key issues and additional analyses

We summarise and critique key assumptions in the company's model in Table 32 below.

Table 32 EAG summary and critique of key features of the economic model

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
Decision problem			
Population	Patients with LS-SCLC who have not progressed following CRT. Based on ITT population of the ADRIATIC trial	It is not explicitly stated if the modelled population includes both the cCRT and sCRT subgroups. Given that the proportion of patients receiving sCRT is small, we view the modelled population is generally reflective of UK clinical practice.	No change
Baseline characteristics (age, height, weight, proportion of female)	Based on ADRIATIC trial	We agree	EAG scenarios: Age: 55.35 years, 67.65 years Weight: 64.91kg, 79.33kg Height: 150.82 cm, 184.34 cm Female: [redacted]
Comparator	Based on ADRIACTIC trial.	We agree	No change
Time horizon	Lifetime (39 years)	We agree	EAG scenario: 10 years
Discounting	3.5%	We agree	No change
Perspective	NHS & PSS	We agree	
Cycle length	4 weeks	We agree	
Clinical effectiveness			
OS- Durvalumab	Base case: 2-knot spline normal Scenarios: 2-knot spline odds	The company have not explored the impact of fitting the survival curves with a range of distributions.	EAG scenarios: All distributions EAG Base case: 1 spline hazard
OS- Watch and wait	Base case: 2-knot spline normal Scenarios: 2-knot spline odds		EAG scenarios: All distributions EAG Base case: 1 spline hazard
PFS- Durvalumab	Base case: 1-knot spline normal Scenarios: Generalised gamma		EAG scenarios: All distributions EAG Base case: Generalised gamma
PFS- Watch and wait	Base case: 1-knot spline normal Scenarios: Generalised gamma		EAG scenarios: All distributions EAG Base case: Generalised gamma

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
Treatment duration	Patients received durvalumab every four weeks until disease progression, intolerable toxicity, or a maximum of 24 months, whichever occurred first.	We agree	No change
Treatment effect waning	No treatment effect waning	Whilst there is no established clinical evidence on treatment effect waning, we view there is uncertainty in the company's assumption due to i) the appraisal committee's conclusion in TA798 which concluded that both 3- and 5-year treatment effect waning scenarios were appropriate for decision making for that appraisal, and ii) median OS follow-up of durvalumab in the ADRIATIC trial (30.75 months) may not be a long enough follow-up to ascertain that there was no treatment effect waning (see section 4.2.5)	EAG scenarios: treatment benefit capped at 5 years, 10 years EAG Base case: No treatment waning
Cure assumption	Base case: 90% cure fraction at 5 years Scenarios: 80% cure fraction; 3 years cure timepoint	Fitting spline models have already accommodated complex hazard functions to the survival curves. Hence, adding the cure function may overestimate the survival functions. Secondly, in TA638, the appraisal committee preferred restricted spline models over mixture model for extrapolating OS. Finally, our clinical experts suggested that while a subset of patients may have been	EAG (exploratory) scenarios: 25% cure fraction at 5 years. 50% cure fraction at 5 years 75% cure fraction at 5 years 25% cure fraction at 3 years 50% cure fraction at 3 years 75% cure fraction at 3 years EAG Base case: No cure assumption

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
		presumed to be cure but some of them may experience long-term toxicities thereby requiring additional needs (section 4.2.4.3)	
Health-related quality of life			
Health state utilities	Based on MMRM using data derived from ADRIATIC trial (see CS 3.5.5 and CS Table 63)	The company explored a set of scenarios using estimates from public literature and durvalumab CASPIAN indication.	No change
Adverse event disutilities	See CS B.3.5.4 and CS Table 62	We agree	No change
Age-related utility decrement	See CS B.3.5.5	We agree	No change
Resource use and costs			
Treatment cost	Durvalumab was sourced from BNF, and the comparator arm did not incur treatment costs (see CS B.3.6.1.1 and CS Table 64)	We agree	No change
Relative dose intensity (RDI)	100% for durvalumab (see CS B.3.6.1.2 and CS Table 65)	We agree	No change
Administration cost	CS B.3.6.1.3 and Table CS Table 66	We agree	No change
Resource use and costs	Based on TA798 and presented in CS Tables 67 and 68 (see CS B.3.6.2)	Uncertainty over the frequency of the resource use for progression-free and progressed disease health states.	EAG base case: Based on clinical advice on resource use (see section 4.2.7.3)
Subsequent treatments	The distribution of patients receiving chemotherapy (with or without immunotherapy) was based on the ADRIATIC trial and adjusted by an Advisory Board of experts to the company[44]. (see CS B.6.4.1, CS Table 70 and response to clarification question B4). The company assumed vial	The model includes only the costs associated with subsequent treatments, but not effects. There is uncertainty over % use of each treatment for progression-free and progressed disease health states.	EAG base case: based on ADRIATIC trial (CS Table 70) EAG scenario: Based on EAG's clinical advice (see section 4.2.7.4)

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
	sharing for the medicaments and a RDI of 100%.		
Adverse event	Inclusion of AE with more than 2% frequency of Grades 3 or 4 adverse events for both arms in the ADRIATIC trial (see CS B.3.6.3 and CS Table 69)	We agree	No change
End-of-life	Based on TA638 inflating the cost using the Consumer Price Inflation (see CS B.2.6.2.1)	We agree	EAG scenario: Based on Georghiou et al. 2012

Source: Produced by the EAG
Abbreviations: EAG, *External Assessment Group*; PFS, Progression-Free Survival; OS, Overall Survival; TTD, Time to treatment Discontinuation; MMRM, Mixed Models for Repeated Measures; BNF, *British National Formulary*; CS, Company Submission; TA, Technology Appraisal; CAV, Cyclophosphamide, Adriamycin and Vincristine.

