Single Technology Appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from AstraZeneca:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation
   b. Association of Respiratory Nurses
   c. British Thoracic Oncology Group

4. **Expert statements from:**
   a. Dr Louise Lim, Consultant Medical Oncologist – clinical expert nominated by AstraZeneca
   b. Dr Thomas Newsom-Davis, Consultant Medical Oncologist – clinical expert nominated by British Thoracic Oncology Group

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre

6. **External Assessment Report addendum** – results of additional scenario analyses

7. **External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Document B

Company evidence submission

December 2024

File name	Version	Contains confidential information	Date
ID5073_Durvalumab in LS-SCLC_DocB_4Dec2024_Redacted	1.0	Yes	4 December 2024

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Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AEPI	Adverse event of potential interest
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
cCRT	Chemotherapy concurrent with radiotherapy
CD80	Cluster of differentiation 80
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
cORR	Confirmed objective response rate
CPI	Consumer Price Inflation
CR	Complete response
CRF	Case report form
CRT	Chemoradiation therapy
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOL	End of life
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	EuroQoL five dimensions five levels
ESMO	European Society for Medical Oncology
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive-stage small-cell lung cancer
EU	European Union
FAS	Full analysis set
GHS	Global Health Score
HCRU	Health care resource utilisation
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IF	Information fraction
imAE	Immune-mediated adverse event
IO	Immune-oncology
IP	Investigational product
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous

IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LCHP	Log-cumulative hazard plots
LS-SCLC	Limited-stage small cell lung cancer
LY	Life-year
LYG	Life-year gained
mAb	Monoclonal antibody
MMRM	Mixed model repeat measurement
MoA	Mechanism/mode of action
MRI	Magnetic resonance imaging
N/A	Not applicable
nAb	Neutralising antibody
NCCN	National Comprehensive Cancer Network
NG	NICE guideline
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reached
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OS24	Proportion of patients alive at 24 months from randomisation
OS36	Proportion of patients alive at 36 months from randomisation
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PF	Progression-free
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
PGIS	Patient Global Impressions Severity
PHA	Proportional hazards assumption
PK	Pharmacokinetics
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once-daily
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
RT	Radiotherapy
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCLC	Small-cell lung cancer
sCRT	Subsequent chemoradiotherapy
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics

SoC	Standard of care
STA	Single technology appraisal
TA	Technology appraisal
TC	Tumour cell
TEAE	Treatment-emergent adverse event
TMB	Tumour mutational burden
TNM	Tumour, node, and metastasis
TRAE	Treatment-related
TSD	Technical support document
TTD	Time to treatment discontinuation
TTDM	Time to death or distant metastasis
UK	United Kingdom
USA	United States of America
VALG	Veterans Administration Lung Study Group
VAS	Visual analogue score
WHO	World Health Organization
WTP	Willingness-to-pay

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

B.1.1 Decision problem

The objective of this single technology appraisal (STA) is to evaluate the clinical and cost-effectiveness of durvalumab monotherapy ('durvalumab') for the treatment of adults with limited-stage small-cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation (CRT) therapy.

The submission covers the technology's anticipated full marketing authorisation for this indication and is in line with the scope issued by the National Institute for Health and Care Excellence (NICE).

Table 1 summarises the decision problem addressed by the company submission.

Table 1: The decision problem

Criteria	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with limited-stage SCLC whose disease has not progressed after chemoradiotherapy	As per Final scope	NA
Intervention	Durvalumab	As per Final scope	NA
Comparators	Established clinical management without durvalumab maintenance: • Active monitoring	As per Final scope	NA
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
Subgroups	If the evidence allows the following subgroups may be considered: • PD-L1 expression • Disease stage • Concurrent (cCRT) or sequential chemoradiation	Pre-planned subgroup analyses of OS and PFS were performed for disease status, receipt of prophylactic cranial irradiation, primary tumour location, time 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 performed for PD-L1 status only.	There are no subgroups within the population that should be considered separately. Clinical data from the ADRIATIC trial demonstrates a consistent treatment effect for durvalumab across the trial population.[1, 2]

Criteria	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	As per Final scope	NA
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

Abbreviations: cCRT, concurrent chemoradiation; NA. not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; SCLC, small-cell lung cancer.

B.1.2 Description of the technology being evaluated

Details of the technology being appraised in the submission are provided in Table 2.

Note on convention: Please note that durvalumab monotherapy, which is the focus of this submission, is referred to as 'durvalumab' from this point forward in the document.

The summary of product characteristics (SmPC) for durvalumab is provided in Appendix C.

Table 2: The technology being evaluated

UK approved name and brand name	Durvalumab (IMFINZI®)
Mechanism of action	Durvalumab is a high-affinity, human, recombinant IgG1κ mAb that selectively blocks the interaction of PD-L1 with receptors PD-1 and CD80.[3] In doing so, it releases the inhibition of immune responses in the tumour microenvironment, resulting in prolonged T-cell activation and anti-tumour activity.
Marketing authorisation/CE mark status	A regulatory submission to the MHRA for durvalumab in LS-SCLC is planned for [redacted], and a marketing authorisation is anticipated in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	***Indication covered in this submission:*** The anticipated indication for durvalumab is for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based CRT.[4] ***Existing indications:*** • Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.[5] • Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).[6] • Durvalumab in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer (BTC).[7] • Durvalumab in combination with tremelimumab is indicated for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).[4] • Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, is indicated for the treatment of adults with resectable (tumours ≥4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.[8]
Method of administration and dosage	Durvalumab 1,500 mg intravenously Q4W until disease progression, intolerable toxicity, or a maximum of 24 months, whichever occurs first.

Additional tests or investigations	No additional tests or investigations outside current practice are expected.
Acquisition cost (including VAT)	Durvalumab is commercially available as a 120 mg vial at a list price of £592 and as a 500 mg vial at a list price of £2,466.[9]
Patient access scheme (if applicable)	Durvalumab has an [redacted] resulting in a [redacted] for consideration in this appraisal.

Abbreviations: ALK, anaplastic lymphoma kinase; BTC, biliary tract cancer; CD, cluster of differentiation; CRT, chemoradiation therapy; EGFR, epidermal growth factor receptor; ES-SCLC, extensive-stage small-cell lung cancer; HCC, hepatocellular carcinoma; IgG1κ, immunoglobulin G1 kappa; LS-SCLC, limited-stage small-cell lung cancer; mAb, monoclonal antibody; MHRA, Medicines and Healthcare Products Regulatory Agency; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein-1, PD-L1, programmed cell death-ligand 1; Q4W, every 4 weeks.

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

- **Limited-stage small-cell lung cancer (LS-SCLC) is a form of small-cell lung cancer (SCLC) where the cancer is contained in a single area that can be treated with radiotherapy[10]**
- **Approximately 30% of patients with SCLC are diagnosed with LS-SCLC[11-13] and these patients have a poor prognosis:**
  - Patients with LS-SCLC have and estimated 5-year overall survival (OS) rate of 29–34% and a median OS of 25–30 months[14-16]
  - Progression-free survival in patients with LS-SCLC is typically 13.5–15.5 months[14-16]
- **In the United Kingdom, the current standard of care (SoC) in LS-SCLC is platinum-based chemoradiation therapy (CRT), where chemotherapy is delivered concurrently (cCRT) or sequentially (sCRT) with twice-daily radiotherapy**
- **UK clinicians confirmed that achieving functional cure is a core goal of disease management in LS-SCLC. UK clinicians confirmed that the majority (90%) of patients who remain progression-free for 3–5 years following CRT have a low risk of disease progression and can be considered to have achieved functional cure**[17-19]
- **However, despite the curative intent of current treatment options, ~75% of patients with locally advanced disease experience disease progression within two years of treatment:[20]**

  - There are currently very few second-line therapeutic options available for patients following relapse[18, 19]
  - Response rates to second-line chemotherapy are approximately 20–30% for patients with a treatment free interval ≥3 months, and 15% for those with a treatment-free interval of <3 months[21]
- **Furthermore, there has been no meaningful innovation in LS-SCLC SoC for decades,[13] leaving patients underserved with limited systemic treatment options**
- **Durvalumab is anticipated for use as the first targeted therapy following CRT in patients with LS-SCLC and would represent a paradigm shift in LS-SCLC management, establishing a new SoC in this underserved population with limited treatment options that have not evolved in decades**

B.1.3.1 Disease overview

Lung cancer is the most frequently diagnosed cancer worldwide, resulting in an estimated figure of 2.5 million new cases and 1.8 million deaths globally in 2022.[22] In the United Kingdom (UK), there were approximately 49,000 new cases of lung cancer between 2017 and 2019, with approximately 35,000 deaths reported for the same period.[23] Lung cancer can be divided into two main groups: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).[24] Small-cell lung cancer is a highly aggressive neuroendocrine carcinoma with poor prognosis,[20, 25] comprising approximately 15% of all lung cancers.[11, 12, 20] In England, approximately 3,400 newly diagnosed cases of SCLC were registered in 2021.[26]

Small-cell lung cancer is classified by the Veterans Administration Lung Study Group (VALG) staging (VA staging) system into limited-stage (LS-SCLC), where the cancer is contained in a single area that can be treated with radiotherapy (one lung and/or nearby lymph nodes), or extensive-stage (ES-SCLC), where the disease has spread beyond a single area that can be treated with radiotherapy (to the other lung or more distant parts of the body).[10] Small-cell lung cancer can also be classified using the Tumour, Node, Metastasis (TNM) staging system, which provides a more detailed assessment of the spread of the disease and is preferred by the American Joint Committee on Cancer (AJCC).[10, 20] Limited-stage small-cell lung cancer generally corresponds to TNM Stage 1–3, and ES-SCLC to TNM Stage 4.[10] Among patients

presenting with SCLC, approximately 30% are diagnosed with LS-SCLC and the reminder diagnosed with ES-SCLC.[11-13] Patients with LS-SCLC have a poor prognosis, with an estimated 5-year overall survival (OS) rate of 29–34% and a median OS of 25–30 months.[14-16] Progression-free survival (PFS) is typically 13.5–15.5 months with current treatment;[14-16] however, ~75% of patients with locally advanced disease experience disease progression within two years of treatment.[20] Despite this, a proportion of patients with LS-SCLC do achieve cure with current standard of care (SoC). This was validated by UK clinicians who confirmed that the majority (90%) of patients who remain progression-free for 3-5 years following CRT have a low risk of recurrence and can be considered to have achieved functional cure.[17]

B.1.3.2 Burden of disease to patients and society

B.1.3.2.1 Clinical burden

Small-cell lung cancer is the most aggressive form of lung cancer, characterised by rapid proliferation, early widespread metastasis, and poor prognosis (see Section B.1.3.4).[13, 20] Most patients are symptomatic at presentation due to rapid tumour growth, resulting in cough, dyspnoea (difficulty breathing), haemoptysis (coughing up blood), and dysphagia (difficulty swallowing).[12, 20] Distant spread may also result in fatigue, anorexia (appetite loss), weight loss, and neurological complaints.[12, 20] In patients with LS-SCLC, the most common metastatic sites include the contralateral lung, brain, liver, bone, bone marrow, and adrenal glands.[12, 20] Brain metastases are particularly common in SCLC, occurring in ~10% of patients at presentation and developing subsequently in a further 40–50% of patients.[20]

As described in Section B.1.3.1, patients with LS-SCLC have a poor prognosis, with a median OS of 25–30 months.[14-16] Nevertheless, clinical experts confirmed that some patients have the potential to achieve functional cure.[17] The majority (90%) of patients who remain progression-free for 3-5 years or longer following CRT have a low risk of recurrence and can be considered to have achieved functional cure[17]. However, despite treatment for LS-SCLC being given with curative intent and an initial therapy response of approximately 90%,[27] there is a high risk of disease relapse, with the majority of patients (~75%) with locally advanced disease experiencing disease recurrence within two years of treatment.[20]

One reason for the poor survival in patients with LS-SCLC is that once the disease progresses, few treatment options are available, and patients are no longer amenable to treatment with curative intent (Section B.1.3.3 and Section B.1.3.4). Patients who are able to tolerate treatment may be considered for a rechallenge with platinum-based chemotherapy or an alternative chemotherapy regimen. In such cases, response rates to second-line chemotherapy are approximately 20–30% for patients with a treatment free interval ≥3 months, and 15% for those with a treatment-free interval of <3 months.[21]

B.1.3.2.2 Quality of life burden

The symptoms associated with SCLC and treatment adversely affect patients' health-related quality of life (HRQoL).[28] The most common symptoms of LS-SCLC that impact HRQoL have been reported as fatigue and shortness of breath, with patients also experiencing the long-term physical effects of treatment, financial implications, and emotional impact of an uncertain prognosis.[29] Real-world evidence (RWE) has demonstrated that patients with stable LS-SCLC disease had improved HRQoL, as measured using utility values, compared with those with progressive disease.[30] Univariable analyses demonstrated the mean health state utility value (HSUV) at diagnosis was statistically significantly higher (i.e. improved HRQoL) in patients with stable disease compared with those with progressive disease (0.775 vs 0.674; p=0.003). In addition, patients with LS-SCLC have reported higher mean HSUVs compared with those with ES-SCLC (0.802 vs 0.718; p=0.005).[30]

Furthermore, LS-SCLC has a high personal and psychologic burden among caregivers, whose duties consumed a substantial portion of their time, and where they experienced similar symptoms and similar impact of SCLC as those reported by patients.[29]

B.1.3.2.3 Economic burden

There is a paucity of evidence evaluating the economic burden of SCLC; however, current evidence suggests the burden to healthcare systems is high. A review of 210 patient records from 2005–2008 demonstrated that mean costs per patient were higher for those with LS-SCLC compared with ES-SCLC ($20 277 vs $12 966).[31] For patients with LS-SCLC, costs were evenly spread between radiotherapy, chemotherapy, and hospitalisation, whereas hospitalisation accounted for over

two-thirds of the total costs for patients with ES-SCLC.[31] Furthermore, the total cost of diagnosis per patient was reported as higher for LS-SCLC (€937) compared with ES-SCLC (€502).[32] Real-world evidence demonstrated that resource use and cost, stratified by stage and platinum sensitivity among patients with SCLC, were greater for LS-SCLC compared with ES-SCLC. Specifically, the costs per patient per month were notably higher for LS-SCLC ($8,024) than ES-SCLC ($7,574), primarily due to increased utilisation of radiation in LS-SCLC compared with ES-SCLC.[33]

B.1.3.3 Current clinical pathway of care

A very small proportion of patients with LS-SCLC present with early-stage disease (Stage I–II; T1–2A, N0, M0) and are eligible for surgical resection.[19, 20] Given the aggressive nature of SCLC, the aim of treatment should be a complete (R0) surgical resection followed by adjuvant chemotherapy.[18] However, this is not considered feasible for most patients with LS-SCLC (Stage I–III; T1–4, N0–3, M0), and chemoradiation therapy (CRT) is therefore considered the standard treatment approach.[18-20]

The clinical pathway for LS-SCLC, as described below, was validated by UK clinicians at a clinical advisory board.[17] In the UK, the current SoC in LS-SCLC is platinum-based chemotherapy delivered concurrently with twice-daily radiotherapy.[18, 19] Thoracic radiotherapy should be initiated as early as possible, preferably with the first or second cycle of chemotherapy as this is associated with improved survival.[18, 34] However, sequential CRT (delayed initiation of radiotherapy following chemotherapy) may be considered for patients unsuitable for concurrent CRT due to poor World Health Organisation/Eastern Cooperative Oncology Group Performance Status (WHO/ECOG PS) (≥2), comorbidities, and/or disease volume.[18, 19] Expert clinical opinion confirmed that patients who receive sCRT for LS-SCLC are expected to benefit from treatment with durvalumab,[17] with precedent from the PACIFIC-6 study where durvalumab demonstrated encouraging efficacy in NSCLC patients following sCRT.[35] In PACIFIC-6, treatment with durvalumab resulted in a median PFS of 10.9 months (95% CI: 7.3, 15.6), and 12-month OS and PFS rates of 84.1% and 49.6%, respectively.[35] This is further supported by an American Society of Clinical Oncology (ASCO) rapid recommendation update which recommends that patients with LS-SCLC and ECOG PS 3–4 who have received sCRT may be offered

durvalumab for up to 2 years if there are no contraindications to immunotherapy and there is improvement in PS.[36]

As LS-SCLC has a high likelihood of brain metastasis,[20] prophylactic cranial irradiation (PCI) may also be considered following CRT.[18] Evidence suggests that PCI decreases the risk of symptomatic brain metastases and prolongs survival;[37, 38] however, the role of PCI in patients with Stage I–II SCLC, elderly patients, and/or patients with poor performance status is still unclear.[18] Additionally, PCI may be associated with mild decline in neurocognitive functioning in ~30% of patients, although evidence on the long-term toxicity of PCI is currently inconclusive.[18]

B.1.3.3.1 NICE guidelines

The NICE guideline (NG) on lung cancer (NG122) provides guidance on the management of LS-SCLC, and is summarised in Table 3.[19] Standard care is CRT administered either as concurrent CRT (cCRT) followed by PCI if patients are able to tolerate this regimen, or sequential CRT (sCRT) if patients are not considered well enough.[19] For patients who relapse following first-line treatment, second-line chemotherapy may be offered alongside palliative radiotherapy.[19] If chemotherapy is not considered suitable, oral topotecan is the only recommended treatment option for these patients.[39]

Table 3: NICE guidance on the treatment of LS-SCLC

Treatment regimen	Approach
Surgery for small-cell lung cancer	• Consider surgery in people with early-stage SCLC (T1–2a, N0, M0)
First-line treatment for limited-stage disease small-cell lung cancer	• Offer people with limited-stage disease SCLC (broadly corresponding to T1–4, N0–3, M0) 4 to 6 cycles of cisplatin-based combination chemotherapy. Consider substituting carboplatin in people with impaired renal function, poor performance status (WHO 2 or more) or significant comorbidity • Offer twice-daily radiotherapy with concurrent chemotherapy to people with limited-stage disease SCLC (broadly corresponding to T1–4, N0–3, M0) and a WHO performance status of 0 or 1, if they present with disease that can be encompassed in a radical thoracic radiotherapy volume. Start the radiotherapy during the first or second cycle of chemotherapy • If the person declines or is unable to have twice-daily radiotherapy, offer once-daily radiotherapy

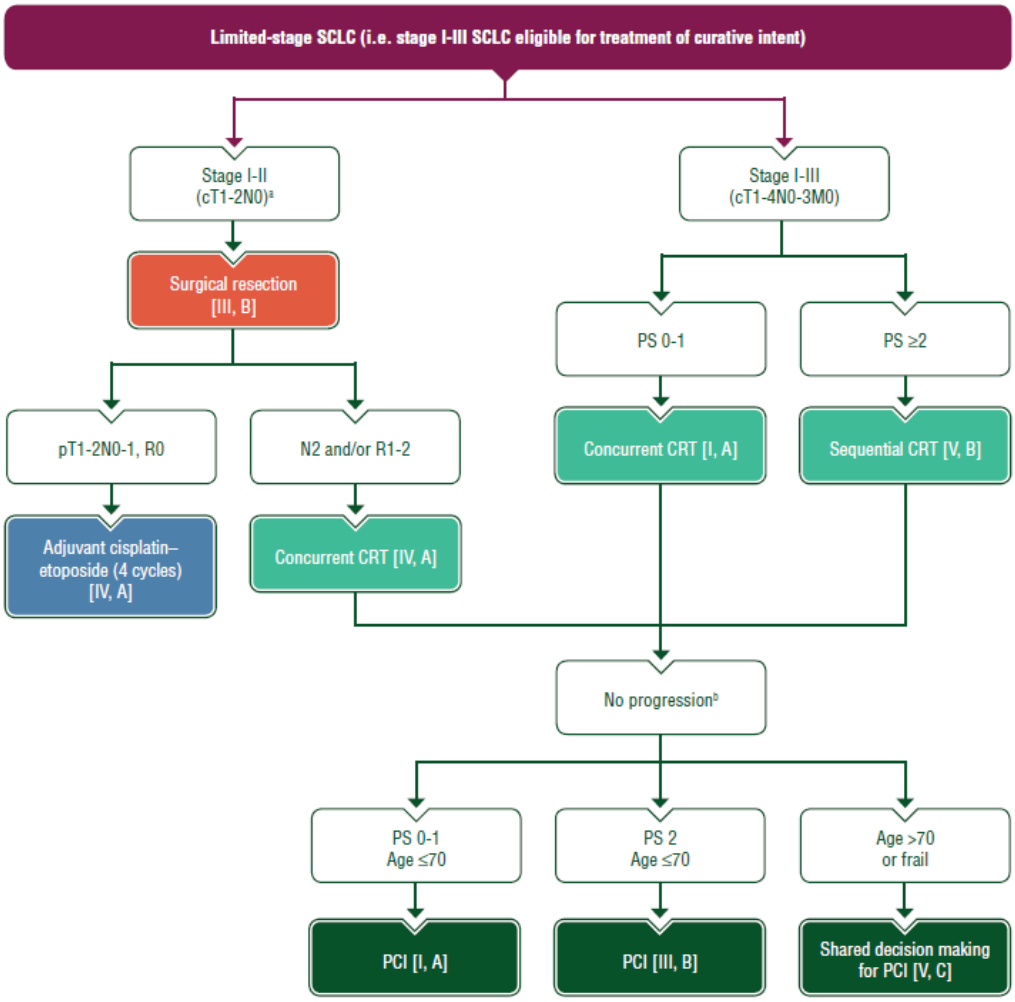
Treatment regimen	Approach
	• Offer sequential radical thoracic radiotherapy to people with limited-stage disease SCLC (broadly corresponding to T1–4, N0–3, M0) who are not well enough for concurrent chemoradiotherapy but who respond to chemotherapy • Offer prophylactic cranial irradiation at a dose of 25 Gy in 10 fractions to people with limited-stage disease SCLC and WHO performance status 0 to 2, if their disease has not progressed on first-line treatment
Second-line treatment for small-cell lung cancer that has relapsed after first-line treatment	• Offer people with SCLC that has relapsed after first-line treatment assessment by a thoracic oncologist • Inform people whose disease has not responded to first-line treatment that there is very limited evidence that second-line chemotherapy will be of benefit • Offer people with relapsed SCLC in whom chemotherapy is a suitable treatment an anthracycline-containing regimen or further treatment with a platinum-based regimen to a maximum of 6 cycles • Offer radiotherapy for palliation of local symptoms to people with SCLC that has relapsed after first-line treatment
Topotecan	• Oral topotecan is recommended as an option only for people with relapsed small-cell lung cancer for whom: o Re-treatment with the first-line regimen is not considered appropriate, and o The combination of CAV is contraindicated

Abbreviations: CAV, cyclophosphamide, doxorubicin, vincristine; Gy, Gray; LS-SCLC, limited-stage-small-cell lung cancer; NG, NICE guideline; NICE, National Institute for Health and Care Excellence; SCLC, small-cell lung cancer; TNM, tumour, node, metastasis; WHO, World Health Organization.
Sources: NICE 2024, NG122;[19] NICE 2009, TA184.[39]

B.1.3.3.2 ESMO guidelines

The European Society for Medical Oncology (ESMO) guidelines may also be relevant to National Health Service (NHS) clinical practice.[18] These guidelines provide similar recommendations to the previously described NICE guideline (section B.1.3.3.1). The first-line treatment algorithm from the ESMO guidelines is presented in Figure 1.