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on the EAG critique of the company's model assumption (see Table 32), we performed a range of additional scenario analyses (see Table 33), which are summarised below:

- **Baseline characteristics:** varying -starting age, weight and height by 10% and proportion of females of [redacted]
- **Time horizon:** 10 years
- **Efficacy:** extrapolating PFS and OS curves using all the distributions
- **Treatment effect waning:**
  - Treatment effect capped at three
  - Treatment effect capped at five years
  - Gradual waning of treatment effect from three years (36 months) to five years (60 months)
- **Cure assumption:**
  - No cure assumption
  - Cure fraction of 25%, 50% and 75% combined with a cure timepoint of 3 or 5 years
- **Resource use:** based on EAG expert comments (see section 4.2.7.3, Table 23 and Table 24)
- **Subsequent treatments:** based on EAG expert comments (see section 4.2.7.4, Table 27)
- **End of life:** consider the PSSRU2023 reference, Georghiou et al. 2012 (see section 4.2.7.6, Table 28)[48]

The EAG exploratory scenarios for survival curves had the following results:

- **PFS – durvalumab arm -** ICER varies from £18,993 (Gompertz) to £21,023 (Exponential).
- **PFS – 'watch and wait' arm -** ICER varies from £17,240 (Exponential) to £19,664 (Gompertz).
- **OS – durvalumab arm -** ICER varies from dominated (northwest quadrant for Gompertz, Weibull and Gamma) to £91,351 (Log-logistic).
- **OS – 'watch and wait' arm** - ICER varies from £10,931 (Weibull) to £20,452 (1-knot spline odds).

Table 33 EAG exploratory scenario analysis with commercial arrangement for durvalumab and list price for the remaining drugs using the corrected EAG's economic model

Parameter	Base case	Scenario	Incr. Cost	Incr. QALY	ICER (£/QALY)
EAG corrected company's revised base case with updated commercial arrangement			[redacted]	[redacted]	£19,160
Baseline characteristics					
Starting age (years)	[redacted]	[redacted]	[redacted]	[redacted]	£17,068
		[redacted]	[redacted]	[redacted]	£22,657
Weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	£19,160
		[redacted]	[redacted]	[redacted]	£19,159
Height (cm)	[redacted]	[redacted]	[redacted]	[redacted]	£19,160
		[redacted]	[redacted]	[redacted]	£19,159
Proportion of female	[redacted]	[redacted]	[redacted]	[redacted]	£19,205
Time horizon (years)	38.5	10	[redacted]	[redacted]	£41,684
Clinical effectiveness					
PFS – durvalumab arm	1-knot spline normal	Exponential	[redacted]	[redacted]	£21,023
		Gompertz	[redacted]	[redacted]	£18,993
		2-knot spline hazard	[redacted]	[redacted]	£19,297
PFS – watch and wait arm	1-knot spline normal	Exponential	[redacted]	[redacted]	£17,240
		Gompertz	[redacted]	[redacted]	£19,664
		2-knot spline hazard	[redacted]	[redacted]	£19,197
PFS – both arms	1-knot spline normal	Exponential	[redacted]	[redacted]	£19,089
		Gompertz	[redacted]	[redacted]	£19,496
		2-knot spline hazard	[redacted]	[redacted]	£19,335
OS – durvalumab arm	2-knot spline normal	Weibull	[redacted]	[redacted]	-£67,319 (NW quadrant)
		Log-normal	[redacted]	[redacted]	£64,345

Parameter	Base case	Scenario	Incr. Cost	Incr. QALY	ICER (£/QALY)
		1-knot spline hazard	[redacted]	[redacted]	£32,021
OS – watch and wait arm	2-knot spline normal	Weibull	[redacted]	[redacted]	£10,931
		Log-normal	[redacted]	[redacted]	£13,592
		1-knot spline hazard	[redacted]	[redacted]	£15,687
OS – both arms	2-knot spline normal	Weibull	[redacted]	[redacted]	£41,456
		Log-normal	[redacted]	[redacted]	£27,050
		1-knot spline hazard	[redacted]	[redacted]	£23,391
Treatment effect waning	No treatment effect waning	Treatment effect capped at three years	[redacted]	[redacted]	£209,980
		Treatment effect capped at five years	[redacted]	[redacted]	£98,046
		Treatment effect starts to gradually wane from three years and the effect ceases at five years	[redacted]	[redacted]	£136,595
Cure assumption	Include	Exclude	[redacted]	[redacted]	£19,272
Cure assumption – fraction and timepoint	cure fraction / cure timepoint: 90% / 5 years	25% / 5 years	[redacted]	[redacted]	£19,240
		50% / 5 years	[redacted]	[redacted]	£19,209
		75% / 5 years	[redacted]	[redacted]	£19,178
		25% / 3 years	[redacted]	[redacted]	£19,281
		50% / 3 years	[redacted]	[redacted]	£19,290
		75% / 3 years	[redacted]	[redacted]	£19,299
Resource use and costs					