Figure 1: Treatment algorithm for LS-SCLC from the ESMO guidelines



Abbreviations: CRT, chemoradiotherapy; ESMO, European Society for Medical Oncology; PCI, prophylactic cranial irradiation; PS, performance status; SCLC, small-cell lung cancer; TNM, tumour, node, metastasis.
Source: Dingemans 2021, ESMO guidelines.[18]

B.1.3.4 Limitations of the current treatment pathway

Unlike NSCLC, in which major advances have been made in targeted therapy, CRT has remained the SoC in LS-SCLC for decades,[13] leaving patients underserved with limited systemic treatment options. Median OS with current treatment is 25–30 months, and median PFS is 13.5–15.5 months.[14-16] Although CRT is administered with curative intent and ~90% of patients achieve an initial response,[27] ~75% of patients with locally advanced disease experience disease progression within two years of treatment.[20]

As indicated by treatment guidelines, there are currently no therapeutic maintenance options following CRT, and very few second-line therapeutic options available for patients following relapse.[18, 19] Patients are typically monitored with routine repeat

imaging to detect disease recurrence, at which point subsequent therapy is pursued if the patient remains a suitable candidate for further treatment. While PCI may be considered, this is typically used only after careful consideration of potential adverse effects that may impact cognitive function.

There is therefore a considerable need for an effective treatment that can substantially improve survival, delay or reduce the risk of disease progression, offer a tolerable safety and toxicity profile, and increase the durability of response to first-line CRT in patients with LS-SCLC.

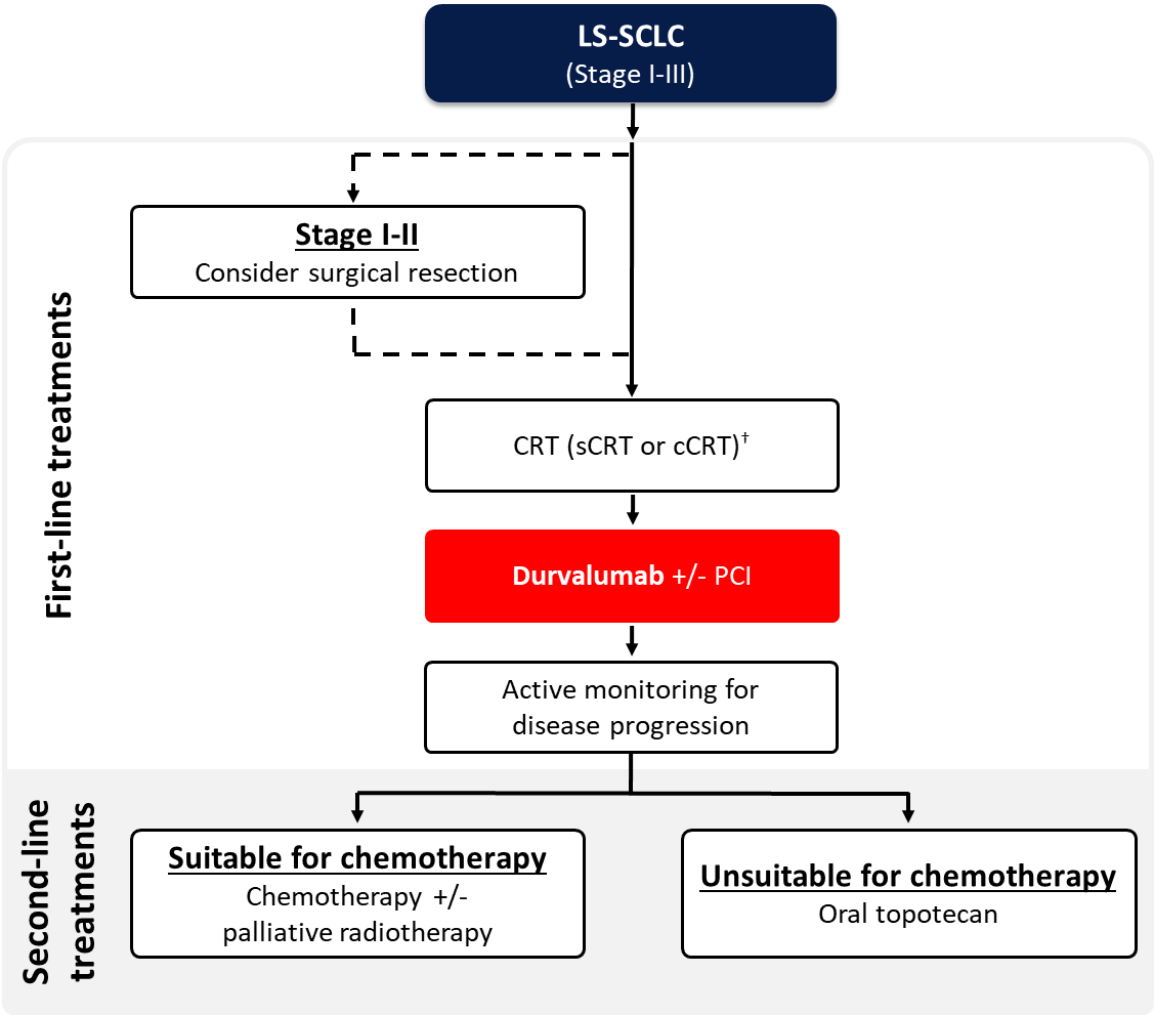
B.1.3.5 Durvalumab place in therapy

Durvalumab is a high-affinity, human, recombinant IgG1κ monoclonal antibody (mAb) that selectively blocks the interaction of programmed death-ligand 1 (PD-L1) with programmed cell death-protein 1 (PD-1) receptors, and cluster of differentiation 80 (CD80) receptors.[3] In doing so, it releases the inhibition of immune responses in the tumour microenvironment, resulting in prolonged T-cell activation and anti-tumour activity.[3] The current consensus on the mode of action (MoA) and associated efficacy of durvalumab involves binding to PD-L1 on the surface of tumour cells, and thus preventing interaction with PD-1.[40]

Durvalumab, the first targeted LS-SCLC treatment regimen being assessed in the UK, has demonstrated efficacy in adults with LS-SCLC following treatment with platinum-based CRT (see Section B.2.6) with a manageable safety profile (see Section B.2.10).[4] This new systemic treatment option, administered after CRT, significantly improves OS, reduces disease recurrence, and is well tolerated with a manageable safety profile. Expert clinical opinion confirmed that patients who receive sCRT for LS-SCLC are also expected to benefit from treatment with durvalumab,[17] with precedent from the PACIFIC-6 study where durvalumab demonstrated encouraging efficacy in NSCLC patients following sCRT,[35] and further supported by an ASCO recommendation for durvalumab in patients with LS-SCLC and ECOG PS 3–4 who have received sCRT.[36]

Durvalumab would establish a new preferred treatment choice as a maintenance therapy following CRT (SoC) in this underserved LS-SCLC population, representing a paradigm shift in management (Figure 2).

Figure 2: Proposed positioning of durvalumab in the current NHS clinical pathway of care for LS-SCLC



†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.
Abbreviations: 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.

B.1.4 Equality considerations

No equality issues have been identified or are foreseen with the use of durvalumab in its proposed indication in LS-SCLC.

B.2 Clinical effectiveness

Clinical effectiveness evidence for durvalumab

Trial design

- **The clinical evidence for durvalumab is derived from ADRIATIC, an ongoing double-blind, multicentre, placebo-controlled, randomised Phase 3 trial:**
  - ADRIATIC compared the efficacy and safety of durvalumab in patients with LS-SCLC who had not progressed following cCRT, and evaluated two active trial arms and one control arm:
    - ◊ ***Durvalumab monotherapy:*** The focus of this submission
    - ◊ ***Durvalumab + tremelimumab combination therapy:*** The tremelimumab arm is blinded until the next planned analysis due to not reaching the pre-specified boundary for statistical significance. This trial arm therefore does not form part of this submission
    - ◊ ***Placebo***

Efficacy

- **Durvalumab is the first and only immunotherapy to provide an effective treatment option for patients with LS-SCLC whose disease has not progressed following cCRT, offering clinically meaningful and statistically significantly improved OS and reduced disease recurrence, compared with the current SoC**
- **ADRIATIC met its dual primary endpoint, with durvalumab demonstrating a statistically significant and clinically meaningful improvement in both OS and PFS versus placebo:**
  - For OS, the hazard ratio (HR) decreased to 0.73 (98.321% confidence interval [CI]: 0.54, 0.98; p=0.01), representing a statistically significant 27% reduction in the risk of death:
    - ◊ Estimated median OS was longer for patients in the durvalumab group compared with placebo (55.9 months vs 33.4 months, respectively), with an estimated improvement in median OS of 22.5 months

    - ◊ OS rates with durvalumab treatment at 24 and 36 months (OS24 and OS36) were higher (68.0% and 56.5%) compared with placebo (58.5% and 47.6%)
  - For PFS, the HR decreased to 0.76 (97.195% CI: 0.59, 0.98; p=0.02), representing a statistically significant 24% reduction in the risk of disease progression or death:
    - ◊ Estimated median PFS was longer for patients in the durvalumab group compared with placebo (16.6 months vs 9.2 months), with an estimated improvement in median PFS of 7.4 months
    - ◊ PFS rates with durvalumab treatment at 18 and 24 months (PFS18 and PFS24) were higher (48.8% and 46.2%) compared with placebo (36.1% and 34.2%)
- **Additionally, the PFS outcomes from the ADRIATIC study align with the opinion of UK clinicians that functional cure is currently achieved in most patients who remain progression-free for 3–5 years after CRT treatment.[17] This is suggested by plateauing of the Kaplan-Meier curves in both the treatment and placebo arms**
- **A similar objective response rate (ORR) (based on unconfirmed responses) was observed for patients treated with durvalumab and placebo (30.3% vs 32.0%; difference in proportion: -1.2%; 95% CI: -11.0, 8.5), with a longer median duration of response (DoR) in the durvalumab group (33.0 vs 27.7 months)**
- **Treatment with durvalumab resulted in an improvement in PFS2 (HR: [redacted]), with a longer estimated median PFS2 compared with placebo**
- **For patients with PD-L1 expression status, an OS and PFS benefit was observed for patients in the durvalumab group compared with placebo, irrespective of PD-L1 expression**
- **For time to death or distant metastasis (TTDM) per Investigator, the HR was [redacted] (95% CI: [redacted]), representing a [redacted] reduction in the risk of TTDM with durvalumab compared with placebo**

- **Prevalence and incidence of durvalumab-specific anti-drug antibodies (ADAs) were low ([redacted]), and consistent with the known immunogenicity profile of durvalumab**
- **Expert clinical opinion confirmed that patients who receive sCRT for LS-SCLC are also expected to benefit from treatment with durvalumab,[17] with precedent from the PACIFIC-6 study where durvalumab demonstrated encouraging efficacy in NSCLC patients following sCRT,[35] and further supported by an ASCO recommendation for durvalumab in patients with LS-SCLC and ECOG PS 3–4 who have received sCRT[36]**

Safety

- **Durvalumab treatment was well tolerated with a safety profile that is manageable and consistent with previous durvalumab studies:**
  - Adverse events (AEs) occurred in a similar proportion of patients in both groups (94.3% with durvalumab vs 88.3% with placebo)
  - The most common AE (≥20% of patients) reported in both treatment groups was radiation pneumonitis (22.9% with durvalumab vs 23.4% with placebo)
  - AEs of Grade 3/4 severity were experienced by a similar proportion of patients in both groups (24.4% with durvalumab vs 24.2% with placebo)
  - Discontinuations due to AEs occurred in a similar proportion of patients in both groups (16.4% with durvalumab vs 10.6% with placebo)
  - Immune-mediated AEs (imAEs) of pneumonitis occurred in [redacted] in the durvalumab group and [redacted] in the placebo group, with the majority of maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2
- No new safety findings were identified for durvalumab in patients with LS-SCLC

Quality of life

- **No clinically meaningful differences in the key patient-reported outcome (PRO) endpoints were observed between treatment groups**
- **There was no detriment in quality of life (QoL) with durvalumab, with stable or slight improvements while on treatment, and a trend towards a longer time to deterioration**

Conclusion

- **Durvalumab is the first and only immunotherapy to provide an effective treatment option for patients with LS-SCLC, significantly improving OS, reducing disease recurrence, and demonstrating a well-tolerated, manageable safety profile compared with placebo**
- **UK clinicians confirmed that a the majority of patients with LS-SCLC who are progression-free from the 3–5-year mark post-CRT will achieve functional cure.[17] This is suggested by plateauing of the Kaplan-Meier curves in both the treatment and placebo arms in the ADRIATIC study**
- **Durvalumab would therefore represent a paradigm shift in LS-SCLC management by significantly improving outcomes in patients with a very poor prognosis, establishing a new SoC in this underserved population with limited treatment options that have not evolved in decades**

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical data assessing the clinical effectiveness and safety of treatments, including durvalumab and relevant comparators for LS-SCLC after CRT.

Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised and relevant comparators, including search strategy, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, list of included studies and list of excluded studies at full paper review is provided in Appendix D.

A total of 31 publications, reporting on 30 studies were identified that met the inclusion criteria specified for this SLR (patients LS-SCLC whose disease has not progressed after CRT). Of these, 1 publication reported data on the ADRIATIC trial, the only study that evaluated durvalumab in patients with LS-SCLC (Spiegel et al. 2024[41]). However, please note that the study publication for the ADRIATIC trial was subsequently published after the time of the SLR electronic searches, and which is presented throughout the submission (Cheng et al. 2024[2]).

B.2.2 List of relevant clinical effectiveness evidence

The efficacy and safety of durvalumab for the treatment of LS-SCLC after CRT was evaluated in a single double-blind, multicentre, placebo-controlled, randomised Phase 3 clinical trial (ADRIATIC). A brief overview of ADRIATIC is presented in Table 4.

Table 4: Clinical effectiveness evidence – ADRIATIC trial design

Study	ADRIATIC (NCT03703297)
Study design	A double-blind, multicentre, placebo-controlled, randomised Phase 3 trial
Population	Adult patients with LS-SCLC whose disease has not progressed after concurrent chemoradiotherapy
Intervention(s)	• Durvalumab monotherapy: Durvalumab (1,500 mg IV) Q4W in combination with tremelimumab placebo (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 placebo • Durvalumab + tremelimumab: 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(s)	• Placebo: 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
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Reported outcomes specified in the decision problem†	• Overall survival (OS) • Progression-free survival (PFS) • Adverse effects of treatment • Health-related quality of life (HRQoL)
All other reported outcomes	• Anti-drug antibodies presence (ADA) • Health economics results • Objective response rate (ORR) • Programmed death-ligand 1 expression (PD-L1) • Time to death or distant metastasis (TTDM) • Time to next therapy or death

†All outcomes specified in the decision problem, and included here, are used in the model.
Abbreviations: ADA, anti-drug antibodies; CSR, clinical study report; HRQoL, health-related quality of life; IV, intravenous; LS-SCLC, limited-stage small-cell lung cancer; ORR, objective response rate; OS, overall survival; • PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q4W, every 4 weeks; TTDM, time to death or distant metastasis.
Sources: ADRIATIC interim CSR.[1]

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

Overview of the durvalumab clinical trial

- The pivotal trial for this submission is ADRIATIC, a double-blind, multicentre, placebo controlled, randomised Phase 3 trial providing pivotal evidence for the efficacy and safety of durvalumab in adult patients with LS-SCLC who have not progressed following cCRT
- ADRIATIC assessed both durvalumab monotherapy (referred to as 'durvalumab' in the submission) and durvalumab in combination with tremelimumab, compared with placebo:
  - The durvalumab monotherapy group is the primary focus in this submission as these patients received durvalumab monotherapy, in line with the proposed licensed indication for durvalumab; data for this treatment group is therefore presented in Document B
- The dual primary objectives of ADRIATIC were to determine the anti-tumour activity of durvalumab, compared with placebo, as measured by OS, and to determine the PFS per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 according to Blinded Independent Central Review (BICR) assessment
- Key secondary endpoints of interest included additional measures of OS and PFS, as well as ORR, PFS2, TTDM, safety, and patient QoL assessed by European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire (EORTC QLQ-C30) and Quality of Life Questionnaire Lung Cancer module (EORTC QLQ-LC13) questionnaires

B.2.3.1 Summary of methodology: ADRIATIC

ADRIATIC is an ongoing double-blind, multicentre, placebo-controlled, randomised Phase 3 trial to assess the efficacy and safety of durvalumab monotherapy and durvalumab in combination with tremelimumab, compared with placebo, in adult patients with LS-SCLC whose disease had not progressed following definitive, platinum-based cCRT.[1]

Two patient cohorts were used to assess durvalumab:[1]

- **Global cohort (n=730):** The cohort that included patients randomised from study sites worldwide (including China) and is the focus of this submission
- **China cohort (n=120):** All patients randomised at sites located in mainland China. There were 120 patients randomised from China (approximately 15% of the global sample size) across the three trial arms, with 95 patients randomised to the durvalumab and placebo groups. This was achieved prior to the closure of global enrolment, with these patients included in both the global cohort and the China cohort. Analysis of the China cohort will be reported separately and is not the focus of this submission.

The focus of this submission is the population of patients who received durvalumab as per the proposed licensed indication.

B.2.3.1.1 Data sources

The methodology for and data from ADRIATIC is drawn from several sources, with the following used to inform the submission:

- **ADRIATIC clinical study report (CSR)**: 31st May 2024; 15th January 2024 data cut-off (DCO) for the primary analysis[1]
- **ADRIATIC clinical study protocol (CSP)**: 27th June 2018
- **ADRIATIC statistical analysis plan (SAP)**: 20th March 2023[42]
- **Study publications**: Cheng et al. 2024[2]

B.2.3.1.2 Study locations

A total of 264 sites were activated across 19 countries worldwide. Of these, ADRIATIC was performed at 164 sites in 19 countries worldwide which randomised at least 1 patient into the global cohort: Argentina (5 sites), Belgium (4 sites), Canada (5 sites), China (24 sites), Czech Republic (4 sites), Germany (11 sites), India (2 sites), Italy (4 sites), Japan (16 sites), Netherlands (4 sites), Poland (5 sites), Russia (10 sites), South Korea (10 sites), Spain (9 sites), Taiwan (9 sites), Turkey (9 sites), United Kingdom (1 site), USA (26 sites), and Vietnam (6 sites).[1]

B.2.3.1.3 Study objective

ADRIATIC had dual primary objectives to determine the anti-tumour activity of durvalumab as measured by OS, and to determine PFS per RECIST 1.1 according to BICR assessment.[1]

Please note that a comprehensive list of secondary and exploratory objectives assessed in ADRIATIC (as detailed in the CSR) is presented here for the purposes of completeness and transparency; however, only those pertaining to the durvalumab monotherapy group have been reported in the submission.

The secondary objectives were to:[1]

- Assess OS, and PFS in patients treated with durvalumab + tremelimumab, compared with placebo, as measured by RECIST 1.1 according to BICR assessment
- Further assess the efficacy of durvalumab and durvalumab + tremelimumab, compared with placebo, by ORR, PFS18, PFS24, TTDM as measured by RECIST 1.1 according to BICR assessment, as well as assessing OS24, OS36, and PFS2
- Assess OS, and PFS as measured by RECIST 1.1 according to BICR assessment, and ORR in patients treated with durvalumab + tremelimumab, compared with durvalumab
- Assess disease-related symptoms and HRQoL in patients treated with durvalumab and durvalumab + tremelimumab, compared with placebo, using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires
- Assess the pharmacokinetics (PK) of durvalumab and durvalumab + tremelimumab
- Investigate the immunogenicity of durvalumab and durvalumab + tremelimumab
- Investigate the relationship between PD-L1 expression and spatial distribution within the tumour microenvironment and clinical outcomes with durvalumab and durvalumab + tremelimumab
- Assess the safety and tolerability profile of durvalumab and durvalumab + tremelimumab, compared with placebo, in patients with LS-SCLC

The exploratory endpoints were to:[1]

- Assess treatment-related AEs (TRAEs) in patients treated with durvalumab and durvalumab + tremelimumab, compared with placebo, using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
- Assess the patients' overall impression of the severity of their cancer symptoms using the Patient Global Impressions Severity (PGIS) scale
- Describe and evaluate health resource use associated with durvalumab and durvalumab + tremelimumab and underlying disease
- Explore the impact of treatment and disease state on health state utility using the EuroQoL 5-dimension, 5-level health state utility index (EQ-5D-5L)
- Collect blood and tissue samples, or leverage residual samples, for analysis of peripheral and tumoral biomarkers (not applicable for China)
- Investigate the relationship between tumour mutational burden (TMB) measured in tumour and/or blood and efficacy outcomes with durvalumab and durvalumab + tremelimumab (TMB-related testing or analysis will not be conducted on samples from China)
- Explore immune-related RECIST (irRECIST) as assessment methodologies for the clinical benefit of durvalumab and durvalumab + tremelimumab, compared with placebo, according to BICR assessment
- Collect and store deoxyribonucleic acid (DNA) from tissue and/or blood according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability, and efficacy) to investigational products and/or susceptibility to disease (optional; not applicable for China)
- Investigate the effect of baseline colonic microbiome on response to treatment and the effect of treatment on the microbiome over time (applicable for the European Union [EU] and North America only)

B.2.3.1.4 Study design

Approximately 724 patients were planned to be randomised.[1] Patients were stratified by stage (I/II vs III) based on TNM classification, and receipt of PCI (yes vs no).[2] All patients were initially randomised using an Interactive Voice/Web Response System (IVRS/IWRS) in a 1:1:1 ratio to one of three treatment groups:[2]

- Durvalumab monotherapy
- Durvalumab in combination with tremelimumab
- Placebo

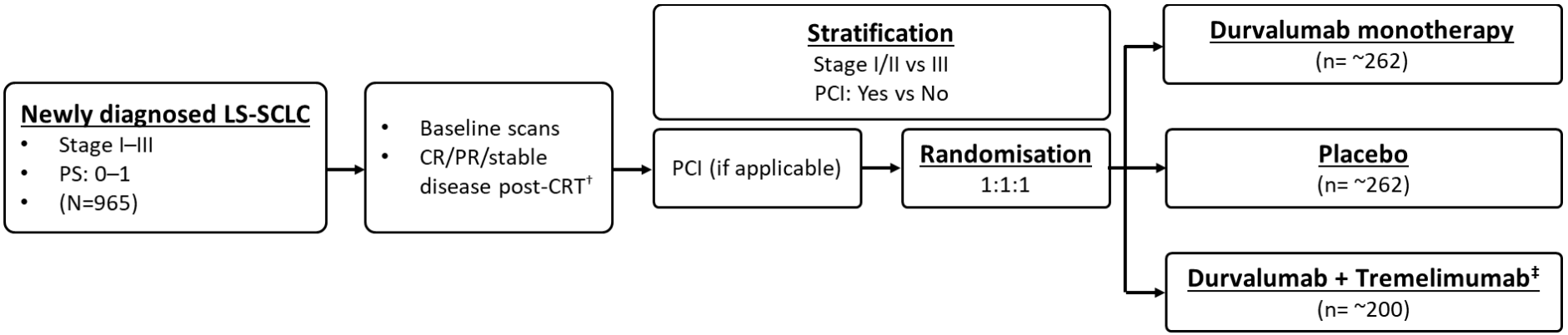
The durvalumab + tremelimumab group was closed to further randomisation following implementation of CSP Version 4.0 and after 600 patients had been randomised. A further 124 patients were planned for randomisation in a 1:1 ratio to either the durvalumab monotherapy or placebo groups;[1] 130 patients were eventually enrolled after the protocol amendment resulting in a total of 530 patients evaluated in the study.[2]

Tumour assessments (computed tomography [CT] or magnetic resonance imaging [MRI]) were conducted at screening, then every 8 weeks for the first 72 weeks (relative to the date of randomisation), followed by every 12 weeks until Week 96, and every 24 weeks thereafter until RECIST 1.1-defined radiological progression. After radiological progression, a follow-up scan was performed no earlier than 4 weeks later, and no later than the next regularly scheduled imaging visit. Scans were evaluated according to RECIST 1.1.[1]

Survival status was assessed at Weeks 8, 12, 16, 24, 32, 40, and 48 following the last dose of study treatment, and every 8 weeks thereafter until study termination or death.[1]

An overview of the ADRIATIC trial design is presented in Figure 3.

Figure 3: Trial design for ADRIATIC



†Chemotherapy: 4 EP cycles (3 permitted). Radiotherapy: 60–66 Gy/QD/6 weeks or 45 Gy/BID/3 weeks. ‡The tremelimumab arm is blinded until the next planned analysis due to not reaching the pre-specified boundary for statistical significance and therefore does not form part of this submission.
Baseline scans include RECIST 1.1 tumour assessment scans and brain MRI or CT scan.
Abbreviations: BID, twice-daily; CR, complete response; CRT, chemoradiation therapy; EP etoposide and platinum chemotherapy; Gy, gray; LS-SCLC, limited-stage small-cell lung cancer; PCI, prophylactic cranial irradiation; PR, partial response; PS, performance status; QD, once-daily.
Source: ADRIATIC interim CSR, Figure 1.[1]

B.2.3.1.5 Study period

Reporting period for ADRIATIC:[1]

- Date first patient was enrolled/study start date: 27th September 2018
- Date last patient was enrolled: 18th August 2021
- DCO date: 15th January 2024
- Clinical data lock date: 12th February 2024
- Date of study completion: 5th March 2026
- Final data cut: Anticipated in quarter 4 (Q4) of 2024
- Median duration of OS follow-up for durvalumab (all patients): 30.75 months
- Median duration of PFS follow-up for durvalumab (all patients): 9.07 months

B.2.3.1.6 Method of randomisation and blinding

B.2.3.1.6.1 Randomisation

All patients were centrally assigned to randomised study treatment using an IVRS/IWRS, with one randomisation list produced for each of the randomisation strata. A blocked randomisation was generated, and all centres used the same list to minimise any imbalance in the number of patients assigned to each treatment group. Randomisation codes were assigned strictly sequentially, within each stratum, as patients became eligible for randomisation.[1]

Where a patient did not meet all the eligibility criteria but was randomised in error, or incorrectly started on treatment, medical judgment was applied on a case-by-case basis to assess the likely benefits and risks to the patient, and a decision was made regarding continuation or discontinuation of treatment.[1]

After closure of randomisation to the durvalumab + tremelimumab group, patients newly randomised to the durvalumab or placebo groups, were to receive only one infusion of durvalumab or placebo from Cycle 1 onwards for the duration of treatment (a maximum of 24 months). Patients no longer received the placebo infusion that was intended to mask the tremelimumab infusion since the actively enrolling experimental group did not include tremelimumab infusion. Therefore, there was no need to maintain blinding with a second placebo infusion.[1]

B.2.3.1.6.2 Blinding

The IVRS/IWRS given to the unblinded pharmacists provided the kit identification number to be allocated to the patient at the dispensing visit. Blinded and unblinded access and notifications were controlled using the IVRS/IWRS. Investigators remained blinded to each patient's assigned study treatment throughout the course of the study. To maintain investigator blinding, the unblinded pharmacist was responsible for the reconstitution and dispensation of all study treatment and to ensure that there are no differences in time taken to dispense following randomisation.[43]

The IVRS/IWRS was programmed with blind-breaking instructions. AstraZeneca was to be notified before the blind was broken unless identification of the study treatment was required for a medical emergency in which the knowledge of the specific blinded study treatment would affect the immediate management of the patient's condition. In this case, AstraZeneca had to be notified within 24 hours after breaking the blind. The date and reason that the blind was broken had to be recorded in the source documentation and case report form (CRF) (electronic or paper), as applicable. Study unblinding did not occur until database lock and all decisions on the evaluability of the data from each individual patient had been made and documented.[43]

B.2.3.1.7 Eligibility criteria

Eligible patients had to have achieved complete response (CR), partial response (PR), or stable disease (SD) and not progressed following definitive, platinum-based cCRT. This cCRT treatment, and PCI treatment (if received per local SoC), had to be completed within 1 to 42 days prior to randomisation and the first dose of study treatment. In addition, the baseline efficacy assessment had to be performed post-CRT as part of the screening procedures within 42 days before randomisation and the first dose of study treatment.

Key inclusion and exclusion criteria for the ADRIATIC trial are presented in Table 5, with the remaining eligibility criteria presented in Appendix N.

Table 5: Eligibility criteria for ADRIATIC

Key inclusion criteria	Key exclusion criteria
• 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 • 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 • Have an 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: – 4 cycles of platinum-based cCRT completed within 1 to 42 days prior to randomisation and the first dose of IP – 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: ◊ Mean lung dose <20 Gy and/or V20 <35% ◊ 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	• Have mixed SCLC and NSCLC histology • Have extensive-stage SCLC • Any history of Grade ≥2 pneumonitis • Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous CRT except for alopecia, vitiligo, and the laboratory values defined in the inclusion criteria: – Patients with Grade ≥2 neuropathy were evaluated on a case-by-case basis after consultation with the Study Physician – Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab could be included only after consultation with the Study Physician • Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients • Patients who received sequential CRT for LS-SCLC (no overlap of RT with chemotherapy) and PCI treatment • Patients whose conditions had progressed while on cCRT

Abbreviations: AJCC, American Joint Committee on Cancer; BID, twice-daily; cCRT, chemotherapy concurrent with radiotherapy; CRT, chemoradiation therapy; CTCAE, Common Terminology Criteria for Adverse Events; 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; NCI, National Cancer Institute; NSCLC, non-small-cell lung cancer; PCI, prophylactic cranial irradiation; PS, performance status; QD, once-daily; RT, radiotherapy; SCLC, small-cell lung cancer; V20, volume receiving ≥20 Gy; V50, volume receiving ≥50 Gy; WHO, World Health Organization.
Sources: ADRIATIC interim CSR.[1]

B.2.3.1.8 Study drugs

All eligible patients were randomised using an IVRS/IWRS in a 1:1:1 ratio to one of three treatment groups:[2]

- **Durvalumab monotherapy:** Durvalumab 1,500 mg was administered intravenously [IV]) every 4 weeks (Q4W) in combination with tremelimumab placebo (IV) Q4W for 4 doses/cycles each, followed by durvalumab 1,500 mg Q4W starting 4 weeks after the final dose of durvalumab + tremelimumab placebo
- **Durvalumab in combination with tremelimumab**: Durvalumab 1,500 mg was administered 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 + tremelimumab
- **Placebo:** Durvalumab placebo was administered 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 both placebos in combination

All randomised patients received two infusions (Durvalumab + placebo, durvalumab + tremelimumab, or placebo + placebo) for 4 cycles (Cycle 1 to Cycle 4), followed by one infusion (Durvalumab, durvalumab, or placebo) from Cycle 5 onwards for the duration of treatment (a maximum of 24 months). After completion of randomisation to the durvalumab + tremelimumab group, patients newly randomised to the durvalumab or placebo groups received only one infusion of durvalumab or placebo from Cycle 1 onwards for the duration of treatment.

B.2.3.1.9 Permitted and disallowed concomitant medications

Restricted, prohibited, and permitted concomitant medications are presented in Table 6.[43]

Table 6: Permitted and disallowed concomitant medications in ADRIATIC

Allowed concomitant therapy	Usage
• Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited"	• To be administered as prescribed by the Investigator
• Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	• Should be used, when necessary, for all patients
• Inactivated viruses, such as those in the influenza vaccine	• Permitted
Prohibited concomitant therapy	**Usage**
• Any investigational anticancer therapy other than those under investigation in this study	• Should not be given concomitantly while the patient is on study treatment
• mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	• Should not be given concomitantly while the patient is on study treatment
• Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	• Should not be given concomitantly while the patient is on study treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable
• Live attenuated vaccines	• Should not be given through 30 days after the last dose of IP
• Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	• Should not be given concomitantly or used for premedication prior to the infusions, with the following permitted exceptions: – Use of immunosuppressive medications for the management of IP-related AEs – Use in patients with contrast allergies – Use of inhaled, topical, and intranasal corticosteroids is permitted • A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea)

Prohibited concomitant therapy	Usage
• Drugs with laxative properties and herbal or natural remedies for constipation	• Should be used with caution through to 90 days after the last dose of tremelimumab or placebo during the study
• Sunitinib	• Should not be given concomitantly or through 90 days after the last dose of tremelimumab or placebo (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
• EGFR TKIs	• Should not be given concomitantly • Should be used with caution in the 90 days post last dose of durvalumab or placebo (saline or dextrose solution) • Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly
• Herbal and natural remedies that may have immune-modulating effects	• Should not be given concomitantly unless agreed by the Sponsor

Abbreviations: AE, adverse event; CTLA 4, cytotoxic T lymphocytes-associated antigen-4; EGFR, epidermal growth factor receptor; IP, investigational product; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TKI, tyrosine kinase inhibitor.
ADRIATIC CSR Appendix 16.1.1.[43]

B.2.3.1.10 Primary efficacy endpoint

The dual primary efficacy endpoints of ADRIATIC were OS, and PFS per BICR according to RECIST 1.1 which are standardised criteria for evaluating response in solid tumours (Table 7).[44]

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.

Table 7: Top-line summary of response criteria per RECIST 1.1

Criteria for evaluation of target lesions	Criteria for evaluation of non-target lesions
Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm	**Complete response (CR):** Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters	**Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits
Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study	
Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)	**Progressive disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression)

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.
Source: Eisenhauer 2009.[44]

B.2.3.1.11 Secondary efficacy endpoints

Definitions of secondary efficacy endpoints assessed in ADRIATIC were as follows:

- **OS24 and OS36:** Proportion of patients alive at 24 and 36 months from randomisation
- **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)
- **ORR:** Number and proportion of patients with at least one visit response of CR or PR (i.e. unconfirmed response) and based on a subset of randomised patients
- **PFS2:** The time from the date of randomisation to the occurrence of a second disease progression or death (i.e. date of PFS2 event or censoring – date of randomisation + 1)
- **TTDM:** The time from the date of randomisation until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST 1.1 or proven by biopsy

B.2.3.1.12 Exploratory endpoints

B.2.3.1.12.1 Health-related quality of life

Exploratory endpoint analyses were conducted using the PRO-CTCAE, PGIS, and EQ-5D-5L questionnaires:

PRO-CTCAE: The number and proportion of patients in each category of the responses for each PRO-CTCAE item were summarised by treatment group and assessment time point.

PGIS: The number and proportion of patients in each category of the PGIS responses were summarised by treatment group, at each assessment time point and overall.

EQ-5D-5L: Descriptive statistics were calculated for each scheduled time point in the study, for each treatment group, and as a total. These reported the number of patients, the number of EQ-5D-5L questionnaires completed at each visit, and the number and proportion responding to each dimension of the EQ-5D-5L. Additionally,

summary statistics were reported for the EQ-5D-5L index score and the EQ-5D-5L Visual Analogue Scale (VAS) score, and the change from baseline for the index and VAS scores. A summary of compliance rate and evaluability rate were provided for each treatment group, by assessment time point and overall.

B.2.3.1.12.2 Health economics

The potential impact the disease and treatment have on healthcare resource use was analysed. The model base case assumes that healthcare resource use utilisation and costs are dependent on a patient's health state (PF and PD) (Section B.3.6.2). This approach aligns with recent submissions to NICE, including TA798 which utilised PACIFIC trial data to assess durvalumab versus best supportive care for the treatment of adults with locally advanced, unresectable NSCLC, ≥1% PD-L1 without progression after concurrent platinum-based chemoradiation,[5] and TA638.[45] The model includes both the resources used and their frequencies with appraisals in analogous settings, such as NSCLC, as it is assumed there would be limited difference between SCLC and NSCLC in terms of resources used. The resource use and costs associated with the PF and PD heath states were presented to clinical experts at an advisory board who agreed which the approach taken in the base case.[17]

B.2.3.1.13 Safety endpoints

Safety endpoints assessed in ADRIATIC:

- Frequency and severity of all AEs and TRAEs
- AEs of special interest (AESI), potential interest (AEPI), imAEs
- AEs in ADA-positive patients
- Frequency of serious AEs (SAEs), discontinuations, and deaths due to AEs

Adverse events were classified by system organ class (SOC) and preferred term using MedDRA version 26.1 and graded using CTCAE v4.03. Treatment emergent AEs were defined as events that were new or worsened on or after receiving the first dose of study treatment through 90 days after the last dose of study treatment.

Adverse events of special interest were defined as AEs with a likely inflammatory or immune-mediated pathophysiological basis resulting from the MoA of durvalumab and requiring more frequent monitoring and/or interventions such as systemic

corticosteroids, immunosuppressants, and/or endocrine therapy. In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions were also considered AESIs; however, these were not assessed for imAE designation because they are common to mAb drugs and occur due to a mechanism of action different from that for imAEs.

B.2.3.1.14 Patient-reported outcomes

Patient-reported outcomes included as secondary endpoints comprised the EORTC QLQ-C30 and the EORTC QLQ-LC13 questionnaires. A description of these measures is provided in Appendix N.

Key outcomes assessed using the EORTC QLQ-C30 and the EORTC QLQ-LC13 questionnaires were as follows:

Adjusted mean change from baseline: Performed using a mixed model repeated measures (MMRM) of all the post-baseline scores for each visit up to disease progression, death or 24 months. The model included treatment, visit, and treatment-by-visit interaction, TNM stage (I/II versus III) and receipt of PCI (yes versus no) as well as baseline score and the baseline score by visit interaction as covariates. Adjusted mean scores were calculated along with corresponding 95% CIs, an estimate of the treatment difference, and p-value.

Additional exploratory analyses were conducted using the PRO-CTCAE, PGIS, and EQ-5D-5L.

Improvement rate: The proportion of subjects with a minimum of two consecutive assessments at least 14 days apart that showed a clinically meaningful improvement (a decrease from baseline score ≥10 for symptom scales/items) from baseline.

Time to deterioration: The time from the date of randomisation until the date of the first clinically meaningful deterioration confirmed at the next available assessment at least 14 days apart, or death. A clinically meaningful change was defined as a change in score from baseline of ≥10 points (for symptoms an increase ≥10; for Global Health Status [GHS] and functions a decrease ≥10).

B.2.3.1.15 Pre-planned subgroups

Pre-planned subgroup analyses of OS and PFS included disease status, receipt of PCI, primary tumour location, time 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, WHO/ECOG PS, and PD-L1 status. Pre-planned subgroup analysis of ORR was also performed for PD-L1 status only.

B.2.3.2 Patient characteristics

B.2.3.2.1 Baseline characteristics and demographics

Patient characteristics at baseline are summarised in Table 8. There were no significant differences observed between groups. The median age was 62 years (range: 28–84 years), with [redacted] of patients aged 65 years or older.[2] The majority of patients were male ([redacted]), with [redacted] and [redacted] of patients of White and Asian ethnicity, respectively, and 90.8% of patients were current or former smokers.[2] Demographic characteristics were well balanced between the treatment groups in terms of age, sex, race, ethnicity, and smoking status. Baseline disease characteristics are presented in Table 8.

Table 8: Demographics and baseline characteristics for patients in ADRIATIC (FAS)

Characteristic	Durvalumab monotherapy (n=264)	Placebo (n=266)	Total (N=530)
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	62.0 (28, 84)	62.0 (28, 79)	[redacted]
Age category, n (%)			
<65 years	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	178 (64.7)	188 (70.7)	[redacted]
Female	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Characteristic	Durvalumab monotherapy (n=264)	Placebo (n=266)	Total (N=530)
Race, n (%)			
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	4 (0.8)
White	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Smoking status			
Never	[redacted]	[redacted]	[redacted]
Smoker	241 (91.3)	240 (90.2)	[redacted]
Ex-smoker	[redacted]	[redacted]	[redacted]
Current smoker	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; SD, standard deviation.
Sources: ADRIATIC interim CSR, Table 10;[1] ADRIATIC study publication Table 1.[2]

B.2.3.2.2 Baseline disease characteristics

Disease characteristics were representative of the intended target population and were well balanced between the two treatment groups. All patients had a WHO/ECOG PS of 0 ([redacted]) or 1 ([redacted]) and most patients had AJCC disease Stage III ([redacted]). PD-L1 status was tumour cells (TC) and tumour-infiltrating immune cells (IC) <1% for [redacted] of patients and TC or IC ≥1% for [redacted] of patients. There were differences of >5% between treatment groups in two disease characteristics categories; 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%), and fewer patients with PD-L1 high status (TC or IC ≥1%) in the durvalumab group compared with placebo (31.8% vs 36.8%) (Table 9).

Table 9: Baseline disease characteristics for patients in ADRIATIC (FAS)

Characteristic	Durvalumab monotherapy (n=264)	Placebo (n=266)	Total (N=530)
WHO/ECOG PS, n (%)			
0 (Normal activity)	132 (50.0)	126 (47.4)	[redacted]
1 (Restricted activity)	132 (50.0)	140 (52.6)	[redacted]
AJCC overall stage, n (%)†			
I	8 (3.0)	11 (4.1)	[redacted]
II	25 (9.5)	23 (8.6)	[redacted]
III	231 (87.5)	232 (87.2)	[redacted]

Characteristic	Durvalumab monotherapy (n=264)	Placebo (n=266)	Total (N=530)
PD-L1 status, n (%)[‡]			
TC and IC <1%	[redacted]	[redacted]	[redacted]
TC or IC ≥1%	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Extent of disease at baseline, n (%)[§]			
No evidence of disease	32 (12.1)	34 (12.8)	[redacted]
Locally advanced (total)	232 (87.9)	232 (87.2)	[redacted]
Respiratory	199 (75.4)	209 (78.6)	[redacted]
Lymph nodes	167 (63.3)	148 (55.6)	[redacted]

[†]AJCC stage is derived from the TNM Stage, AJCC overall stage is at diagnosis as reported by Investigator on eCRF. AJCC 8th Edition. [46] [‡]Testing was retrospective and not required for randomisation. [§]A patient could have one or more sites of disease reported.
Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative oncology Group; eCRF, electronic case report form; FAS, full analysis set; IC, immune cell; PD-L1, programmed cell death-ligand 1; PS, performance status; TC, tumour cell; TNM, tumour, node and metastasis; WHO, World Health Organization.
Sources: ADRIATIC interim CSR, Table 11;[1] ADRIATIC study publication Table 1.[2]

B.2.3.2.3 Prior cancer-related therapies

B.2.3.2.3.1 Concurrent chemoradiation and prophylactic cranial irradiation

A summary of prior cCRT and PCI is presented in Table 10, with no notable differences in chemotherapy, radiotherapy, or PCI observed between treatment groups. Most patients (88.3%) received 4 cycles of platinum-based chemotherapy and were categorised based on the platinum-based chemotherapy received during the first cycle; [redacted] of patients received cisplatin while [redacted] received carboplatin (Table 10). A similar platinum agent switch was observed in both groups (5.7% with durvalumab vs 5.6% with placebo).