Parameter	Base case	Scenario	Incr. Cost	Incr. QALY	ICER (£/QALY)
Resource use (frequency per year)	TA798	Clinical expert advice to the EAG	[redacted]	[redacted]	£20,404
Subsequent treatment distribution	Advisory Board opinion to the company	Clinical expert advice to the EAG	[redacted]	[redacted]	£23,925
End-of-life	TA638	Georghiou et al 2012 (£13,314)	[redacted]	[redacted]	£18,812

Source: Produced by the EAG
Abbreviations: EAG, External Assessment Group; PFS, Progression-Free Survival; OS, Overall Survival; TTD, Time to Discontinuation; MMRM, Mixed Models for Repeated Measures; BNF, British National Formulary; CS, Company Submission; TA, Technology Appraisal; CAV, Cyclophosphamide, Adriamycin and Vincristine

6.2 EAG's preferred assumptions

Based on the EAG critique of the company's model discussed in sections 4.2.4.14.2.4 to 4.2.7 , we have identified five key aspects of the company base case with which we disagree. Our preferred model assumptions are as follows:

- Overall survival curves for both the treatments: 1-knot spline hazard (see section 4.2.4.2)
- Progression-free survival curves for both the treatments: generalised gamma (see section 4.2.4.1)
- No cure assumption (see section 4.2.4.3)
- Resource use based on EAG clinical expert advice. For our base case, we use the lower estimates for parameters where a range of values was provided (see section 4.2.7.3)
- Subsequent treatment distribution based on the ADRIATIC trial (see section 4.2.7.4)

Table 34 shows the cumulative cost-effectiveness results for durvalumab versus 'watch and wait' of adding the EAG's preferred model assumptions one at a time to the EAG corrected company's revised base case with the updated commercial arrangement. Including all the EAG's preferred assumptions increases the ICER from £19,160 to £29,396 per QALY.

Table 34 EAG's preferred model assumptions: cumulative change to ICER

Model	Section in EAG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
EAG corrected company revised base-case with updated commercial arrangement	5.3.2	[redacted]	[redacted]	£19,160
EAG preferred assumptions run on the above model version				
+ OS distribution for durvalumab and comparator: 1-knot spline hazard	4.2.4.2	[redacted]	[redacted]	£23,391
+ PFS distribution for durvalumab and comparator: generalised gamma	4.2.4.1	[redacted]	[redacted]	£23,298
+ No cure assumption	4.2.4.3	[redacted]	[redacted]	£23,181
+ Resource use suggested by the EAG clinical advice	4.2.7.3	[redacted]	[redacted]	£24,861
+ Subsequent treatment distribution from the ADRIATIC trial (based on CS Table 70)	4.2.7.4	[redacted]	[redacted]	£29,396
EAG preferred base case		[redacted]	[redacted]	**£29,396**

Source: Produced by the EAG

We re-ran the probabilistic sensitivity analysis (PSA) on the EAG base case model. The cost-effectiveness scatterplot is shown in Figure 15. The probabilistic results are aligned with the deterministic results (see Table 35), with a 7.6% difference in the ICER.

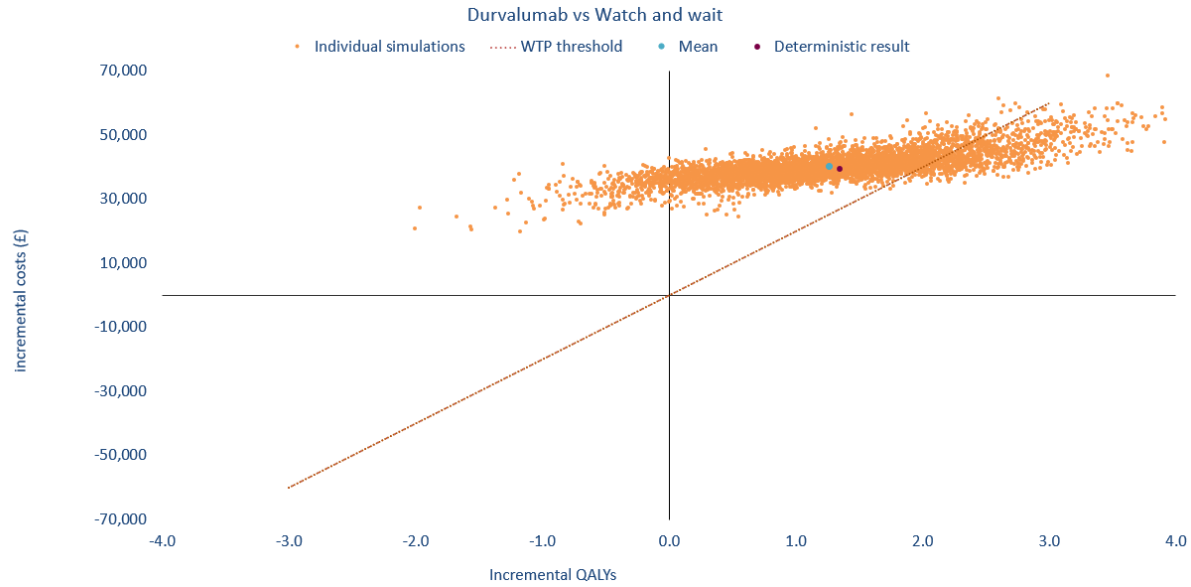

Figure 15 PSA scatterplot graph for durvalumab vs watch and wait using EAG preferred assumptions