Most patients received the intended dose of radiotherapy; [redacted] of patients received a concurrent once daily (QD) radiotherapy regimen with a total dose of 60–66 Gy, and [redacted] of patients received a twice daily (BID) radiotherapy regimen with a total dose of 45 Gy (Table 10).

Best response to previous cCRT was CR for [redacted] of patients and PR for [redacted] of patients, and approximately half of patients (53.8%) received PCI (Table 10).

During an advisory board meeting with UK clinical experts, it was confirmed that the prior therapies in the ADRIATIC trial were aligned with the treatment options typically used in UK clinical practice for patients with LS-SCLC patients.[17]

Table 10: Prior cCRT and PCI therapies received by patients in ADRIATIC (FAS)

Characteristic	Durvalumab monotherapy (n=264)	Placebo (n=266)	Total (N=530)
Number of chemotherapy cycles, n (%)			
2	0 (0.0)	1 (9.40)	1 (0.2)
3	29 (11.0)	31 (11.7)	60 (11.3)
4	234 (88.6)	234 (88.0)	468 (88.3)
6	1 (0.4)	0 (0.0)	1 (0.2)
Chemotherapy regimen, n (%)†			
Cisplatin + etoposide	173 (65.5)	178 (66.9)	[redacted]
Carboplatin + etoposide	91 (34.5)	88 (33.1)	[redacted]
Radiotherapy regimen (total dose Gy), n (%)‡			
QD	195 (73.9)	187 (70.3)	[redacted]
<57	[redacted]	[redacted]	[redacted]
≥60 to ≤66	[redacted]	[redacted]	[redacted]
≥57 to ≤70 (excluding ≥60 to ≤66)	[redacted]	[redacted]	[redacted]
>70	[redacted]	[redacted]	[redacted]
BID	69 (26.1)	79 (29.7)	[redacted]
<42.75	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]
≥42.75 to ≤47.25 (excluding 45)	[redacted]	[redacted]	[redacted]
>47.25	[redacted]	[redacted]	[redacted]
Best response to cCRT, n (%)			
CR	31 (11.7)	34 (12.8)	[redacted]
PR	191 (72.3)	200 (75.2)	[redacted]
SD	42 (15.9)	32 (12.0)	[redacted]
PCI regimen, n (%)			
Yes	142 (53.8)	143 (53.8)	285 (53.8)
No	122 (46.2)	123 (46.2)	245 (46.2)

†Chemotherapy regimen based on first cycle of chemotherapy. ‡Chest irradiation.
Abbreviations: BID, twice daily; cCRT, chemotherapy concurrent with radiotherapy; CR, complete response; FAS, full analysis set; Gy, Gray; PCI, prophylactic cranial irradiation; PR, partial response; QD, once daily; SD, stable disease.
Sources: ADRIATIC interim CSR, Table 12;[1] ADRIATIC study publication Table 1.[2]

B.2.3.3 Expert elicitation/opinion

UK clinical expert opinion was sought to support the submission for durvalumab in patients with LS-SCLC whose disease has not progressed after CRT. Expert opinion was collected at an in-person advisory board meeting, via a round table discussion in October 2024.

The objectives of the advisory board were to understand the current patient pathway for LS-SCLC in the UK, and to gain insight into clinical opinion on the ADRIATIC trial design, outcomes, and data supporting the use of durvalumab in LS-SCLC. A total of 8 clinical experts participated in the advisory board based on their extensive expertise in the field of oncology and LS-SCLC.

Experts were asked to complete a series of questions prior to the meeting to help inform the discussion. In addition, experts were provided with pre-read material prior to the advisory board, which contained background information on the ADRIATIC clinical trial. All information provided to the experts was consistent with the evidence provided in the submission. Meeting notes from this advisory board are provided in the reference pack accompanying this submission as a ‘Data on file’ reference.

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

B.2.4.1 Definitions of patient populations and analysis sets

Definitions of population analysis sets and respective patient numbers from the durvalumab and placebo groups in ADRIATIC are provided in Table 11 and Table 12, respectively.

Efficacy evaluation was performed using the full analysis set (FAS) which comprised all 530 randomised patients: 264 patients in the durvalumab group and 266 patients in the placebo group. There were two patients included in the FAS but excluded from the safety analysis set (SAS) (one in each treatment group) who were randomised but not treated.

Table 11: Definitions of patient analysis sets in ADRIATIC

Analysis set	Definition
FAS	All patients who were randomised and received any amount of study treatment. The FAS was used for used for all efficacy analyses (including PROs)
CAS	The first 600 patients randomised across all three treatment arms for analyses involving the durvalumab + tremelimumab group:† • durvalumab + tremelimumab versus placebo • durvalumab + tremelimumab versus durvalumab
SAS	All patients who received at least one dose of study treatment
CSAS	All patients from the CAS who received at least one dose of study treatment†
FPAS	All patients with evaluable PD-L1 data within the FAS
CPAS	All patients with evaluable PD-L1 data within the CAS†
PK analysis set	All patients who received at least one dose of study treatment and who had any evaluable post-dose data
ADA analysis set	All patients in the SAS who had non-missing baseline ADA and at least one non-missing post-baseline ADA result of the same study treatment: • Durvalumab ADA analysis set consists of all patients in the SAS who had a non-missing baseline durvalumab ADA result and at least one non-missing post-baseline durvalumab ADA result. • Tremelimumab ADA analysis set consists of all patients in the SAS who had a non-missing baseline tremelimumab ADA result and at least one non-missing post-baseline tremelimumab ADA result†

†Analyses of durvalumab + tremelimumab, and thus data for this analysis set, are not included in this interim CSR.
Abbreviations: ADA, anti-drug antibody(ies); CAS, combination analysis set; CPAS, combination PD-L1 analysis set; CSAS, combination safety analysis set; FAS, full analysis set; FPAS, full PD-L1 analysis set; PD-L1, programmed cell death-ligand 1; PK, pharmacokinetic; PRO, patient-reported outcome; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Section 9.8.2.[1]

Table 12: Number of patients in each analysis set in ADRIATIC

Analysis set, n (%)	Treatment group		
	Durvalumab	**Placebo**	**Total**
FAS	264 (100)	266 (100)	530 (100)
SAS	262 (99.2)	265 (99.6)	527 (99.4)
FPAS	162 (61.4)	171 (64.3)	333 (62.8)
PK analysis set	258 (97.7)	173 (65.0)	431 (81.3)
ADA analysis set	207 (78.4)	179 (67.3)	386 (72.8)
Durvalumab ADA analysis set	206 (78.0)	175 (65.8)	381 (71.9)

Abbreviations: ADA, anti-drug antibody(ies); FAS, full analysis set; FPAS, full PD-L1 analysis set; PD-L1, programmed cell death-ligand 1; PK, pharmacokinetic; PRO, patient-reported outcome; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Section 9.8.2.[1]

B.2.4.2 Hypothesis objective

The objective of ADRIATIC was to demonstrate superiority of the OS and PFS benefit of durvalumab versus placebo in patients with LS-SCLC whose disease has not progressed after cCRT.

The hypothesis of improved OS and PFS could be tested using the global cohort upon fulfilment of the criteria presented in Table 13.

Table 13: Criteria used to establish the hypothesis of improved OS and PFS

OS criteria	PFS criteria
Approximately: • 348 OS events across the durvalumab and placebo groups had occurred (66.4% maturity) (Primary analysis) • 242 OS events across the durvalumab and placebo groups had occurred (46.2% maturity) (IF 69.5%) • 299 OS events across the durvalumab and placebo groups had occurred (57.1% maturity) (IF 85.9%)	• 370 PFS BICR events had occurred across the durvalumab and placebo groups if the true PFS HR was 0.65 (Primary analysis) • 308 PFS BICR events had occurred across the durvalumab and placebo groups (58.8% maturity) (IF 83.2%)

Abbreviations: BICR, Blinded Independent Central Review; HR, hazard ratio; IF, information fraction; OS, overall survival; PFS, progression-free survival.
Source: ADRIATIC interim CSR, Section 9.8.3.[1]

B.2.4.3 Statistical analysis

Statistical analyses were conducted for each endpoint as follows:

- **OS:** Analysed using a stratified log-rank test (stratified by disease status and receipt of PCI) to assess statistical inference. The treatment effect was estimated by HR and its 95% CI based on a Cox proportional hazards model (stratified by disease status and receipt of PCI). Sensitivity analyses were performed to assess treatment bias. Subgroup analyses were conducted using unstratified Cox proportional hazards models to assess the consistency of treatment effect across expected prognostic and/or predictive factors. Kaplan-Meier (KM) plots of OS were presented by treatment, with median OS and estimated OS rates at 24 and 36 months presented
- **PFS:** Analysed using the same methodology as for OS, with sensitivity analyses performed to assess evaluation-time bias, attrition bias, and ascertainment bias (using site Investigator assessments according to

RECIST 1.1). KM plots of PFS were presented by treatment, with median PFS and estimated PFS rates at 18 and 24 months presented

- **PFS2:** Analysed by treatment group using stratified log-rank tests, using the same methodology as for PFS
- **ORR:** Analysed using a stratified Cochran-Mantel-Haenszel (CMH) test adjusting for the same factors as the primary endpoint PFS. DoR was assessed using KM estimates and CIs
- **TTDM:** Analysed by treatment group using stratified log-rank tests, using the same methodology as for PFS
- Remaining secondary endpoints were summarised descriptively

B.2.4.4 Determination of sample size and power calculation

Approximately 965 patients (336 patients per treatment group) were planned to be recruited to randomise approximately 724 patients into the global cohort (1:1:1) to durvalumab (approximately 262 patients), durvalumab + tremelimumab (approximately 200 patients), or placebo (approximately 262 patients). Following implementation of CSP Version 4.0, after 600 patients had been randomised, it was planned that a further 124 patients would subsequently be randomised 1:1 to the durvalumab or placebo groups until a total of 724 patients had been randomised. The study was powered to demonstrate the superiority of the OS and PFS benefits for the primary comparison of durvalumab versus placebo.

B.2.4.4.1 OS

The primary OS analysis was planned to occur when approximately 348 death events occurred (66.4% maturity) in the durvalumab and placebo groups. The study was expected to have 80% power to demonstrate a statistically significant superior difference in OS between treatment if the true OS HR was 0.73 for durvalumab versus placebo. The true OS HR of 0.73 translated to an approximate 8.9-month benefit in median OS over 24 months on placebo if OS was exponentially distributed, with the smallest statistically significant treatment difference being a HR of 0.798.

Up to three interim analyses (IA) of OS were planned to be performed. The first was at the time of the PFS IA, with approximately 242 death events anticipated across the durvalumab and placebo groups (IF 69.5%, 46.2% maturity), to provide 48% power to detect an OS HR of 0.73 (critical value=0.725). Another IA provided 68%

power to detect an OS HR of 0.73 (critical value=0.770) with approximately 299 death events anticipated across the durvalumab and placebo groups (IF 85.9%, 57.1% maturity). 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[47] 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.

B.2.4.4.2 PFS

The study was planned to have approximately 90% power to demonstrate a statistically significant superior difference in PFS between durvalumab and placebo, at an overall 2-sided significance level of 0.5% with 370 PFS BICR events if the true PFS HR was 0.65 for durvalumab versus placebo. The true HR of 0.65 translated to a 5.4-month benefit in median PFS over 10 months on placebo if PFS was exponentially distributed. The smallest statistically significant treatment difference was a HR of 0.743 (critical value). A recruitment period of approximately 38 months was expected for the primary PFS analysis.

An IA of PFS was planned when approximately 308 PFS BICR events had occurred across the durvalumab and placebo groups (IF 83.2%, 58.8% maturity) with the study having 75% power to detect a PFS HR of 0.65 (critical value=0.700) at a 0.184% significance level. The 2-sided alpha level (0.5%) was split between the interim and primary analyses using the Lan-DeMets[47] 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.

B.2.4.5 Data management and patient withdrawals

Discontinuation from study treatment, for any reason, did not impact patients' participation in the study. Patients were to continue attending subsequent study visits, and data collection was to continue according to the CSP. If the patient did not agree to continue in-person study visits, a modified follow-up was arranged to ensure

the collection of endpoints and safety information. Patients who permanently discontinued study treatment for reasons other than RECIST 1.1-defined radiological progressive disease (PD) were to continue to have RECIST scans performed every 8 weeks ± 1 week for the first 72 weeks (relative to the date of randomisation) and then every 12 weeks ± 1 week thereafter up to 96 weeks (relative to the date of randomisation) and then every 24 weeks ± 1 week thereafter until RECIST 1.1-defined radiological PD plus at least one additional follow-up scan or death (whichever came first).

If a patient was discontinued for RECIST 1.1-defined radiological PD, the patient should have had one follow-up scan performed no later than the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD. All patients were followed up for survival until the end of the study.

Patients will be considered lost to follow-up only if no contact has been established by the time the study has completed, such that there is insufficient information to determine the patient's status at this time.

Patients were free to withdraw from the study at any time. Patients who withdrew consent for further participation in the study did not receive any further investigational product (IP) or undergo further study observation, except for follow-up for survival, which continued until the end of the study, unless the patient had expressly withdrawn consent to survival follow-up.

B.2.4.6 Participant flow in the relevant randomised controlled trials

Between 28th September 2018 and 18th August 2021, 939 patients were enrolled at 164 sites in 19 countries, including 1 site in the UK. In total, 730 patients were randomly assigned to treatment.[2] Of these, 264 patients were assigned to the durvalumab group, and 200 patients assigned to the durvalumab +tremelimumab group; 263 (99.6%) patients received durvalumab treatment. The remaining 266 patients were assigned to the placebo group and 265 (99.6%) of these patients received treatment (Table 14).

Discontinuations of study treatment due to adverse events (AEs) were reported for 175 patients (66.5%) in the durvalumab group and in 195 patients (73.6%) in the placebo group (Table 14).

The most frequently reported reasons for discontinuing of study treatment were PD (46.0% with durvalumab and 58.1% with placebo) and AE (16.3% with durvalumab and 10.9% with placebo). The number of patients who terminated the study was 124 (47.0%) in the durvalumab group and 155 (58.3%) in the placebo group.[2] The reasons for terminating the study were death (43.6% with durvalumab and 54.1% with placebo) and patient withdrawal (3.4% with durvalumab and 4.1% with placebo) (Table 14).

At the DCO, 140 (53.0%) patients in the durvalumab group and 111 (41.7%) patients in the placebo group remained in the study and in survival follow-up (Table 14).

Full details of participant flow based on the FAS population are presented in Appendix D.

Table 14: Summary of patient disposition in ADRIATIC (FAS)

Disposition, n (%)	Durvalumab	Placebo	Total
Patients enrolled†	-	-	939 (100)
Patients randomised	264 (28.1)	266 (28.3)	530 (56.4)
Patients not randomised	-	-	209 (22.3)
Death			[redacted]
Screen failure			[redacted]
Withdrawal by patient			[redacted]
FAS	264 (100)	266 (100)	530 (100)
Patients who received treatment	263 (99.6)	265 (99.6)	528 (99.6)
Patients who did not receive treatment	1 (0.4)	1 (0.4)	2 (0.4)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Withdrawal by patient	1 (0.4)	0 (0.0)	1 (0.2)
Patients ongoing treatment at DCO	0 (0.0)	0 (0.0)	0 (0.0)
Patients who completed treatment‡	88 (33.5)	70 (26.4)	158 (29.9)
Patients who discontinued treatment	175 (66.5)	195 (73.6)	370 (70.1)
Patient decision	10 (3.8)	11 (4.2)	21 (4.0)
AE	43 (16.3)	29 (10.9)	72 (13.6)
Severe non-compliance to protocol	0 (0.0)	1 (0.4)	1 (0.2)
Disease progression	121 (46.0)	154 (58.1)	275 (52.1)
Other	[redacted]	[redacted]	[redacted]
Patients ongoing study at DCO	[redacted]	[redacted]	[redacted]
Patients who terminated study	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]

Disposition, n (%)	Durvalumab	Placebo	Total
Patients who died after study termination§	[redacted]	[redacted]	[redacted]

† Informed consent received. ‡Subjects who completed durvalumab monotherapy have "Maximum cycle of immunotherapy reached" on eCRF. §Obtained from public records or survival follow up. Subjects are also included in the Death row above.
Abbreviations: AE, adverse event; DCO, data cut-off; eCRF, electronic case report form; FAS, full analysis set.
Source: ADRIATIC interim CSR, Table 14.1.1;[1] ADRIATIC study publication.[2]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

ADRIATIC is an ongoing double-blind, multicentre, placebo-controlled, randomised Phase 3 trial. The study was conducted in accordance with the International Council for Harmonisation Declaration of Helsinki and Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.[2] An Independent Data Monitoring Committee was established to confirm the safety and tolerability of the proposed dose and schedule, and for the planned interim analyses.

Prior to study initiation, the study protocol and informed consent forms were approved by each site's Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as required by applicable regional legal requirements. Amendments to the protocol were documented in the study protocol and approved by the IRB/IEC before changes were implemented.

A summary of the quality assessment results for ADRIATIC is provided in Table 15, with a complete quality assessment of ADRIATIC provided in Appendix D.

Table 15: Quality assessment results – ADRIATIC

Criteria	Grade	Details
Was randomisation carried out appropriately?	Yes	Randomisation was carried out in a 1:1:1 fashion by 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.
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.
Were the care providers, participants and outcome	Yes	The study was double-blind; the patients, Investigator and study centre staff were blinded to the durvalumab/placebo allocation. To maintain the

Criteria	Grade	Details
assessors blind to treatment allocation?		blind, an otherwise 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.
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.
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.
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 contact with missing patients. Procedures for accounting for missing, unused, and spurious data are described in the SAP.

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.

B.2.6 Clinical effectiveness results of the relevant studies

As outlined in Sections B.2.1 and B.2.2, the Phase 3 ADRIATIC trial is the only study that assessed the clinical efficacy of durvalumab in adult patients with LS-SCLC whose disease has not progressed after cCRT.

B.2.6.1 Dual primary efficacy outcomes

B.2.6.1.1 Overall survival

Improving and extending OS is important for patients and an important indicator of treatment efficacy. Overall survival is considered the most appropriate and reliable endpoint in randomised controlled oncology clinical studies as it is not subject to investigator bias.[48] As of the DCO for OS-IA1, overall OS data maturity In ADRIATIC

was 49.2%;[2] 43.6% of patients in the durvalumab group and 54.9% of patients in the placebo group had died.

ADRIATIC met its primary endpoint for OS with a statistically significant and clinically meaningful improvement in OS with durvalumab treatment compared with placebo.

The median duration of OS follow-up in all patients was 30.75 months in the durvalumab group and 28.63 months in the placebo group. At the DCO, durvalumab treatment resulted in a clinically meaningful and statistically significant improvement in (i.e. longer) OS compared with placebo (HR: 0.73; 98.321% CI: 0.54, 0.98; p=0.01), corresponding to a 27% reduction in the risk of death.[2] The KM-estimated median OS was longer with durvalumab compared with placebo (55.9 months; 95% CI: 37.3, not reached [NR] versus 33.4 months; 95% CI: 25.5, 39.9),[2] representing an estimated improvement in median OS of 22.5 months (Table 16 and Figure 4).