Source: EAG preferred assumptions based on the corrected company's' economic model
Abbreviation: PSA: probabilistic sensitivity analysis, QALY Quality-adjusted life year, WTP: willingness to pay

Table 35 Probabilistic sensitivity analysis results with commercial arrangement price for durvalumab – EAG base case

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER (£/QALY)	NMB (£) for a WTP of £30,000
Watch and wait	[redacted]	[redacted]	[redacted]	£31,629	-£2,062
Durvalumab	[redacted]	[redacted]	[redacted]		
Increment	[redacted]	[redacted]	[redacted]		

Source: Produced by the EAG from the corrected company's economic model
Abbreviations: LYG, Life-year gained; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio; NMB, Net Monetary Benefit; WTP, Willingness to pay
[a] Discounted at 3.5% per year, with no severity modifier applied to QALYs

6.3 Scenario analysis

We performed a range of scenarios analyses on the EAG preferred base case to analyse the impact of changing some of the model assumptions. We have grouped these scenarios into three categories:

- Company base case assumptions that were modified in the EAG preferred analysis
- Selection of relevant company scenarios described in section 5.2.2
- Selection of relevant EAG exploratory scenarios described in section 6.1

Table 36 below summarises the results of the scenarios conducted on the EAG preferred base case. The ICER varied between £24,861 (subsequent treatment distribution – key opinion leaders, based on CS Table 71) and £253,707 (treatment effect capped at three years). The scenarios that have the most significant effect on the cost-effectiveness are:

- **Selection of OS curve**- the ICER varied between £25,102 (2-knot spline normal, company assumption) and £42,533 (Gompertz, worst fit) per QALY
- **Distribution of subsequent treatment-** the ICER varied between £24,861 (key opinion leaders, company assumption) and £32,478 (clinical advice to the EAG) per QALY
- **Treatment effect waning-** the ICER varied between £121,944 (treatment effect capped at five years) and £253,707 (treatment effect capped at three years) per QALY

Table 36 Scenario analyses conducted on the EAG preferred base case with updated commercial arrangement price for durvalumab and list price for the remaining drugs

Scenario	Scenario	Incr. Cost (£)	Incr. QALYs	ICER (£/QALY)
EAG Base case		[redacted]	[redacted]	£29,396
Company base case assumptions				
OS distribution for both arms: 1-knot spline hazard	2-knot spline normal for both arms	[redacted]	[redacted]	£25,102
PFS distribution for both arms: generalised gamma	1-knot spline normal for both arms	[redacted]	[redacted]	£29,234
No cure assumption	Cure fraction 90%, and cure timepoint of 60 months for both arms	[redacted]	[redacted]	£28,601
Resource use suggested by the EAG clinical advice	CS Tables 67 and 68	[redacted]	[redacted]	£27,716
Subsequent treatment distribution from	Key opinion leaders' assumption (ADRIATIC Advisor Board report).	[redacted]	[redacted]	£24,861

Scenario	Scenario	Incr. Cost (£)	Incr. QALYs	ICER (£/QALY)
ADRIATIC data (CS Table 70)				
Selected company scenarios presented in the submission				
OS distribution for durvalumab and comparator: 1-knot spline hazard	2-knot splice odds	[redacted]	[redacted]	£26,112
Health state utility values: [redacted]	PF: [redacted] PD: [redacted]	[redacted]	[redacted]	£29,426
	PF: [redacted] PD: [redacted]	[redacted]	[redacted]	£29,422
	PF: [redacted] PD: [redacted]	[redacted]	[redacted]	£29,516
Vial sharing: Included	Excluded	[redacted]	[redacted]	£29,392
EAG selected scenarios				
OS distribution for both arms: 1-knot spline hazard	Gompertz (worst fit)	[redacted]	[redacted]	£42,533
	Log-normal (Best BIC fit)	[redacted]	[redacted]	£33,712
	1-knot spline odds	[redacted]	[redacted]	£31,372
	Generalised gamma	[redacted]	[redacted]	£35,552
PFS distribution for both arms: generalised gamma	Exponential (worst fit)	[redacted]	[redacted]	£35,094
	3-knot spline hazard	[redacted]	[redacted]	£29,625
	2-knot spline normal	[redacted]	[redacted]	£29,492
	3-knot spline odds	[redacted]	[redacted]	£29,449
No treatment effect waning	Treatment effect capped at three years	[redacted]	[redacted]	£253,707
	Treatment effect capped at five years	[redacted]	[redacted]	£121,994
	Treatment effect starts to wane from three years and the effect ceases in five years	[redacted]	[redacted]	£166,294