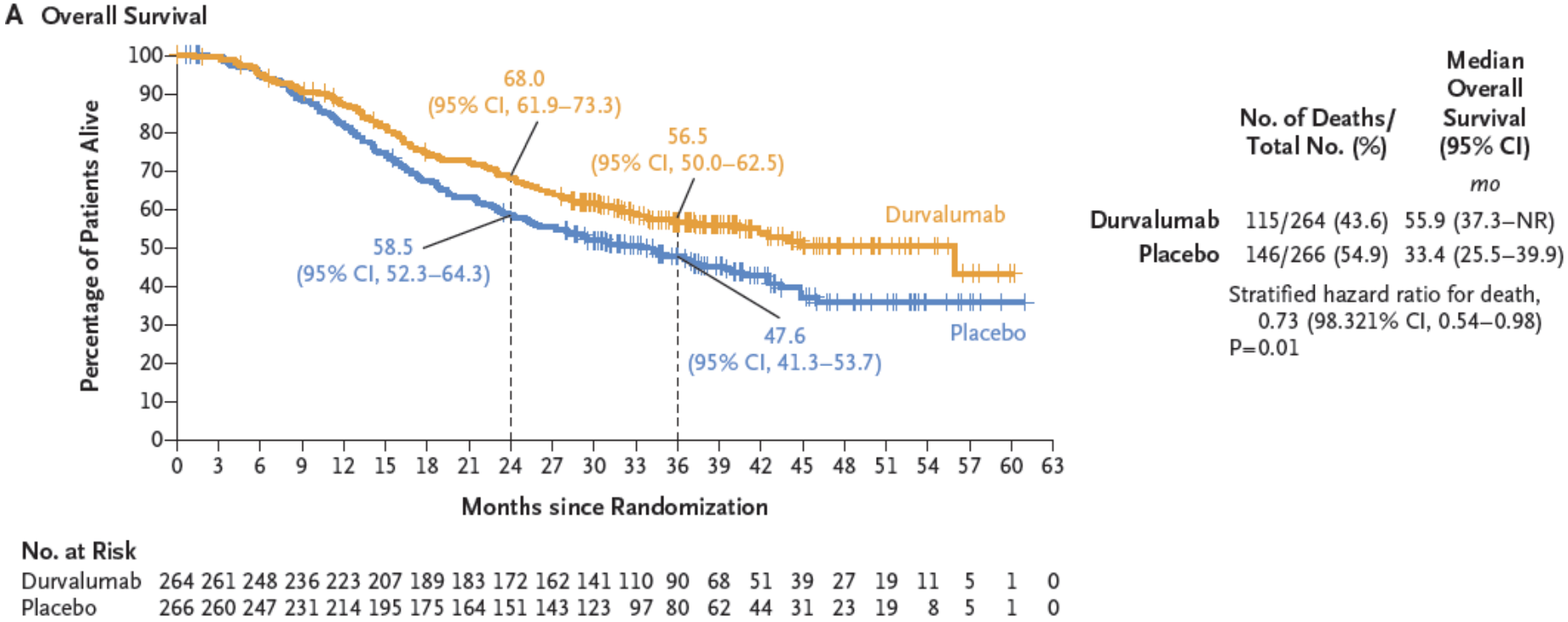
The OS KM curves separated after approximately 8 months, and demonstrated a clear and sustained separation, which increased over time and was sustained thereafter, as reflected in the landmark estimates of OS at 24 months and 36 months (OS24 and OS36) that favoured durvalumab treatment (68.0% and 56.5%, respectively) over placebo (58.5% and 47.6%, respectively) (Table 16).[2]

Table 16: OS (FAS)

Outcome	Durvalumab (n=264)	Placebo (n=266)
Number of deaths, n (%)	115 (43.6)	146 (54.9)
Censored patients, n (%)	[redacted]	[redacted]
Still in survival follow-up†	[redacted]	[redacted]
Terminated prior to death‡	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrawn consent	[redacted]	[redacted]
Other	[redacted]	[redacted]
OS, months		
Median (95% CI)§	55.9 (37.3, NR)	33.4 (25.5, 39.9)
Survival rate at 24 months (OS24), %		
Rate (95% CI)§	68.0 (61.9, 73.3)	58.5 (52.3, 64.3)
Survival rate at 36 months (OS36), %		
Rate (95% CI)§	56.5 (50.0, 62.5)	47.6 (41.3, 53.7)
HR¶,††	0.73	
98.321% CI¶,‡‡	0.54, 0.98	
95% CI¶	0.57, 0.93	
p-value§§	0.01	

†Includes patients known to be alive at DCO. ‡Includes patients with unknown survival status or patients who were lost to follow-up. §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. ¶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. ††A HR <1 Favours durvalumab to be associated with a longer survival than placebo. ‡‡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. §§The analysis was performed using the stratified log-rank test, adjusting for receipt of PCI (yes vs no).
Abbreviations: CI, confidence interval; DCO, data cut-off; FAS, full analysis set; HR hazard ratio; OS, overall survival; OS24, OS at 24 months from randomisation; OS36, OS at 36 months from randomisation; PCI, prophylactic cranial irradiation; NR, not reached.
Source: ADRIATIC interim CSR Table 14.2.2.1.A;[1] ADRIATIC study publication Figure 1A.[2]

Figure 4: KM plot of OS (FAS)



	No. of Deaths/ Total No. (%)	Median Overall Survival (95% CI)
		mo
Durvalumab	115/264 (43.6)	55.9 (37.3–NR)
Placebo	146/266 (54.9)	33.4 (25.5–39.9)

Stratified hazard ratio for death, 0.73 (98.321% CI, 0.54–0.98)
P=0.01

Tick marks indicate censored data, and dashed lines the times of the landmark analyses at 24 months and 36 months. Formal testing for the proportional-hazards assumption provided a p-value of 0.91, which indicated the plausibility of the assumption.
Abbreviations: CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; NR, not reached; OS, overall survival.
Source: ADRIATIC study publication Figure 1A.[2]

B.2.6.1.1.1 Sensitivity analysis of overall survival

Sensitivity analysis supported the robustness of the primary analysis. A KM plot of time to censoring (where the censoring indicator of OS was reversed) showed there was no difference in the pattern of censoring for the OS endpoint between treatment groups (Appendix N). There were [redacted] and [redacted] patients censored prematurely (i.e., survival status not defined at the DCO) in the durvalumab and placebo groups, respectively, and [redacted] and [redacted] patients censored >24 weeks before the DCO in the durvalumab and placebo groups, respectively (Appendix N).

Effect of covariates

In a Cox proportional hazards model, stratified by receipt of PCI and including covariates for treatment, sex, age at randomisation, smoking status, WHO/ECOG PS at baseline, region, race, time from last dose of cCRT to randomisation, prior platinum chemotherapy, prior radiotherapy regimen, and best response to cCRT, the OS effect of durvalumab treatment compared with placebo (HR: [redacted]) (Appendix N) was similar to the estimate from a model excluding covariates (HR: [redacted]), suggesting the covariates did not have an effect on the OS HR estimate.

B.2.6.1.1.2 Subgroup analyses

Subgroup analyses of OS demonstrated a broadly consistent treatment effect in favour of durvalumab treatment, with a HR <1.0 for most prespecified subgroups (Figure 5 and Appendix E).

Two subgroups demonstrated an OS HR point estimate ≥1: patients with a time of ≥84 days from last dose of radiotherapy to randomisation in this study (HR: [redacted]); and patients with TNM Stage I or II based on IVRS (HR: [redacted]) (Appendix E). The number of events in these subgroups was relatively small, leading to a high degree of uncertainty in the HR estimates, as characterised by the wide CIs. The study was not sized for any of the individual subgroup evaluations and no adjustments were made for multiple testing subgroup analyses.

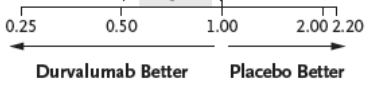
Effect of treatment

A global interaction test was performed by comparing the fit of a Cox proportional hazards model including treatment, all stratification variables, and stratification variables by treatment interactions, with the fit of the model that excludes the interaction terms. This returned a non-statistically significant result ([redacted]), suggesting that the observed treatment effect was largely consistent across the strata levels (Appendix E).

Figure 5: Forest plot of OS by subgroup (FAS)

B Subgroup Analysis of Overall Survival

Subgroup	Durvalumab	Placebo	Hazard Ratio for Death (95% CI)
	no. of deaths/total no. of patients (%)		
All patients, intention-to-treat analysis	115/264 (43.6)	146/266 (54.9)	0.73 (0.57–0.93)
Age at randomization			
<65 yr	69/160 (43.1)	83/162 (51.2)	0.76 (0.55–1.04)
≥65 yr	46/104 (44.2)	63/104 (60.6)	0.70 (0.48–1.02)
Sex			
Male	79/178 (44.4)	108/188 (57.4)	0.70 (0.52–0.93)
Female	36/86 (42)	38/78 (49)	0.83 (0.52–1.31)
Race			
White	60/130 (46.2)	77/137 (56.2)	0.75 (0.53–1.05)
Asian	53/131 (40.5)	64/121 (52.9)	0.72 (0.50–1.04)
Geographic region			
Asia	51/129 (39.5)	62/120 (51.7)	0.72 (0.50–1.04)
Europe	41/94 (44)	64/112 (57.1)	0.67 (0.45–0.98)
North America or South America	23/41 (56)	20/34 (59)	0.98 (0.54–1.80)
WHO performance-status score at screening			
0	48/133 (36.1)	74/131 (56.5)	0.55 (0.38–0.79)
1	67/131 (51.1)	72/135 (53.3)	0.94 (0.67–1.31)
Smoking status			
Current or former smoker	108/241 (44.8)	138/240 (57.5)	0.72 (0.56–0.92)
Nonsmoker	7/23 (30)	8/26 (31)	NC
Tumor–node–metastasis stage			
I or II	11/33 (33)	12/34 (35)	0.92 (0.40–2.11)
III	104/231 (45.0)	134/232 (57.8)	0.71 (0.55–0.91)
Previous chemotherapy			
Carboplatin–etoposide	31/91 (34)	46/88 (52)	0.56 (0.35–0.89)
Cisplatin–etoposide	84/173 (48.6)	100/178 (56.2)	0.82 (0.61–1.10)
Previous radiotherapy schedule			
Once daily	92/195 (47.2)	107/187 (57.2)	0.72 (0.55–0.95)
Twice daily	23/69 (33)	39/79 (49)	0.68 (0.40–1.14)
Best response to concurrent CRT			
Complete response	12/31 (39)	15/34 (44)	0.90 (0.41–1.92)
Partial response	88/191 (46.1)	116/200 (58.0)	0.76 (0.57–1.00)
Stable disease	15/42 (36)	15/32 (47)	0.54 (0.25–1.13)
Time from end of concurrent CRT to randomization			
<14 days	14/32 (44)	24/32 (75)	0.47 (0.24–0.91)
14 to <28 days	37/79 (47)	51/80 (64)	0.59 (0.38–0.90)
≥28 days	64/153 (41.8)	71/154 (46.1)	0.90 (0.64–1.27)
Receipt of prophylactic cranial irradiation			
Yes	53/142 (37.3)	67/143 (46.9)	0.75 (0.52–1.07)
No	62/122 (50.8)	79/123 (64.2)	0.71 (0.51–0.99)



HR (Durvalumab vs placebo) and 95%CI are displayed on a logarithmic scale.
Size of circle is proportional to the number of events.
Band represents the 95% CI for the main OS HR.
Abbreviations: CRT, chemotherapy concurrent with radiotherapy; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; HR, hazard ratio; IVRS Interactive Voice Response System; OS, overall survival; PCI, prophylactic cranial irradiation; PR, partial response; PS, performance score; SD, stable disease; TNM, tumour, node, metastasis; WHO, World Health Organization.
Sources: ADRIATIC study publication Figure 1B.[2]

B.2.6.1.2 Progression-free survival

Prolonging PFS and avoiding disease progression to ES-SCLC is important for patients and an important indicator of treatment efficacy. Progression-free survival is considered a recognised endpoint in oncology trials as it is assessed prior to survival and therefore not subject to any potential confounding effect of subsequent therapy. As of the DCO for PFS-IA, overall PFS data maturity was 58.1%;[2] PFS events were reported for 52.7% of patients in the durvalumab group and 63.5% of patients in the placebo group.

ADRIATIC met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS with durvalumab treatment compared with placebo.

The median duration of PFS follow-up in all patients was 9.07 months in the durvalumab group and 7.39 months in the placebo group. At the DCO, durvalumab treatment resulted in a clinically meaningful and statistically significant improvement in (i.e. longer) PFS per BICR compared with placebo (HR: 0.76; 97.195% CI: 0.59, 0.98; p=0.02), corresponding to a 24% reduction in the risk of disease progression death.[2] The KM-estimated median PFS was longer with durvalumab treatment compared with placebo (16.6 months; 95% CI: 10.2, 28.2 versus 9.2 months; 95% CI: 7.4, 12.9), representing an estimated improvement in median PFS of 7.4 months (Table 17 and Figure 6).[2]

The PFS KM curves separated after approximately 6 months, and demonstrated a clear and sustained separation, which increased over time and was sustained thereafter, as reflected in the landmark estimates of PFS at 18 months and 24 months (PFS18 and PFS24) that favoured durvalumab treatment (48.8% and 46.2%, respectively) over placebo (36.1% and 34.2%, respectively) (Table 17).

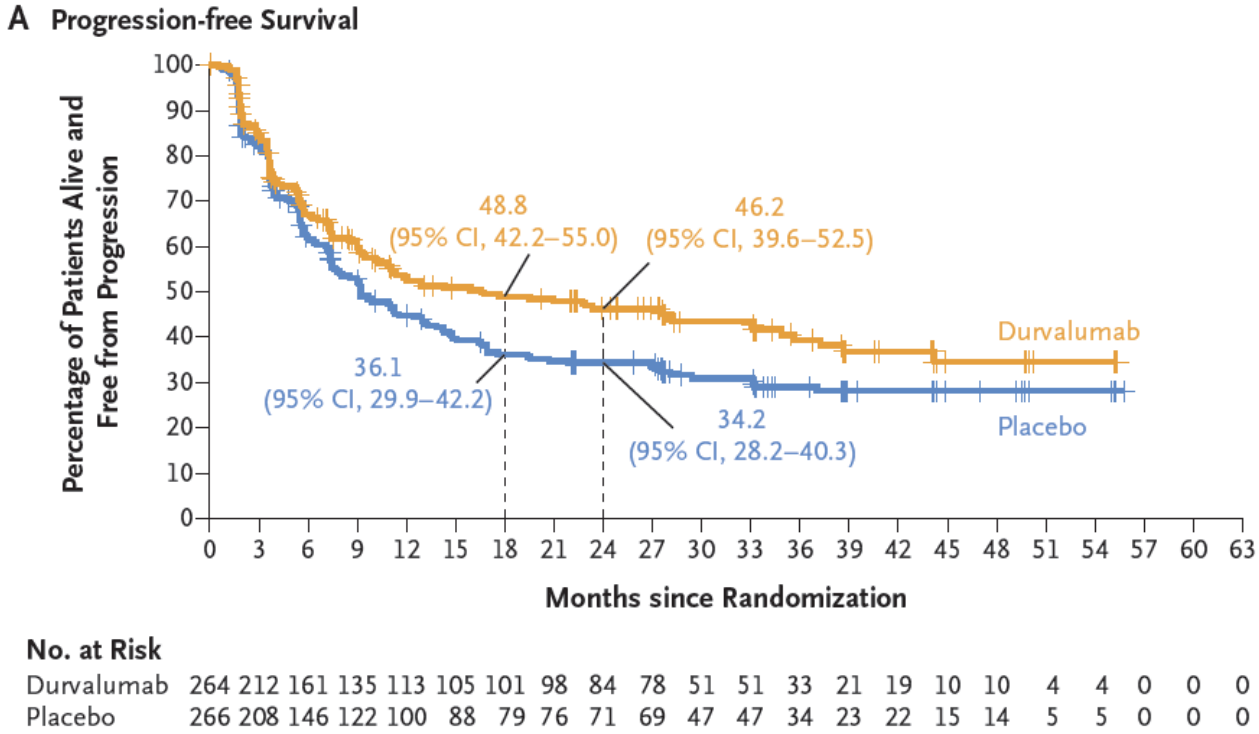
The PFS outcomes from the ADRIATIC study align with the opinion of UK clinicians that functional cure is currently achieved in most patients who remain progression-free for 3–5 years after CRT treatment.[17] This is suggested by plateauing of the Kaplan-Meier curves in both the treatment and placebo arms.

Table 17: PFS per BICR (FAS)

Outcome	Durvalumab (n=264)	Placebo (n=266)
Total events, n (%)†	139 (52.7)	169 (63.5)
RECIST progression	126 (47.7)	158 (59.4)
Target lesions‡	[redacted]	[redacted]
Non-target lesions‡	[redacted]	[redacted]
New lesions‡	[redacted]	[redacted]
Death in absence of progression	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Censored RECIST progression§	[redacted]	[redacted]
Censored death¶	[redacted]	[redacted]
Progression-free at time of analysis††	[redacted]	[redacted]
Lost to follow-up‡‡	[redacted]	[redacted]
Withdrawn consent‡‡	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]
PFS, months		
Median (95% CI)§§	16.6 (10.2, 28.2)	9.2 (7.4, 12.9)
PFS at 18 months (PFS18), %		
Rate (95% CI)§§	48.8 (42.2, 55.0)	36.1 (29.9, 42.2)
PFS at 24 months (PFS24), %		
Rate (95% CI)§§	46.2 (39.6, 52.5)	34.2 (28.2, 40.3)
HR¶¶,†††	0.76	
98.816% CI¶¶,‡‡‡	0.53, 1.08	
97.195% CI¶¶,‡‡‡	0.59, 0.98	
95% CI¶¶	0.61, 0.95	
p-value§§§	0.02	

†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. ‡Target lesions, non-target lesions and new lesions are not necessarily mutually exclusive categories. §RECIST progression event occurred after two or more missed visits or within two visits of baseline where the patient had no evaluable visits or did not have a baseline assessment. ¶Death occurred after two or more missed visits in the absence of RECIST progression. ††Includes patients, known to be alive, or with no evaluable baseline RECIST assessment (censored at Day 1). ‡‡Patients censored at last evaluable RECIST assessment. §§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. ¶¶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. †††A HR < 1 favours durvalumab to be associated with a longer event-free survival than placebo. ‡‡‡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. §§§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).
Abbreviations: BICR, Blinded Independent Central Review; CI, confidence interval; DCO, data cut-off; FAS, full analysis set; HR hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; PFS18, PFS at 18 months following randomisation; PFS24 PFS at 24 months following randomisation; PCI, prophylactic cranial irradiation; RECIST, Response Evaluation Criteria In Solid Tumours.
Source: ADRIATIC interim CSR Table 14.2.1.1.A;[1] ADRIATIC study publication.[2]

Figure 6: KM plot of PFS per BICR (FAS)



	No. of Events/ Total No. (%)	Median Progression-free Survival (95% CI)
		mo
Durvalumab	139/264 (52.7)	16.6 (10.2–28.2)
Placebo	169/266 (63.5)	9.2 (7.4–12.9)

Stratified hazard ratio for disease progression or death, 0.76
(99.816% CI, 0.53–1.08)
(97.195% CI, 0.59–0.98)
P=0.02

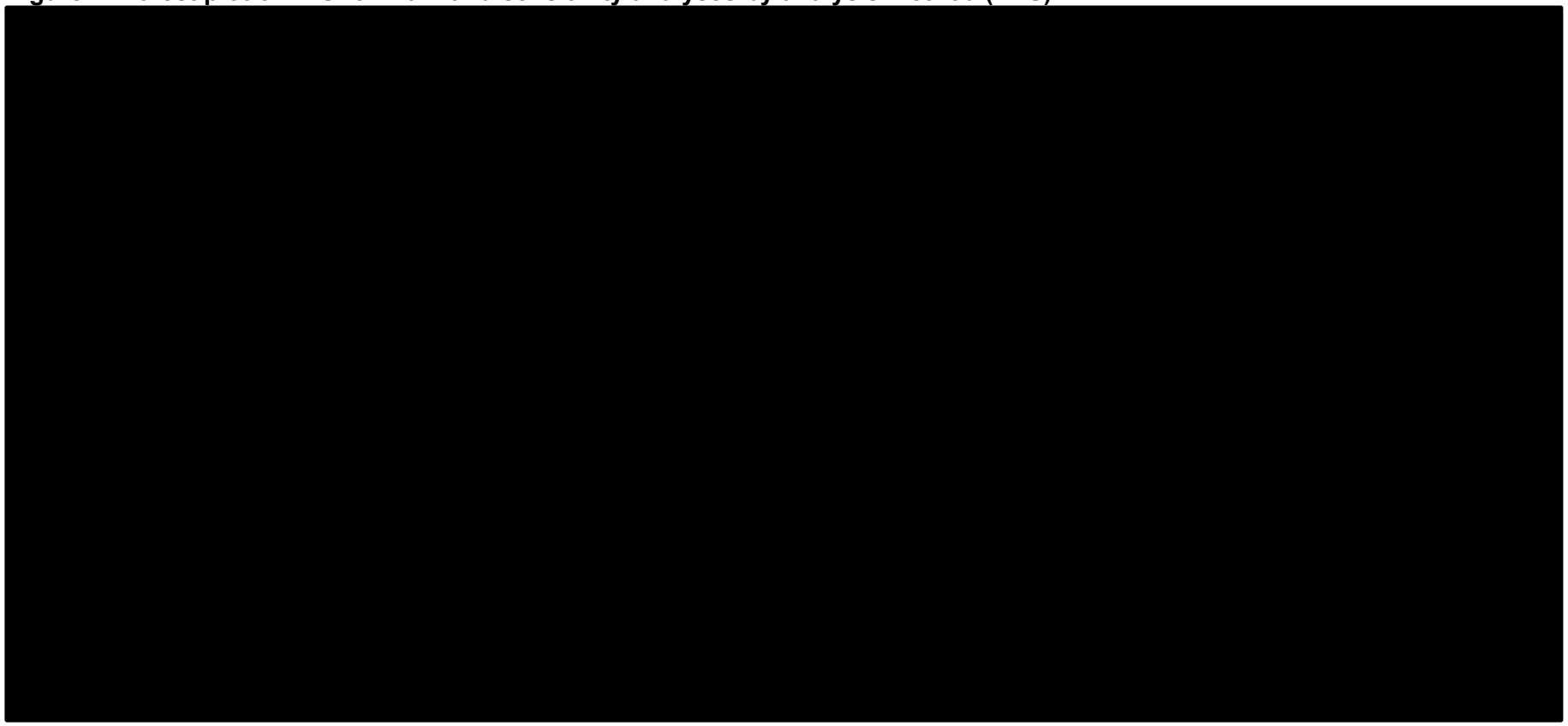
Kaplan–Meier curves for progression-free survival as assessed by means of blinded independent central review.
Tick marks indicate censored data, and dashed lines the times of the landmark analyses at 18 months and 24 months.
Formal testing for the proportional-hazards assumption provided a P value of 0.79, indicating the plausibility of the assumption.
Abbreviations: BICR, Blinded Independent Central Review; CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival.
Source: ADRIATIC study publication Figure 2A.[2]

B.2.6.1.2.1 Sensitivity analysis of progression-free survival

Pre-specified sensitivity analysis assessing evaluation-time, attrition, and ascertainment bias supported the robustness of the primary analysis (Figure 7):

- Interval censored analysis of PFS by BICR to assess evaluation-time bias: HR: [redacted])
- Analysis of PFS per BICR using alternative censoring rules to assess attrition bias: HR: [redacted])
- Analysis of PFS per Investigator assessments to assess ascertainment bias: HR: [redacted])

Figure 7: Forest plot of PFS for main and sensitivity analyses by analysis method (FAS)



HR (Durvalumab vs placebo) and 95%CI are displayed on a logarithmic scale.
Size of circle is proportional to the number of events.
Band represents the 95% CI for the main PFS HR.
Abbreviations: CI, confidence interval; Durva, durvalumab; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival.
Sources: ADRIATIC interim CSR Figure 14.2.1.11.1.A; Forest plot for analyses in [a] Table 14.2.1.1.A, [b] Table 14.2.1.3.A, [c] Table 14.2.1.4.1.A, and [d] Table 14.2.1.2.A.[1]

A KM plot of time to censoring (where the censoring indicator of PFS per BICR was reversed) showed patients in the durvalumab group were potentially censored for PFS earlier compared with the placebo group (Appendix N). There were [redacted] ([redacted]) and [redacted] ([redacted]) patients censored prematurely (i.e., the latest scan prior to DCO was >1 scheduled tumour assessment interval plus 2 weeks) in the durvalumab and placebo groups, respectively, and [redacted] ([redacted]) and [redacted] ([redacted]) patients censored >24 weeks before the DCO, respectively (Appendix N).

Effect of covariates

In a Cox proportional hazards model, stratified by receipt of TNM disease stage and PCI, and including covariates specified for OS in Section B.2.6.1.1.1, the PFS effect of durvalumab treatment compared with placebo (HR: [redacted]) was similar to the estimate from a model excluding covariates (HR: [redacted]) (Appendix N), suggesting the covariates did not have an effect on the PFS HR estimate.

B.2.6.1.2.2 Subgroup analyses

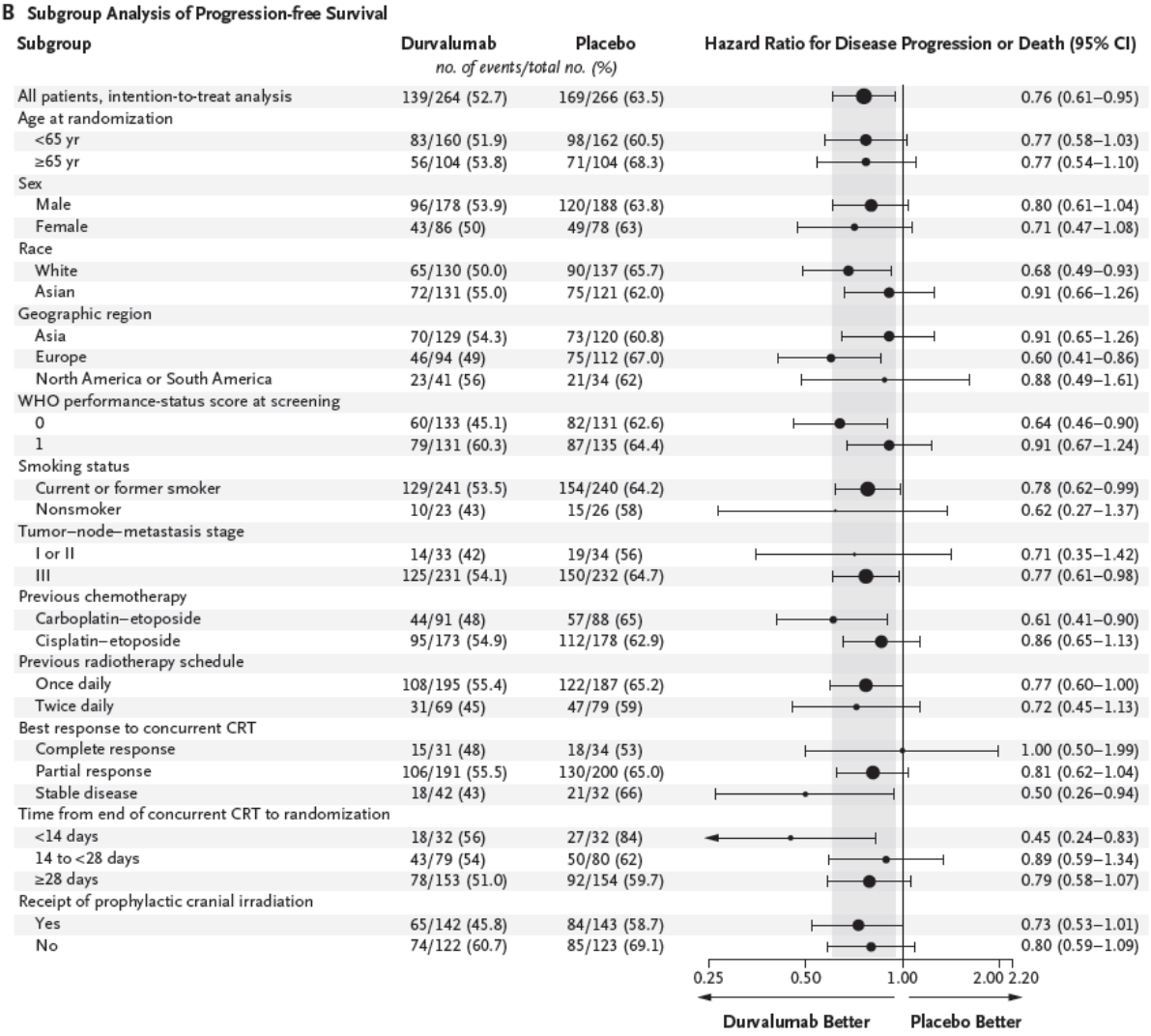
Subgroup analyses of PFS per BICR demonstrated a broadly consistent treatment effect in favour of durvalumab treatment, with a HR <1.0 for most prespecified subgroups (Figure 5 and Appendix E).

Two subgroups demonstrated a PFS HR point estimate ≥1: patients with a time of ≥84 days from last dose of radiotherapy to randomisation in this study (HR: [redacted]); and patients who had best response of CR to prior cCRT (HR: [redacted]) (Appendix E). The number of events in these subgroups was relatively small, leading to a high degree of uncertainty in the HR estimates, as characterised by the wide CIs. The study was not sized for any of the individual subgroup evaluations and no adjustments were made for multiple testing subgroup analyses.

Effect of treatment

A global interaction test was performed as described for OS in Section B.2.6.1.1.2. This returned a non-statistically significant result ([redacted]), suggesting that the observed treatment effect was largely consistent across the strata levels (Figure 8 and Appendix E).

Figure 8: Forest plot of PFS per BICR by subgroup (FAS)



PFS in prespecified subgroups. The size of the circle is proportional to number of events across the two trial groups. The arrow indicates that the 95% confidence interval extends outside the graphed area.
Abbreviations: cCRT, chemotherapy concurrent with radiotherapy; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; HR, hazard ratio; IVRS Interactive Voice Response System; PCI, prophylactic cranial irradiation; PFS, progression-free survival; PR, partial response; PS, performance score; SD, stable disease; TNM, tumour, node, metastasis; WHO, World Health Organization.
Sources: ADRIATIC study publication Figure 2B.[2]

B.2.6.2 Secondary efficacy outcomes

Relevant secondary efficacy outcomes for durvalumab that were assessed in ADRIATIC are presented in this section, with additional supporting secondary outcomes presented in Appendix N.

B.2.6.2.1 Objective response rate

Objective response rate (ORR) was assessed in patients with measurable disease at baseline. Based on unconfirmed responses per BICR, ORR was similar between groups (30.3% with durvalumab versus 32.0% with placebo; difference in proportion: -1.2%; 95% CI: -11.0, 8.5). Confirmed ORR per BICR was also similar between groups ([redacted] with durvalumab versus [redacted] with placebo; difference in proportion: [redacted]) (Table 18). ORR per Investigator was higher in the durvalumab group compared with placebo (see Section B.2.6.2.1.1).

Table 18: ORR per BICR (FAS)

Outcome	Durvalumab (n=264)	Placebo (n=266)
Unconfirmed ORR		
Number of patients	175	169
Responders, n (%)†	53 (30.3)	54 (32.0)
95% CI	23.6, 37.7	25.0, 39.6
Difference in proportion vs placebo‡	-1.2	
95% CI	-11.0, 8.5	
Confirmed ORR		
Number of patients	175	169
Responders, n (%)†	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Difference in proportion vs placebo‡	[redacted]	
95% CI	[redacted]	

†ORR is defined as the number (%) of patients with at least one visit response of CR or PR. Patients who did not have measurable disease at baseline (ie, CR after cCRT) are excluded from the analysis. Patients who discontinued treatment without progression, received a subsequent anti-cancer therapy, and then responded are not included as responders. A confirmed response of CR/PR means that a response of CR/PR was recorded at one visit and confirmed by repeat imaging ≥28 days after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. ‡The analysis was performed using a Cochran-Mantel-Haenszel test stratified by TNM stage (Stage I/II vs III) and receipt of PCI (yes vs no). CIs were calculated using Miettinen and Nurminen's method.
Response was determined by the RECIST-based assessment of the BICR.
n=Patients with ORR defined.
CIs for the response rate within each group were produced using the exact methods of Clopper-Pearson.
A difference in proportion >0% favours durvalumab over placebo.
Stratification factors are based on the values entered into the IVRS.
Abbreviations: BICR, Blinded Independent Central Review; cCRT, chemotherapy concurrent with radiotherapy; CI, confidence interval; CR, complete response; FAS, full analysis set; ORR, objective response rate; PCI, prophylactic cranial irradiation; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours; TNM, tumour, node, metastasis.
Source: ADRIATIC interim CSR Table 14.2.3.1.1.A and 14.2.3.2.1.A.[1]

B.2.6.2.1.1 Sensitivity analysis for ORR

ORR per Investigator was numerically higher compared with ORR per BICR in the durvalumab group (Table 19). Based on unconfirmed responses per Investigator, ORR was higher in the durvalumab group compared with placebo ([redacted] with durvalumab versus [redacted] with placebo; difference in proportion: [redacted]). Confirmed ORR per Investigator was also higher in the durvalumab group compared with placebo ([redacted] with durvalumab versus [redacted] with placebo; difference in proportion: [redacted]) (Table 19).

Table 19: ORR per Investigator (FAS)

Outcome	Durvalumab (n=264)	Placebo (n=266)
Unconfirmed ORR		
Number of patients	[redacted]	[redacted]
Responders, n (%)†	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Difference in proportion vs placebo‡	[redacted]	
95% CI	[redacted]	
Confirmed ORR		
Number of patients	[redacted]	[redacted]
Responders, n (%)†	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Difference in proportion vs placebo‡	[redacted]	
95% CI	[redacted]	

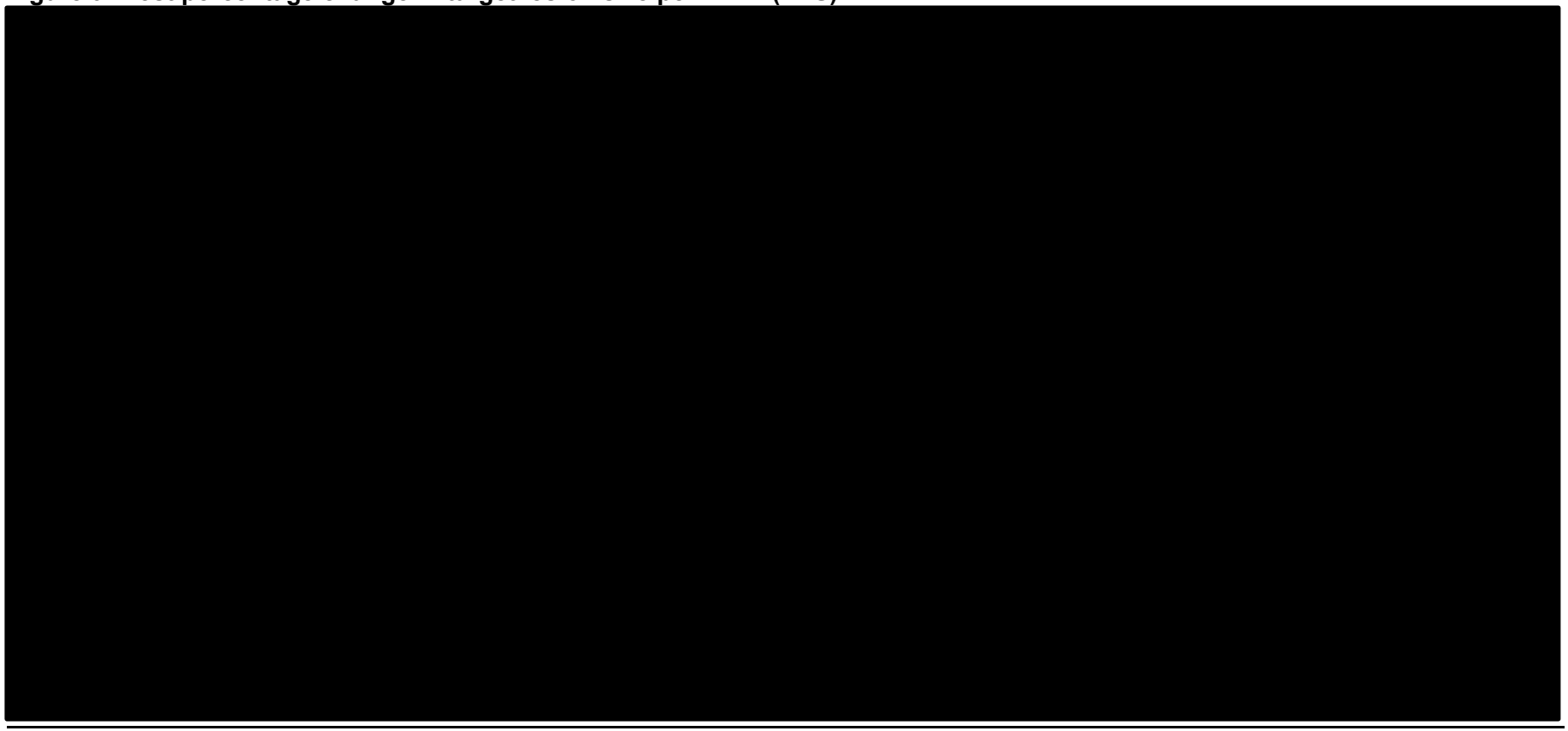
†ORR is defined as the number (%) of patients with at least one visit response of CR or PR. Patients who did not have measurable disease at baseline (ie, CR after cCRT) are excluded from the analysis. Patients who discontinued treatment without progression, received a subsequent anti-cancer therapy, and then responded are not included as responders. A confirmed response of CR/PR means that a response of CR/PR was recorded at one visit and confirmed by repeat imaging ≥28 days after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. ‡The analysis was performed using a Cochran-Mantel-Haenszel test stratified by TNM stage (Stage I/II vs III) and receipt of PCI (yes vs no). CIs were calculated using Miettinen and Nurminen's method.
Response was determined by the RECIST-based assessment of the BICR.
n=Patients with ORR defined.
CIs for the response rate within each group were produced using the exact methods of Clopper-Pearson.
A difference in proportion >0% favours durvalumab over placebo.
Stratification factors are based on the values entered into the IVRS.
Abbreviations: BICR, Blinded Independent Central Review; cCRT, chemotherapy concurrent with radiotherapy; CI, confidence interval; CR, complete response; FAS, full analysis set; ORR, objective response rate; PCI, prophylactic cranial irradiation; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours; TNM, tumour, node, metastasis.
Source: ADRIATIC interim CSR Table 14.2.3.3.1.A and 14.2.3.4.1.A.[1]

B.2.6.2.1.2 Best change from baseline in target lesion size (tumour shrinkage)

The best change in target lesion size was defined as the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. The

majority of patients in both treatment groups with measurable disease at baseline had a reduction in tumour size. The best improvement in target lesion size per BICR was a mean change of [redacted] and a median change of [redacted] (range: [redacted]) in the durvalumab group, compared with a mean change of [redacted] and a median change of [redacted] (range: [redacted]) in the placebo group. Best percentage change from baseline in target lesion size per BICR for patients with measurable disease at baseline are presented in Figure 9.

Figure 9: Best percentage change in target lesion size per BICR (FAS)



Target lesion size is the sum of diameters of target lesions.
Assessments up to and including the first progressive disease are considered when identifying the best percentage change from baseline.
n=Patients with a best percentage change from baseline.
Dotted reference lines at -30% and 20% indicate thresholds for PR and progressive disease, respectively.
Patients with progressive disease as best overall response are marked with a dot.
Patients with best percentage change <-100 or >100 are marked with a hash.
Abbreviations: BICR, Blinded Independent Central Review; Durva, durvalumab; FAS, full analysis set; PCI, prophylactic cranial irradiation; PR, partial response; TNM, tumour, node, metastasis.
Source: ADRIATIC interim CSR Figure 14.2.10.3.A.[1]

B.2.6.2.1.3 Best objective response

At the DCO, 53 (30.3%) patients in the durvalumab group and 54 (32.0%) patients in the placebo group had an unconfirmed response per BICR. Of these patients, 5 (2.9%) patients in the durvalumab group and 4 (2.4%) patients in the placebo group had a best objective response (BOR) of CR, and 48 (27.4%) patients in the durvalumab group and 50 (29.6%) patients in the placebo group had a BOR of PR.[2] Stable disease was reported for 53.7% of patients in the durvalumab group and 45.0% of patients in the placebo group.[2]

A total of [redacted] patients in the durvalumab group and [redacted] patients in the placebo group had a confirmed response per BICR. Of these patients, [redacted] patients in the durvalumab group and [redacted] patients in the placebo group had a confirmed BOR of CR, and [redacted] patients in the durvalumab group and [redacted] patients in the placebo group had a confirmed BOR of PR.

B.2.6.2.1.4 Duration of response

The median (95% CI) duration of response (DoR) per BICR for patients with an unconfirmed response was longer in the durvalumab group compared with placebo (33.0 months [22.4, NR] with durvalumab versus 27.7 months [9.6, NR] with placebo).[2] The median (95% CI) DoR per BICR for patients with a confirmed response was also longer in the durvalumab group compared with placebo ([redacted] with durvalumab versus [redacted] with placebo). Based on KM estimates, 71.0% (95% CI: 57.0, 82.0) and 55.0% (95% CI: 39.0, 68.0) of patients in the durvalumab and placebo groups, respectively, were estimated to remain in response at 18 months after onset of response using unconfirmed responses (Table 20 and Figure 10).[2]

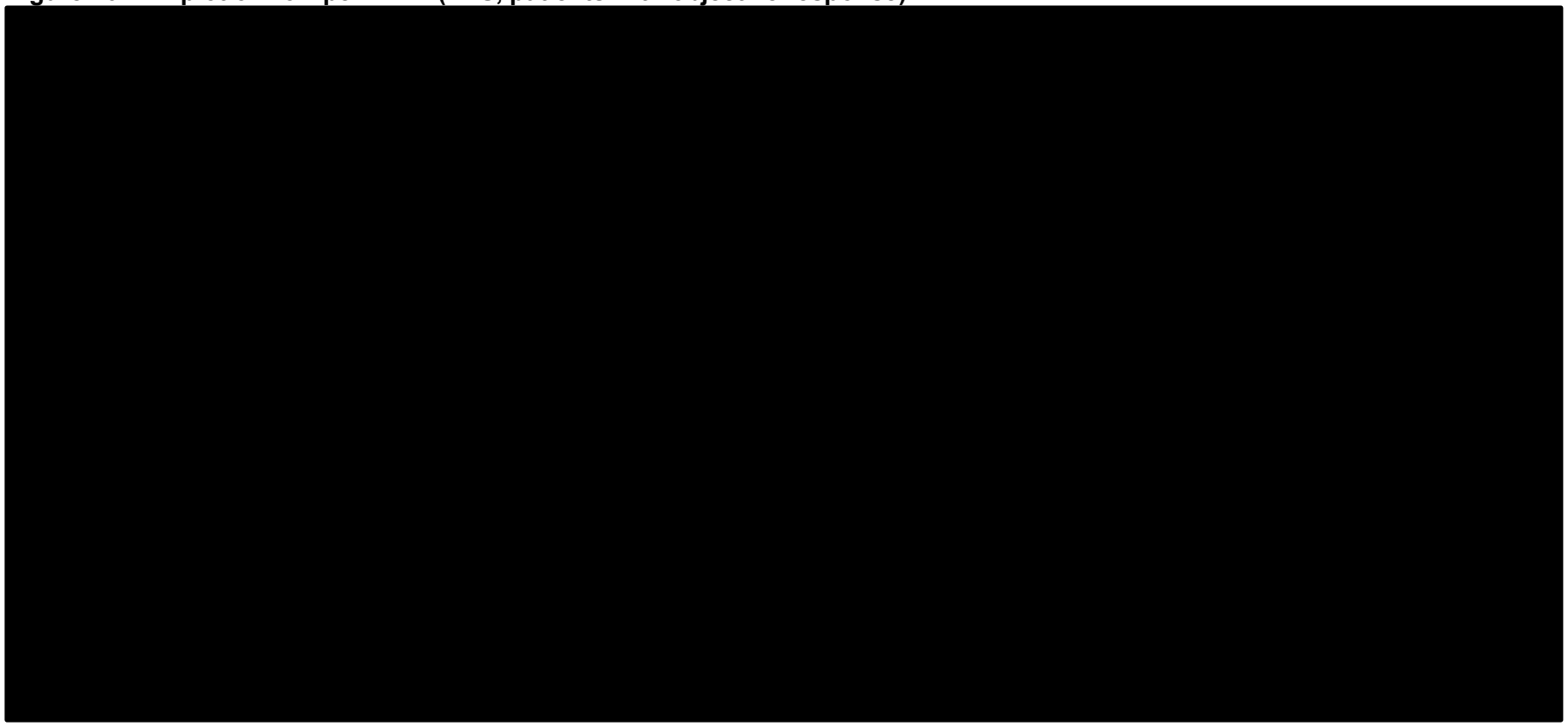
Table 20: DoR per BICR (FAS, patients with unconfirmed and confirmed ORR)