Scenario	Scenario	Incr. Cost (£)	Incr. QALYs	ICER (£/QALY)
Subsequent treatment distribution from the ADRIATIC trial (CS Table 70)	Subsequent treatment distribution suggested by the EAG clinical advice (Table 27)	[redacted]	[redacted]	£32,478
Resource use suggested by the EAG clinical advice	Consider that the resource use for the 'watch and wait' arm (PF health state) is equal to the durvalumab off-treatment (Table 23)	[redacted]	[redacted]	£29,281
Resource use suggested by the EAG clinical advice	Consider the middle range value in the resource use for the PF and PD health states (Table 23 and Table 24)	[redacted]	[redacted]	£29,440
Resource use suggested by the EAG clinical advice	Consider the upper range value in the resource use for the PF and PD health states (Table 23 and Table 24)	[redacted]	[redacted]	£29,485

Source: Produced by the EAG

6.4 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost-effectiveness of durvalumab compared to "wait & watch" for patients with LS-SCLC whose disease has not progressed following CRT. The model included characteristics of the patients with LS-SCLC who were included in the ADRIATIC trial, who had all previously received cCRT. The focus of the company submission and therefore this report, is on the patients who received cCRT.

The EAG considers the structure of the model to be appropriate and consistent with previous cost-effectiveness models for SCLC. The company made some corrections and changes to the model in response to clarification questions. The EAG identified a set of errors in the company's revised model, which we corrected. Incorporating these corrections changed the company's revised base case ICER to £19,160

[redacted]

The EAG identified a set of assumptions and input parameter values that we prefer to those used in the company's revised base case analysis. See Table 32 for a description of and justification for these assumptions. The EAG's preferred assumptions increased the ICER for durvalumab versus 'watch and wait' from £19,160 (EAG corrected company revised base case) to £29,396 per QALY. The results are most sensitive to changes in the overall survival curve for durvalumab, the resource use for each health state and the subsequent treatment distribution.

The key uncertainties regarding the cost-effectiveness of durvalumab are:

- selection of survival curves for extrapolation of overall survival (see section 4.2.4.2)
- applying a cure assumption to the OS and PFS curves of both the treatment arms (see section 4.2.4.3)
- resource use for progression-free and progressed disease health states (see section 4.2.7.3)
- distribution of each subsequent treatment for progression-free and progressed disease health states (see section 4.2.7.4)
- assumption surrounding treatment effect waning (see section 4.2.5)

To assess the impact of the above uncertainties on the overall cost-effectiveness results, the EAG performed a range of scenarios analyses on our preferred base case (shown in Table 36). The ICERs obtained from these scenarios varied between £24,861 (subsequent treatment distribution – key opinion leaders, based on CS Table 71) and £253,707 (treatment effect capped at three years).

7 REFERENCES

1. Ambrosini V, Nicolini S, Caroli P, et al. PET/CT imaging in different types of lung cancer: An overview. *European Journal of Radiology* 2012;81(5):988-1001.

2. Khakwani A, Rich AL, Tata LJ, al. e. Small-cell lung cancer in England: trends in survival and chemotherapy using the National Lung Cancer Audit. *PLoS One* 2014;9(2):e89426.

3. National Lung Cancer Audit. *The National Lung Cancer Audit. Data and statistics (for 2022)*. https://www.lungcanceraudit.org.uk/data/

4. BMJ Best Practice. *Small Cell Lung Cancer*. https://bestpractice.bmj.com/topics/en-gb/1081 (accessed 11/02/2025).

5. Simon GR, Turrisi A. Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:324S-39S.

6. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. *Nature Reviews Disease Primers* 2021;7(1):3.

7. Pickett K, Hawa A, Cooper K, et al. Tarlatamab for previously treated advanced small-cell lung cancer. A single Technology Appraisal: Southampton Health Technology Assessments Centre, 2024.

8. Salem A, Mistry H, Hatton M, al. e. Association of Chemoradiotherapy With Outcomes Among Patients With Stage I to II vs Stage III Small Cell Lung Cancer. Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncology* 2019;5(3):e185335.

9. Cancer Research UK. *Durvalumab (Imfinzi)*. https://www.cancerresearchuk.org/about-cancer/treatment/drugs/durvalumab (accessed 11/02/2025).

10. AstraZeneca. Data on file. Durvalumab (IMFINZI) draft Summary of Product Characteristics. 2024.

11. National Institute for Health and Care Excellence. *Lung cancer: diagnosis and management. NICE guideline [NG122]. Published: 28 March 2019. Last updated: 08 March 2024*. https://www.nice.org.uk/guidance/ng122 (accessed October 2024).

12. National Institute for Health and Care Excellence. Topotecan for the treatment of relapsed small-cell lung cancer. Technology appraisal guidance. TA184. Published: 25 November 2009. https://www.nice.org.uk/guidance/ta184 (accessed October 2024).

13. Cheng Y, Spigel DR, Cho BC, et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. *New England Journal of Medicine* 2024.

14. ClinicalTrials.gov. Study of Durvalumab + Tremelimumab, Durvalumab, and Placebo in Limited Stage Small-Cell Lung Cancer in Patients Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC). https://clinicaltrials.gov/study/NCT03703297 (accessed October 2024).

15. AstraZeneca. Data on file. Clinical Study Report Appendix 16.1.1. Protocol and Protocol Amendments. A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Stage I-III Limited Disease Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC). 2018.

16. Spigel DR, Cheng Y, Cho BC, et al. ADRIATIC: Durvalumab (D) as consolidation treatment (tx) for patients (pts) with limited-stage small-cell lung cancer (LS-SCLC): American Society of Clinical Oncology, 2024.