Outcome	Durvalumab (n=53)	Placebo (n=54)	Durvalumab (n=45)	Placebo (n=44)
	Unconfirmed		Confirmed†	
Number of responders who progressed or died	**22**	**23**	**16**	**19**
DoR from onset of response, months‡,§				
Median (95% CI)	33.0 (22.4, NR)	27.7 (9.6, NR)	[redacted]	[redacted]
25th percentile, 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	Durvalumab (n=53)	Placebo (n=54)	Durvalumab (n=45)	Placebo (n=44)
	Unconfirmed		Confirmed†	
Patients remaining in response, %§				
At 16 months	[redacted]	[redacted]	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]	[redacted]	[redacted]
At 18 months	71.0	55.0	[redacted]	[redacted]

†A confirmed response of CR/PR means that a response of CR/PR was recorded at 1 visit and confirmed by repeat imaging ≥28 days after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. ‡DoR is the time from the first documented response (CR/PR) until the date of first documented progression or death in the absence of disease progression. 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. §Calculated using the KM technique. CI for median DoR is derived based on Brookmeyer-Crowley method with log-log transformation.
Response was determined by the RECIST-based assessment of the BICR.
n=Patients with ORR defined.
CIs for the response rate within each group were produced using the exact methods of Clopper-Pearson.
Abbreviations: BICR, Blinded Independent Central Review; CI, confidence interval; CR, complete response; DoR, duration of response; FAS, full analysis set; KM, Kaplan-Meier; NR, not reached; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours.
Source: ADRIATIC interim CSR Table 14.2.5.1 and 14.2.5.2;[1] ADRIATIC study publication Figure 2B.[2]

Figure 10: KM plot of DoR per BICR (FAS, patients with objective response)



Response was determined by the RECIST-based assessment of the BICR.
Circle indicates a censored observation.
Abbreviations: BICR, Blinded Independent Central Review; DoR, duration of response; Durva, durvalumab; FAS, full analysis set; KM, Kaplan-Meier; RECIST, Response Evaluation Criteria In Solid Tumours.
Source: ADRIATIC interim CSR Figure 14.2.5.3.1.A.[1]

B.2.6.2.2 Progression-free survival 2

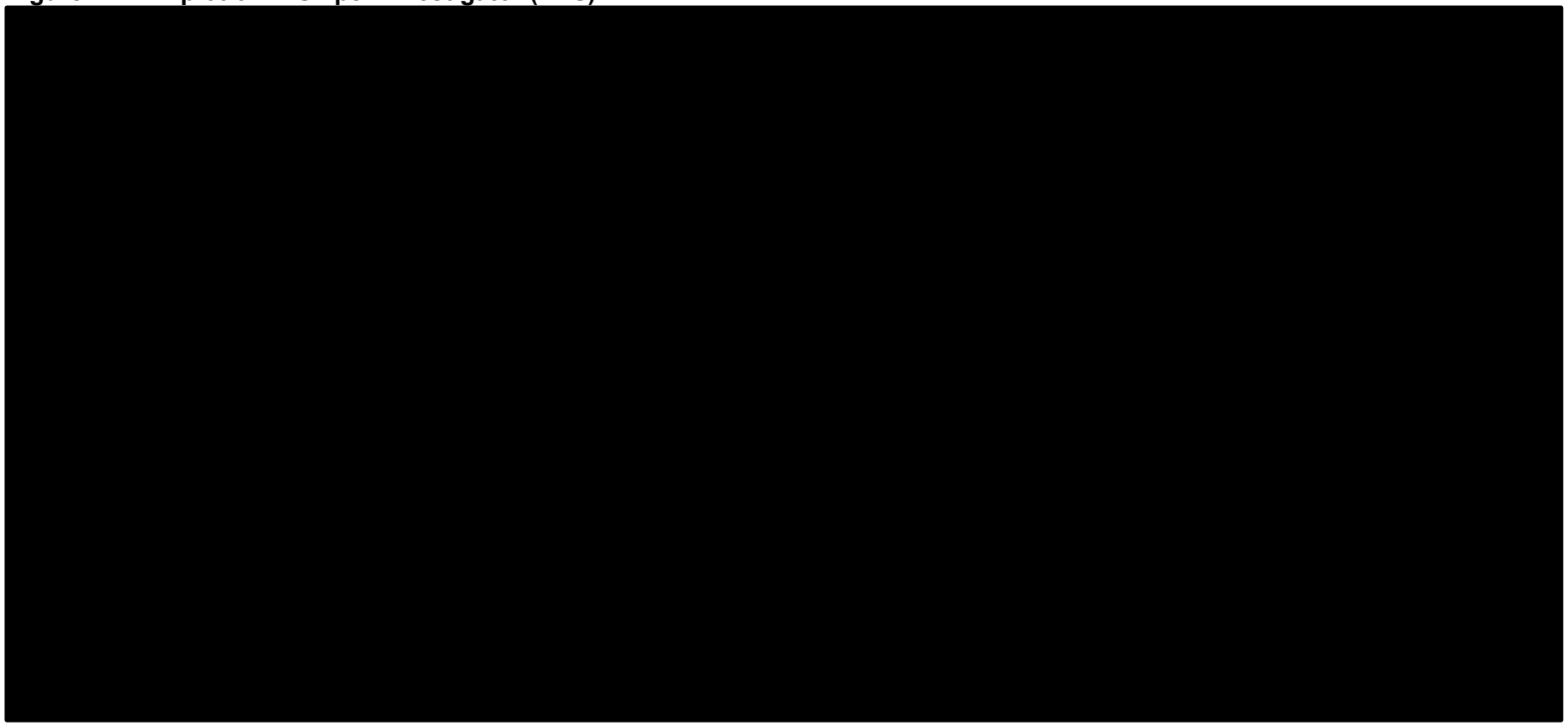
Progression-free survival 2 events were defined as a second disease progression, as determined by the Investigator, or death. At the DCO, PFS2 events were reported for fewer patients in the durvalumab group compared with placebo ([redacted] patients with durvalumab versus [redacted]) patients with placebo). Treatment with durvalumab resulted in an improvement in PFS2 (HR: [redacted]), and a longer KM-estimated median PFS2 (median PFS2 not reached) compared with placebo ([redacted]) (Table 21 and Figure 11).

Table 21: PFS2 per Investigator (FAS)

Outcome	Durvalumab (n=264)	Placebo (n=266)
Total events, n (%)†	[redacted]	[redacted]
Second disease progression	[redacted]	[redacted]
Symptomatic progression	[redacted]	[redacted]
Objective radiological progression	[redacted]	[redacted]
Other	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Censored second progression‡	[redacted]	[redacted]
Censored death§	[redacted]	[redacted]
Alive and second progression-free	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrawn consent	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]
Median PFS2, months¶	[redacted]	[redacted]
95% CI for median PFS2¶	[redacted]	[redacted]
HR††, ‡‡	[redacted]	
95% CI for HR††	[redacted]	

†Patients who had a first PFS event, but no second event were censored at last available PFS2 assessment. Patients who died as a first PFS were then censored for PFS2 at the date of death. Patients who had a first PFS event and then died subsequently had their PFS2 event at date of death. Patients without any first PFS event were censored at their last available scan. Patients who experienced second progression or died after two or more missed visits were censored at last PFS2 assessment prior to the two missed visits. ‡Second progression occurred after two or more missed visits. § Death in absence of second progression after two or more missed visits. ¶Calculated using the KM technique. CI for median time to event is derived based on Brookmeyer-Crowley method with log-log transformation. ††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. ‡‡HR <1 favours durvalumab to be associated with a longer event-free survival than placebo.
Second progression is determined by the Investigator according to local standard clinical practice.
Stratification factors are based on the values entered into the IVRS.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR hazard ratio; IVRS, interactive voice response system; PFS, progression-free survival; PFS2; time from randomisation to second progression or death; PCI, prophylactic cranial irradiation; NR, not reached; TNM, tumour, node, metastasis.
Source: ADRIATIC interim CSR Table 14.2.7.1.A.[1]

Figure 11: KM plot of PFS2 per Investigator (FAS)



Abbreviations: CI, confidence interval; Durva, durvalumab; FAS, full analysis set; KM, Kaplan-Meier; NR, not reached; PFS2, time from randomisation to second progression or death.
Source: ADRIATIC interim CSR Figure 14.2.7.2.1.A.[1]

B.2.6.2.3 Time to death or distant metastases

Time to death or distant metastases (TTDM) per BICR was analysed as a secondary endpoint, with TTDM per Investigator included as a planned sensitivity analysis (Table 22). Both TTDM per BICR and per Investigator were consistent with each other, suggesting an improvement in TTDM with durvalumab compared with placebo (TTDM per BICR HR: [redacted] and TTDM per Investigator HR: [redacted]) (Table 22). However, due to the incomplete BICR data available at this IA, no conclusions regarding the endpoint of BICR-assessed TTDM were drawn.

Table 22: TTDM per BICR and per Investigator (FAS)

Outcome	Durvalumab (n=264)	Placebo (n=266)	Durvalumab (n=264)	Placebo (n=266)
	Unconfirmed		Confirmed†	
Total events, n (%)†	[redacted]	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]	[redacted]
Death in absence of distant metastases	[redacted]	[redacted]	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored distant metastasis‡	[redacted]	[redacted]	[redacted]	[redacted]
Censored death§	[redacted]	[redacted]	[redacted]	[redacted]
Distant metastasis free at time of analysis	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawn consent	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]	[redacted]	[redacted]
Median TTDM (months)¶	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for median TTDM¶	[redacted]	[redacted]	[redacted]	[redacted]
HR, D vs placebo††, ‡‡	[redacted]		[redacted]	
95% CI for HR††	[redacted]		[redacted]	

†Patients who had not developed distant metastasis or died were censored at the time of the latest date of assessment from their last RECIST assessment. Patients who had distant metastasis or died after two or more missed visits were censored at the time of the latest RECIST assessment prior to the two missed visits. Patients with no evaluable visits or with no baseline data were censored at Day 1 unless they died within two visits of baseline. ‡Distant metastasis occurred after two or more missed visits or within two visits of baseline where the patient had no evaluable visits or did not have a baseline assessment. §Death which occurred after two or more missed visits in the absence of distant metastasis. ¶Calculated using the KM technique. CI for median time to event is derived based on Brookmeyer-Crowley method with log-log transformation. ††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.
‡‡A HR <1 favours durvalumab to be associated with a longer event-free survival than placebo.
Distant metastasis was determined by the RECIST-based assessment of the BICR or Investigator.
Note: Date and location information for new lesions used to support TTDM analysis by BICR were incomplete.
Stratification factors are based on the values entered into the IVRS.

Abbreviations: BICR, Blinded Independent Central Review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IVRS, interactive voice response system; KM, Kaplan-Meier; NR, not reached; PCI, prophylactic cranial irradiation; RECIST, Response Evaluation Criteria In Solid Tumours; TNM, tumour, node, metastasis; TTDM, time to death or distant metastases.
Source: ADRIATIC interim CSR Table 14.2.6.1.A and 14.2.6.2.A.[1]

B.2.6.3 Exploratory endpoints

Exploratory endpoints relating to HRQoL assessed by PRO-CTCAE (Section B.2.6.4.2.1), PGIS (Section B.2.6.4.2.2), and EQ-5D-5L (Section B.2.6.4.2.3), and health economics (hospital admissions) are discussed in the respective sections in the submission document. Details of the PRO measures/questionnaires are presented in Appendix N.

B.2.6.4 Health-related quality of life

Preserving HRQoL and avoiding disease progression and worsening health states is important for patients, with HRQoL considered a major endpoint when investigating the clinical benefit of new therapeutic strategies for patients, and an important indicator of treatment efficacy as well as safety and tolerability.[49]

Patient-reported outcome (PRO) measures were included as secondary endpoints in the study and assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires. The PRO-CTCAE, PGIS, and EQ-5D-5L questionnaires were collected as exploratory endpoints (Section B.2.6.3). Patient-reported outcome endpoints demonstrated that durvalumab resulted in no detriment in QoL, with stable or slight improvements while on treatment, and a trend towards a longer time to deterioration.

B.2.6.4.1 EORTC QLQ-C30 and QLQ-LC13

B.2.6.4.1.1 Compliance

Compliance at baseline for EORTC QLQ-C30 was similar between treatment groups ([redacted] with durvalumab versus [redacted] with placebo) and remained [redacted] through Week 16, [redacted] through Week 36, and [redacted] through Week 84 for both treatment groups. Overall, compliance was moderate during the study and similar between treatment groups with an overall rate of [redacted] for the durvalumab group compared with [redacted] for the placebo group.

Compliance at baseline for EORTC QLQ-LC13 was also similar between treatment groups ([redacted] with durvalumab versus [redacted] with placebo) and remained [redacted] through

Week 16, [redacted] through Week 36, and [redacted] through Week 84 for both treatment groups. Overall compliance rates were [redacted] for the durvalumab group and [redacted] for the placebo group.

B.2.6.4.1.2 Baseline scores

For context, a high score on a functional or GHS/QoL scale (scale of 0 to 100) represents a high level of functioning or global HRQoL, while a high score on a symptom scale/item represents a high level of symptom burden. A minimum clinically meaningful change is defined as a change in the score from baseline of ≥10 for scales/items from the QLQ-C30 and the QLQ-LC13 questionnaires.

For both treatment groups, mean baseline EORTC QLQ-C30 GHS/QoL scores were [redacted] and functional scores were [redacted], exceeding SCLC reference values,[50] indicating that patients experienced good functional health at the start of the study. Baseline EORTC QLQ-C30 symptom scores were comparable between the treatment groups, with a higher symptom score corresponding to higher/worse symptom burden, and fatigue mean scores rated highest in both treatment groups ([redacted] with durvalumab versus [redacted] with placebo).

Baseline EORTC QLQ-LC13 scores for the primary symptoms of dyspnoea, cough and chest pain were comparable between treatment groups, with higher scores representing a higher level of symptom burden. All mean scores were [redacted] at baseline, with cough mean scores rated highest in both treatment groups ([redacted] with durvalumab versus [redacted] with placebo).

B.2.6.4.1.3 Change from baseline

Overall, there were no clinically important differences in changes from baseline between treatment groups for any of the key PRO variables. Both groups reported small, non-significant deterioration in functioning, with statistically significant less improvement in appetite loss reported for durvalumab compared with placebo ([redacted]) (Table 23).

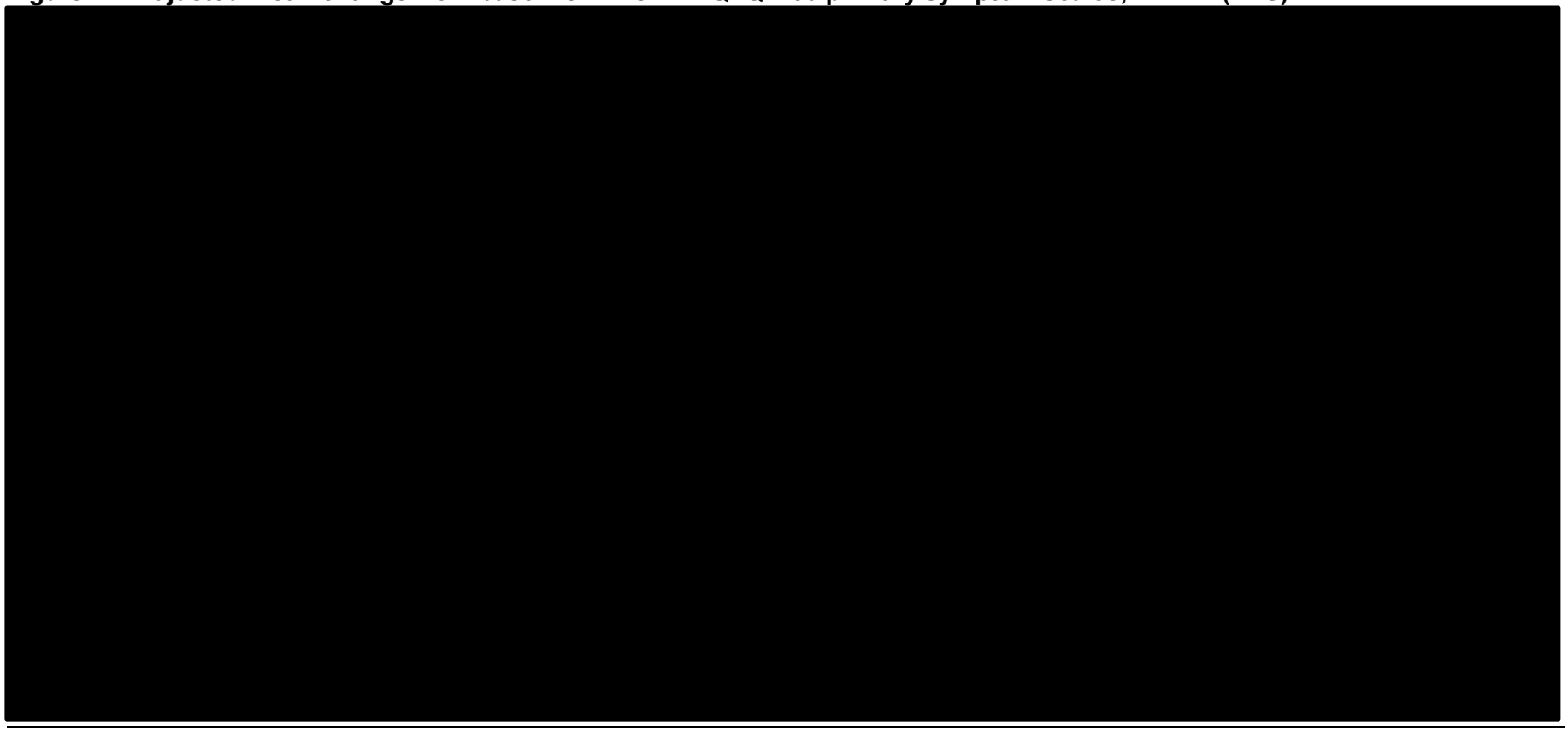
The adjusted mean change from baseline in the EORTC QLQ-C30 and EORTC QLQ-LC13 primary subscales from mixed model repeat measurement (MMRM) over time are presented in Figure 12 and Figure 13, respectively.

Table 23: Change from baseline (average over 24 months) in key EORTC QLQ-C30 and QLQ-LC13 endpoints, MMRM (FAS)

Subscale	Durvalumab (n=264)	Placebo (n=266)
QLQ-C30, adjusted mean (95% CI)		
GHS/QoL†	[redacted]	[redacted]
Physical functioning†	[redacted]	[redacted]
Role functioning†	[redacted]	[redacted]
Fatigue‡	[redacted]	[redacted]
Appetite loss‡	[redacted]	[redacted]
QLQ-LC13, adjusted mean (95% CI)		
Dyspnoea‡	[redacted]	[redacted]
Cough‡	[redacted]	[redacted]
Chest pain‡	[redacted]	[redacted]

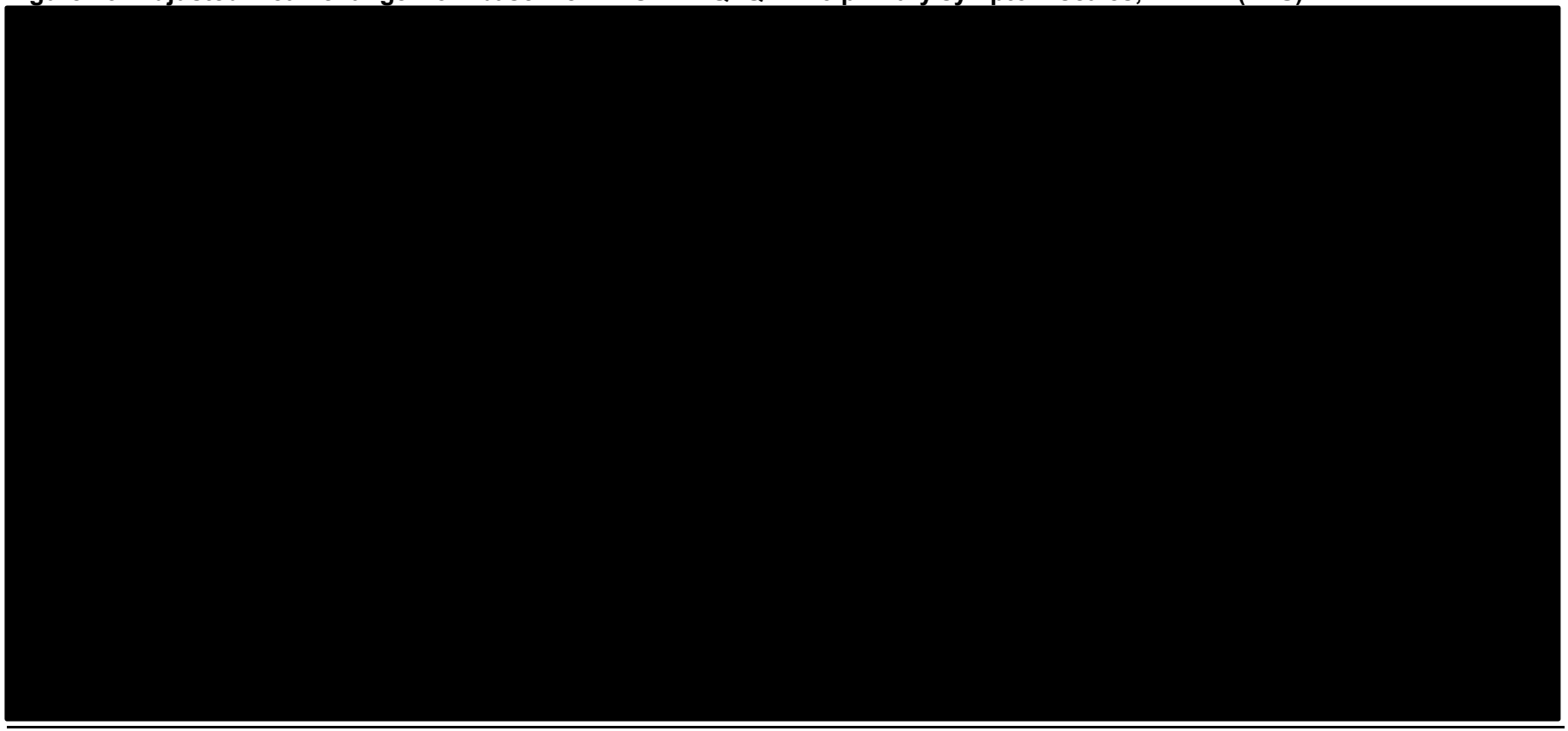
†Negative change from baseline indicates deterioration in GHS/QoL and functioning scales. ‡Positive change from baseline indicates deterioration in symptom scales
Analysis was performed, making use of all data from baseline up to progressive disease, death or 24 months, by using a MMRM model with treatment, TNM stage (Stage I/II versus III), receipt of PCI (yes vs no), visit, and the interaction between treatment and visit as fixed factors, baseline score and interaction between baseline score and visit as covariates. A toeplitz with heterogeneity covariance matrix was used to model the within-patient error and the Kenward-Roger approximation was used to estimate the degrees of freedom. Restricted maximum likelihood (REML) estimation was used. No adjustments have been made to the significance level for testing. Adjusted mean represents the change from baseline (averaged over all visits, giving each visit equal weight).
Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module; FAS, full analysis set; GHS, Global Health Score; MMRM, mixed model repeat measurement; PCI, prophylactic cranial irradiation; QoL, quality of life; TNM, tumour, node, metastasis.
Source: ADRIATIC interim CSR Table 14.2.12.10.A.[1]

Figure 12: Adjusted mean change from baseline in EORTC QLQ-C30 primary symptom scales, MMRM (FAS)



EORTC QLQ-C30 scale was scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores, and a higher level of functioning for functioning scores and GHS/QoL.
Error bars represent the 95% CI for each respective adjusted mean.
N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis.
Abbreviations: Durva, durvalumab; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30 item Core Quality of Life Questionnaire; FAS, full analysis set; GHS, Global Health Score; MMRM, mixed model repeat measurement; QoL, quality of life.
Source: ADRIATIC interim CSR Figure 14.2.12.11.A.[1]

Figure 13: Adjusted mean change from baseline in EORTC QLQ-LC13 primary symptom scales, MMRM (FAS)



EORTC QLQ-LC13 scale was scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores, and a higher level of functioning for functioning scores and GHS/QoL.
Error bars represent the 95% CI for each respective adjusted mean.
N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis.
For symptom scale items in EORTC QLQ-LC13, for Week 0 to 8 the number of patients are presented vertically in 3 rows. The first row contains Weeks 0, 3 and 6, second row contains Weeks 1, 4 and 7, and the third row contains Weeks 2, 5 and 8.
Abbreviations: Durva, durvalumab; EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module; FAS, full analysis set; GHS, Global Health Score; MMRM, mixed model repeat measurement; QoL, quality of life.
Source: ADRIATIC interim CSR Figure 14.2.12.11.A.[1]

B.2.6.4.1.4 Improvement rate

Treatment with durvalumab resulted in a non-statistically significant numerical improvement (OR >1) in fatigue, appetite loss, dyspnoea, and cough, and a statistically significantly higher proportion of patients reporting an improvement in chest pain compared with placebo ([redacted]) (Table 24 and Figure 14).