17. National Institute for Health and Care Excellence. Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation. Technology appraisal guidance. TA798. Published: 22 June 2022. Available at: *https://www.nice.org.uk/guidance/ta798* (Accessed October 2024).

18. National Institute for Health and Care Excellence. Single Technology Appraisal. TA638. Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID1504]. Committee Papers. 2020. Available at: *https://www.nice.org.uk/guidance/ta638/documents/committee-papers* (Accessed November 2024).

19. Delgado A, Kumar Guddati A. Clinical endpoints in oncology - a primer. *American Journal of Cancer Research* 2021;11(4):1121-31.

20. EORTC Quality of Life. *EORTC QLQ-C30*. https://qol.eortc.org/questionnaires/core/eortc-qlq-c30/ (accessed 10/03/2025).

21. Bergman B, Aaronson NK, Ahmedzai S, et al. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur J Cancer* 1994;30A(5):635-42.

22. Coon CD, Schlichting M, Zhang X. Interpreting Within-Patient Changes on the EORTC QLQ-C30 and EORTC QLQ-LC13. *Patient* 2022;15(6):691-702.

23. National Cancer Institute DoCCaPS. *Overview (PRO-CTCAE)*. https://healthcaredelivery.cancer.gov/pro-ctcae/overview.html (accessed 10/03/2025).

24. Euroqol. *EQ-5D-5L*. https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/ (accessed 10/03/2025).

25. EQ-5D. EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument: EuroQol Research Foundation, 2021.

26. AstraZeneca. Data on file. Statistical Analysis Plan. A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC). 2023.

27. AstraZeneca. Data on file. Interim Clinical Study Report. A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC). 2024.

28. Bell Gorrod H, Latimer N, Abrams KR. NICE DSU Technical Support Document 24: Adjusting survival time estimates in the presence of treatment switching: An update to TSD 16, 2024.

29. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *The Lancet Oncology* 2017;18(8):1116-25.

30. Walls GM, Mistry H, Barlesi F, et al. Long-term outcomes after concurrent once-or twice-daily chemoradiation in limited-stage small-cell lung cancer: a brief report from the CONVERT trial: Elsevier, 2024.

31. Bogart J, Wang X, Masters G, et al. High-Dose Once-Daily Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: CALGB 30610 (Alliance)/RTOG 0538. *Journal of Clinical Oncology* 2023;41(13):2394-402.

32. Rutherford MJ, Lambert PC, Sweeting MJ, et al. NICE DSU technical support document 21: flexible methods for survival analysis. *Decision Support Unit, ScHARR, University of Sheffield* 2020.

33. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. NICE process and methods [PMG36]. Published: 31 January 2022. Last updated: 31 October 2023. Available at: *https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation#measuring-and-valuing-health-effects-in-cost-utility-analyses* (Accessed November 2024).

34. Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. *Pharmacoeconomics* 2023;41(2):199-207.

35. Hernández-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: the switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. *Journal of Health Economics* 2017;55:139-52.

36. Mehra R, Yong C, Seal B, et al. Cost-effectiveness of durvalumab after chemoradiotherapy in unresectable stage III NSCLC: a US healthcare perspective. *Journal of the National Comprehensive Cancer Network* 2021;19(2):153-62.

37. Alava MH, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. 2022.

38. Kuehne N, Hueniken K, Xu M, et al. Longitudinal Assessment of Health Utility Scores, Symptoms and Toxicities in Patients with Small Cell Lung Cancer Using Real World Data. *Clinical Lung Cancer* 2022;23(2):e154-e64.

39. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *The Lancet* 2019;394(10212):1929-39.

40. National Institute for Health and Care Excellence. British National Formulary (BNF). Available at: *https://bnf.nice.org.uk/* (Accessed November 2024).

41. England NHS. 2022/23 National Cost Collection data. 2024. Available at: *https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/*. (Accessed November 2024).

42. United Kingdom G. Guidance. Drugs and pharmaceutical electronic market information tool (eMIT). Available at: *https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit* (Accessed November 2024).

43. National Institute for Health and Care Excellence. British National Formulary. Carboplatin [Specialist drug]. Medicinal forms. Available at: https://bnf.nice.org.uk/drugs/carboplatin-specialist-drug/medicinal-forms/ (Accessed November 2024).

44. AstraZeneca. Data on file. AstraZeneca UK MC: KEE input (advisory board) on limited-stage small cell lung cancer (durvalumab). ID: REF- 254603. November 2024.

45. National Institute for Health and Care Excellence. Single Technology Appraisal. Tarlatamab for previously treated advanced small-cell lung cancer [ID6364]. Committee Papers. 2025. Available at: *https://www.nice.org.uk/guidance/indevelopment/gid-ta11423* (Accessed March 2025). https://www.nice.org.uk/guidance/indevelopment/gid-ta11423.

46. National Institute for Health and Care Excellence. Nivolumab for previously treated non-squamous non-small-cell lung cancer. Technology appraisal guidance. TA484. Published: 01 November 2017. Available at: *https://www.nice.org.uk/guidance/ta484* (Accessed November 2024).

47. Jones KC, Weatherly H, Birch S, et al. Unit costs of health and social care 2022 manual. 2023.

48. Georghiou T, Davies S, Davies A, Bardsley M. Understanding patterns of health and social care at the end of life: Nuffield Trust, 2012:57.

49. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. *Palliative Medicine* 2015;29(10):9.

8 APPENDICES

Appendix 1 EAG's critical appraisal of the methodology of the company's systematic review

Table 37 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The review question was not presented. However, the PICOD framework used to structure the study eligibility criteria for the review is described in CS Appendix D.1.2.
Were appropriate sources of literature searched?	Yes	Healthcare databases (including MEDLINE, Embase, CENTRAL, CDRS, CMR, DARE, ACP Journal Club, International HTA Database and NHS EED), conferences, clinical trial registries and references lists of evidence syntheses were searched (CS Appendices D.1.1.1 and D.1.1.2).
What time period did the searches span and was this appropriate?	Yes	Healthcare databases were searched from inception to 7th June 2024 (CS Appendix D.1.1.1) and conferences were searched from 2022 (CS section D.1.1.1 and D.1.2). The searches were marginally out-of-date when the CS was received by the EAG (7 months old). The EAG ran the company's MEDLINE search with a date limit from June 2024 and did not identify any additional relevant RCTs.
Were appropriate search terms used and combined correctly?	Unclear	The only concern the EAG has about the search terms is that different, less broad non-RCT terms were used in the Embase searches compared to the MEDLINE searches (CS Appendix D.1.1). It is unclear why this is the case. This may present a

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
		risk that relevant non-RCT studies could have been missed.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	The study eligibility criteria are supplied in CS Appendix Table 2 and are relevant to the decision problem. However, any studies identified of patients who are receiving or who have received sCRT were not considered for data extraction (CS Appendix D.1.2). The company states in clarification responses A3 and A4 that none of the publications identified in relation to this population mentioned durvalumab in the abstract or they were published prior to durvalumab becoming available.
Were study selection criteria applied by two or more reviewers independently?	Yes	Title/abstract screening and full text screening were undertaken by two independent reviewers (CS Appendix D.1.2)
Was data extraction performed by two or more reviewers independently?	Yes	Data were extracted by one reviewer and checked by another (CS Appendix D.1.2). While data extraction was not carried out independently by two reviewers, the EAG considers the company's approach acceptable.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The company used the Cochrane risk-of-bias (ROB) 2 tool to assess the risk of bias of the identified RCT (CS Appendix D.1.2).
Was risk of bias assessment (or other study quality assessment) conducted by	Yes	CS Appendix D.1.2 states that this was carried out in a "double-blind manner".

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
two or more reviewers independently?		
Is sufficient detail on the individual studies presented?	Yes	One relevant trial was identified and details about the trial methodology, participant characteristics, statistical analysis and results are provided in CS sections B.2.2, B.2.3.1, B.2.3.2, B.2.4 and B.2.6, respectively.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	N/A	No meta-analysis or ITC was undertaken.

Source: EAG created table.
ACP, American College of Physicians; CDRS, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CMR, Cochrane Methodology Register; CS, company submission; DARE, Database of Abstracts of Reviews of Effects; EAG, External Assessment Group; HTA, Health Technology Assessment; ITC, indirect treatment comparison; NHS EED, National Health Service Economic Evaluation Database; PICOD, population, intervention, comparator, outcomes, and study design; RCT(s), randomised controlled trial(s); ROB, risk of bias; sCRT, sequential chemoradiotherapy.

Appendix 2 List of the ADRIATRIC trial key participant inclusion criteria, with comments from the EAG's clinical experts

Table 38 ADRIATIC trial key participant inclusion criteria

Key inclusion criteria	EAG's clinical experts' comments
• Age ≥18 years at time of screening; for patients aged <20 years and enrolled in Japan, a written informed consent was obtained from the patient and their legally acceptable representative	• We did not ask our experts to comment on this.
• Have histologically and/or cytologically documented LS-SCLC (Stage I to III SCLC) according to the AJCC Staging Manual or the IASLC Staging Manual in Thoracic Oncology. • Patients who were Stage I or II had to be medically inoperable as determined by the investigator	• No comments
• Have an WHO/ECOG PS of 0 or 1 at enrolment and randomisation	• One expert commented that patients who have previously received sCRT do not tend to have a PS of 0 or 1. The other expert commented that they would expect to see higher PS scores in practice as sCRT is given to patients who are less fit and who have very large tumour burden that cannot be treated safely with cCRT.
• Received four cycles of first-line cCRT consisting of platinum-based therapy plus etoposide	• No comments
• No progression after the receipt of definitive cCRT: • 4 cycles of platinum-based cCRT completed within 1 to 42 days prior to randomisation and the first dose of IP	• One expert noted that in practice carboplatin and etoposide are used intravenously on day 1 and

Key inclusion criteria	EAG's clinical experts' comments
• The chemotherapy regimen had to contain platinum and IV etoposide, administered as per local standard-of-care regimens • Received a total dose of radiation of 60 to 66 Gy over 6 weeks for standard QD radiation schedules or 45 Gy over 3 weeks for hyperfractionated BID radiation schedules. Sites were encouraged to adhere to mean organ radiation dosing as follows: i) Mean lung dose <20 Gy and/or V20 <35%, ii) Heart V50 <25% • RT had to have commenced no later than the end of Cycle 2 of chemotherapy • Receipt of 3 cycles of platinum-based cCRT was permitted if the patient had achieved disease control and in the opinion of the Investigator, no additional benefit would be expected with additional cycle of chemotherapy	then etoposide is given orally on days 2 and 3. • One expert commented that in clinical practice, in cCRT, the aim is to start RT alongside chemotherapy in Cycle 2 of chemotherapy. • One expert said that in practice, if the timing between CRT and receipt of durvalumab were to be 1 to 42 days, it might mean that fewer people will receive PCI because it would be difficult to deliver as time is needed to image patients, give PCI and for patients to recover

Source: Reproduced from CS Table 5 with comments from the EAG's clinical experts added.
AJCC, American Joint Committee on Cancer; BID, twice daily; cCRT, Concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; Gy, Gray; IASLC, International Association for the Study of Lung Cancer; IP, investigational product; IV, intravenous; LS-SCLC, limited stage small cell lung cancer; PCI, prophylactic cranial irradiation; PS, performance status; QD, once daily; RT, radiotherapy; SCLC, small cell lung cancer; sCRT, sequential chemoradiotherapy; WHO, World Health Organization.

Appendix 3 Critical appraisal assessment of the ADRIATIC trial

Table 39 Comparison of the company and EAG's critical appraisal of the ADRIATIC trial

Question	Company response	Company comments	EAG response	EAG comments
Was randomisation carried out appropriately?	Yes	Randomisation was carried out in a 1:1:1 fashion by IVRS/IWRS	Yes	Randomisation was stratified with one list for each stratum. All centres used the same list. We assume the randomisation sequence was determined by computer as part of the IVRS/IWRS.
Was the concealment of treatment allocation adequate?	Yes	Study was double-blind; the patients, investigator and study centre staff were blinded to the durvalumab/placebo allocation. For durvalumab and placebo, the IV bag was covered with a translucent or opaque sleeve after preparation by an unblinded third party pharmacist.	Yes	CS. B.2.3.1.6.1 states that *"Randomisation codes were assigned strictly sequentially, within each stratum, as patients became eligible for randomisation."* This suggests that the randomisation sequence was determined centrally, in a fixed order which participating sites had no involvement in and no knowledge of the sequence. This reduces the risk of any potential investigator prioritising patients with certain characteristics to be the next in line for randomisation and receive the treatment that they wish them to receive.

Question	Company response	Company comments	EAG response	EAG comments
				The company's comment may not necessarily be in relation to concealment of allocation but seems to describe maintaining blinding once a patient has been randomised.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline patient characteristics were generally well balanced between treatment groups, including ECOG PS, disease status, and PD-L1 expression.	Yes	The CS reports (Section B.2.3.2.2) there were two disease characteristics with >5% difference between trial arms at baseline. Notably, there were more patients with locally advanced disease involving the lymph nodes at study entry as assessed by the Investigator in the durvalumab group compared with placebo (63.6% vs 36.8%). The CS does not discuss what implications this may have for the study results and conclusions.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	The study was double-blind; the patients, Investigator and study centre staff were blinded to the durvalumab/placebo allocation. To maintain the blind, an otherwise	Yes	Investigator blinding was possible because they had no involvement in reconstitution and dispensing of treatments. Patient blinding was possible through the use of placebo infusions (NB. The CS does not state what solution was used for placebo infusion and whether this was identical in appearance to the durvalumab

Question	Company response	Company comments	EAG response	EAG comments
		uninvolved third-party pharmacist unblinded to the durvalumab/placebo prepared the durvalumab/placebo infusion as specified by the randomisation and IVRS. The IVRS/IWRS provided the kit identification number to the unblinded pharmacist.		infusion; the trial CSR states, [redacted]
Were there any unexpected imbalances in drop-outs between groups?	No	At the time of the interim analysis (15th January 2024 DCO) 175 patients in the durvalumab monotherapy group had discontinued durvalumab and 124 patients had terminated the study. In the placebo group, 195 patients had discontinued placebo, and 140 patients had terminated the study.	No	There were no unexpected imbalances in drop-outs or reasons for drop-out between the durvalumab and placebo arms (CS Appendix Figure 2).

Question	Company response	Company comments	EAG response	EAG comments
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The primary and key secondary outcomes listed in the methodology section are consistent with those reported in the results section.	No	The EAG has not identified any outcomes for which results were not reported.
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	Analyses in the overall population were conducted on the FAS (i.e., ITT), comprising all patients randomised to treatment. The analysis included patients who were randomised but did not go on to receive treatment. Patients were considered lost to follow-up if no contact has been established by the time the study was complete. Investigators documented all attempts to re-establish	Yes	All outcomes were analysed in the FAS population, which is akin to an ITT analysis. OS and PFS censoring rules appear appropriate.

Question	Company response	Company comments	EAG response	EAG comments
		contact with missing patients. Procedures for accounting for missing, unused, and spurious data are described in the SAP.		

Source: Reproduced from CS Table 15 with added EAG comments. Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).
Abbreviations: DCO data cut-off; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IEC, independent ethics committee; IRB, institutional review board; ITT, intention-to-treat; IV, intravenous; IVRS/IWRS, interactive voice response system/interactive web response system; PD-L1, programmed cell death-ligand 1; PS, performance status; SAP, statistical analysis plan.