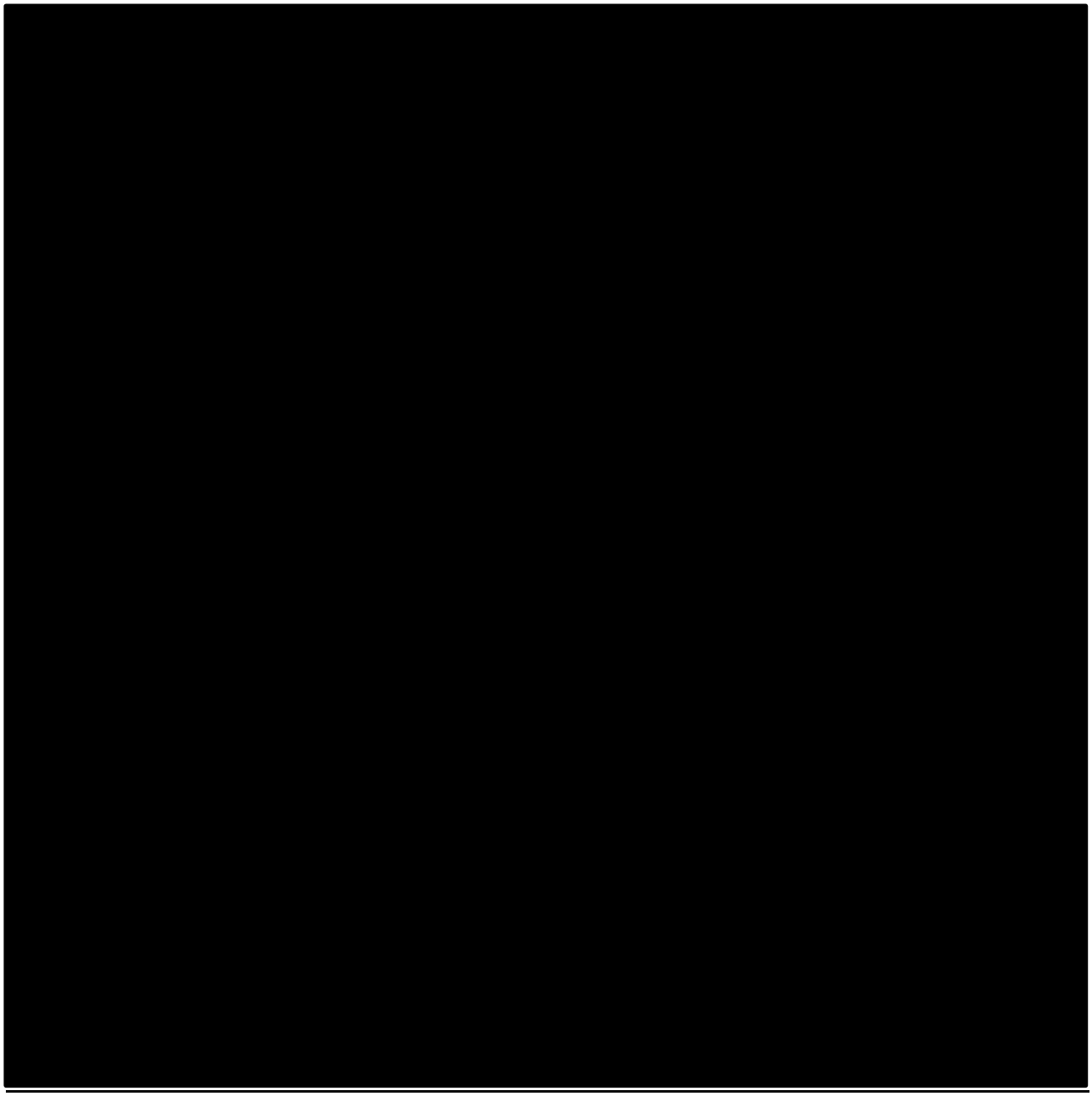
Table 24: Improvement rate of EORTC QLQ-C30 and QLQ-LC13 subscales/items (FAS)

Subscale	Durvalumab (n=264)	Placebo (n=266)
QLQ-C30 GHS/QoL		
Patients with baseline score ≤90, n	[redacted]	[redacted]
Patients with improvement, n (%)	[redacted]	[redacted]
Improvement rate, n (%)†	[redacted]	[redacted]
Odds ratio, durvalumab vs placebo‡,§	[redacted]	
95% CI‡	[redacted]	
QLQ-C30 physical functioning		
Patients with baseline score ≤90, n	[redacted]	[redacted]
Patients with improvement, n (%)	[redacted]	[redacted]
Improvement rate, n (%)†	[redacted]	[redacted]
Odds ratio, durvalumab vs placebo‡,§	[redacted]	
95% CI‡	[redacted]	
QLQ-C30 role functioning		
Patients with baseline score ≤90, n	[redacted]	[redacted]
Patients with improvement, n (%)	[redacted]	[redacted]
Improvement rate, n (%)†	[redacted]	[redacted]
Odds ratio, durvalumab vs placebo‡,§	[redacted]	
95% CI‡	[redacted]	
QLQ-C30 fatigue symptom		
Patients with baseline score ≥10, n	[redacted]	[redacted]
Patients with improvement, n (%)	[redacted]	[redacted]
Improvement rate, n (%)†	[redacted]	[redacted]
Odds ratio, durvalumab vs placebo‡,§	[redacted]	
95% CI‡	[redacted]	
QLQ-C30 appetite loss symptom		
Patients with baseline score ≥10, n	[redacted]	[redacted]
Patients with improvement, n (%)	[redacted]	[redacted]
Improvement rate, n (%)†	[redacted]	[redacted]
Odds ratio, durvalumab vs placebo‡,§	[redacted]	
95% CI‡	[redacted]	

Subscale	Durvalumab (n=264)	Placebo (n=266)
QLQ-LC13 dyspnoea symptom		
Patients with baseline score ≥10, n	[redacted]	[redacted]
Patients with improvement, n (%)	[redacted]	[redacted]
Improvement rate, n (%)[†]	[redacted]	[redacted]
Odds ratio, durvalumab vs placebo[‡,§]	[redacted]	
95% CI[‡]	[redacted]	
QLQ-LC13 cough symptom		
Patients with baseline score ≥10, n	[redacted]	[redacted]
Patients with improvement, n (%)	[redacted]	[redacted]
Improvement rate, n (%)[†]	[redacted]	[redacted]
Odds ratio, durvalumab vs placebo[‡,§]	[redacted]	
95% CI[‡]	[redacted]	
QLQ-LC13 chest pain symptom		
Patients with baseline score ≥10, n	[redacted]	[redacted]
Patients with improvement, n (%)	[redacted]	[redacted]
Improvement rate, n (%)[†]	[redacted]	[redacted]
Odds ratio, durvalumab vs placebo[‡,§]	[redacted]	
95% CI[‡]	[redacted]	

[†]Improvement rate is defined as the number (%) of patients with a minimum of two consecutive assessments at least 14 days apart that show a clinically meaningful improvement from baseline. [‡]The analysis was performed using a logistic regression model, with treatment as a factor and adjusting for TNM stage (Stage I/II vs III) and receipt of PCI (yes vs no), with 95% CI calculated by profile likelihood. [§]An odds ratio >1 favours D over placebo. Logistic regression models are presented for subscales/items with >20 randomised patients in at least one treatment group.
Stratification factors are based on the values entered into the IVRS.
All scores are presented as transformed scores ranging from 0 to 100.
Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module; FAS, full analysis set; GHS, Global Health Score; IVRS, interactive voice response system; PCI, prophylactic cranial irradiation; QoL, quality of life; TNM, tumour, node, metastasis.
Source: ADRIATIC interim CSR Table 14.2.12.3.A.[1]

Figure 14: Forest plot of improvement rate of EORTC QLQ-C30 and QLQ-LC13 subscales/items (FAS)



Odds ratio (durvalumab vs placebo) and 95% CI for subscales/items.
Size of circle is proportional to the number of events.
Abbreviations: CI, confidence interval; Durva, durvalumab; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module; FAS, full analysis set; QoL, quality of life.
Source: ADRIATIC interim CSR Table 14.2.12.2.A and Figure 14.2.12.4.1.A.[1]

B.2.6.4.1.5 Time to deterioration

Treatment with durvalumab resulted in a non-statistically significant longer time to deterioration (HR >1) in GHS/QoL, role functioning, and chest pain compared with placebo (Table 25 and Figure 15). Overall, functioning and symptom impact was low, and maintained over the first 40 weeks of the study, with small non-statistically significant deteriorations.

Table 25: Time to deterioration of EORTC QLQ-C30 and QLQ-LC13 subscales/items (FAS)

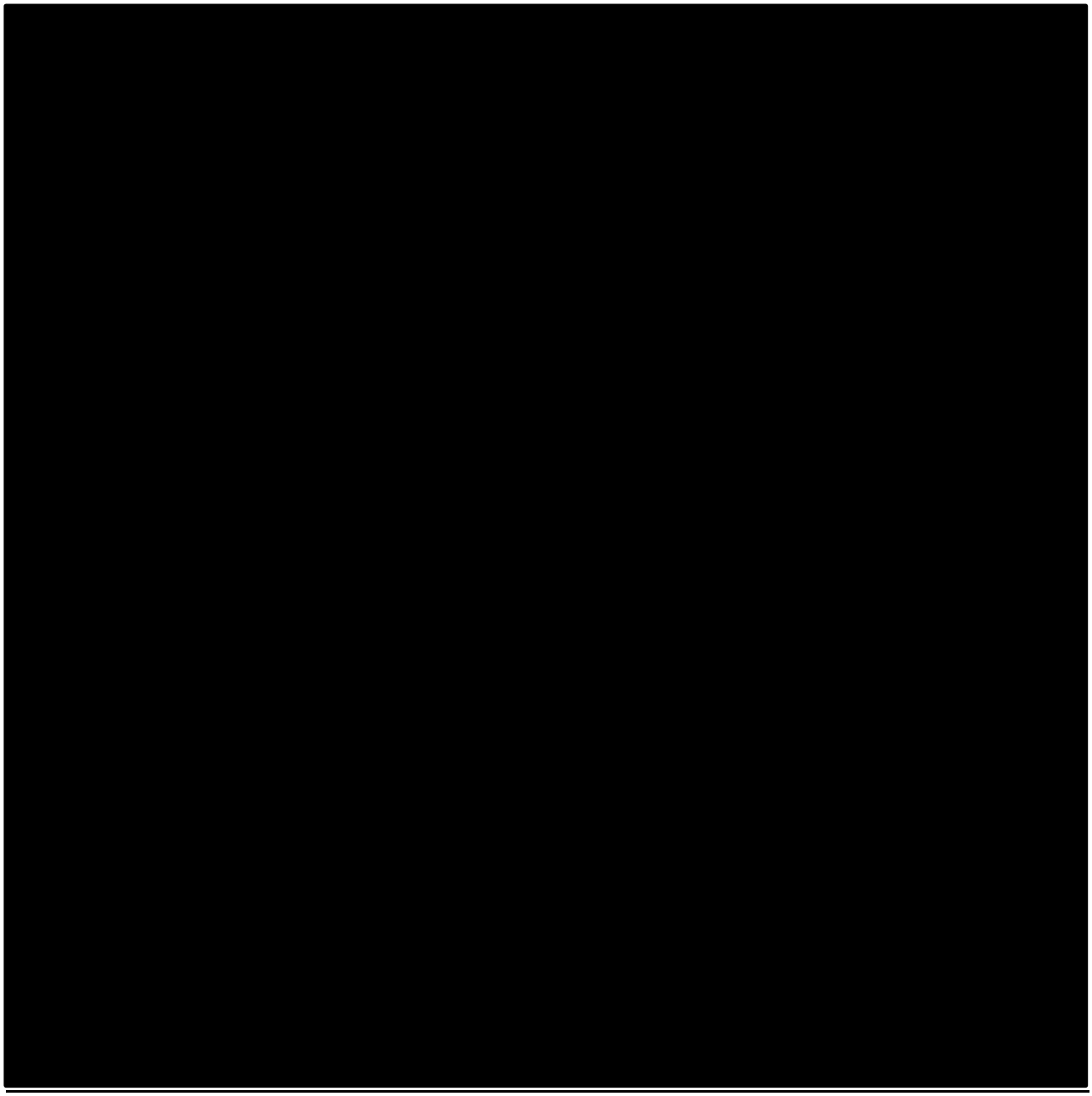
Subscale	Durvalumab (n=264)	Placebo (n=266)
QLQ-C30 GHS/QoL		
Patients with baseline score ≥10, n	[redacted]	[redacted]
Total events, n (%)†	[redacted]	[redacted]
Deterioration	[redacted]	[redacted]
Death in absence	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Median time to deterioration, months‡	[redacted]	[redacted]
95% CI for median time to deterioration‡	[redacted]	[redacted]
HR, durvalumab vs placebo§,¶	[redacted]	
95% CI for HR§	[redacted]	
QLQ-C30 physical functioning		
Patients with baseline score ≥10, n	[redacted]	[redacted]
Total events, n (%)†	[redacted]	[redacted]
Deterioration	[redacted]	[redacted]
Death in absence	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Median time to deterioration, months‡	[redacted]	[redacted]
95% CI for median time to deterioration‡	[redacted]	[redacted]
HR, durvalumab vs placebo§,¶	[redacted]	
95% CI for HR§	[redacted]	
QLQ-C30 role functioning		
Patients with baseline score ≥10, n	[redacted]	[redacted]
Total events, n (%)†	[redacted]	[redacted]
Deterioration	[redacted]	[redacted]
Death in absence	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Median time to deterioration, months‡	[redacted]	[redacted]
95% CI for median time to deterioration‡	[redacted]	[redacted]

Subscale	Durvalumab (n=264)	Placebo (n=266)
HR, durvalumab vs placebo[§,¶]		
95% CI for HR[§]		
QLQ-C30 fatigue symptom		
Patients with baseline score ≤90, n		
Total events, n (%)[†]		
Deterioration		
Death in absence		
Censored patients, n (%)		
Median time to deterioration, months[‡]		
95% CI for median time to deterioration[‡]		
HR, durvalumab vs placebo[§,¶]		
95% CI for HR[§]		
QLQ-C30 appetite loss symptom		
Patients with baseline score ≤90, n		
Total events, n (%)[†]		
Deterioration		
Death in absence		
Censored patients, n (%)		
Median time to deterioration, months[‡]		
95% CI for median time to deterioration[‡]		
HR, durvalumab vs placebo[§,¶]		
95% CI for HR[§]		
QLQ-LC13 dyspnoea symptom		
Patients with baseline score ≤90, n		
Total events, n (%)[†]		
Deterioration		
Death in absence		
Censored patients, n (%)		
Median time to deterioration, months[‡]		
95% CI for median time to deterioration[‡]		
HR, durvalumab vs placebo[§,¶]		
95% CI for HR[§]		

Subscale	Durvalumab (n=264)	Placebo (n=266)
QLQ-LC13 cough symptom		
Patients with baseline score ≤90, n	[redacted]	[redacted]
Total events, n (%)†	[redacted]	[redacted]
Deterioration	[redacted]	[redacted]
Death in absence	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Median time to deterioration, months‡	[redacted]	[redacted]
95% CI for median time to deterioration‡	[redacted]	[redacted]
HR, durvalumab vs placebo§,¶	[redacted]	
95% CI for HR§	[redacted]	
QLQ-LC13 chest pain symptom		
Patients with baseline score ≤90, n	[redacted]	[redacted]
Total events, n (%)†	[redacted]	[redacted]
Deterioration	[redacted]	[redacted]
Death in absence	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Median time to deterioration, months‡	[redacted]	[redacted]
95% CI for median time to deterioration‡	[redacted]	[redacted]
HR, durvalumab vs placebo§,¶	[redacted]	
95% CI for HR§	[redacted]	

†Patients who had not shown a clinically meaningful deterioration or died, or patients who showed a clinically meaningful deterioration or died after two or more missed visits were censored prior to the two missed visits: - at the latest evaluable PRO assessment, if available; - at Day 1 if there were no evaluable visits. ‡Calculated using the KM technique. CI for median time to deterioration is derived based on Brookmeyer-Crowley method with log-log transformation. §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. ¶A HR <1 favours durvalumab to be associated with a longer event-free survival than placebo.
Time to deterioration is defined as the time from randomisation until the date of the first clinically meaningful deterioration (i.e., for symptoms: an increase ≥10; for GHS and functions: a decrease ≥10) that is confirmed at the next available assessment at least 14 days apart, or death.
Stratification factors are based on the values entered into the IVRS.
All scores are presented as transformed scores ranging from 0 to 100.
Abbreviations: CI, confidence interval; durvalumab EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module; FAS, full analysis set; GHS, Global Health Score; HR, hazard ratio; IVRS, interactive voice response system; NR, not reached; PCI, prophylactic cranial irradiation; PRO, patient-reported outcome; TNM, tumour, node, metastasis.
Source: ADRIATIC interim CSR Table 14.2.12.5.A.[1]

Figure 15: Time to deterioration of EORTC QLQ-C30 and QLQ-LC13 subscales/items (FAS)



Hazard ratio (D vs placebo) and 95% CI for subscales/items are displayed on a logarithmic scale.
Size of circle is proportional to the number of events.
Abbreviations: CI, confidence interval; D, durvalumab; Durva, durvalumab; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module; FAS, full analysis set; QoL, quality of life.
Source: ADRIATIC interim CSR Table 14.2.12.5.A and Figure 14.2.12.7.1.A.[1]

B.2.6.4.2 Exploratory endpoints

B.2.6.4.2.1 PRO-CTCAE

Baseline PRO-CTCAE symptom scores were similar between treatment groups. Across all visits, most patients reported no symptoms or mild symptoms, which occurred rarely and did not interfere much with their daily activities. Few patients reported severe or very severe symptoms, or symptoms occurring frequently or almost constantly. The results were similar in both treatment groups.

B.2.6.4.2.2 PGIS

Baseline PGIS scores of symptom severity were similar between treatment groups. At baseline, [redacted] of patients in the durvalumab group and [redacted] in the placebo group reported “No symptoms”, which decreased to [redacted] and [redacted], respectively, at Week 8. The proportions of patients with no, very mild, or mild symptoms in the durvalumab group were similar to the placebo group at all visits. The proportions of patients with severe and very severe symptoms were low, and similar between treatment groups.

B.2.6.4.2.3 EQ-5D-5L

Compliance rates for EQ-5D-5L were approximately [redacted] at baseline and were generally similar across treatment groups for the first 152 weeks [redacted] for the majority of timepoints). Overall, the compliance rate was acceptable ([redacted]) for the durvalumab group up to Week 96.

Baseline mean values were [redacted] for the EQ-5D-5L index score and [redacted] for the VAS score in both treatment groups with index scores approximately [redacted] and [redacted], respectively at Week 8. The measurements for both scales were similar between treatment groups and stable over time.

B.2.6.5 Conclusion

ADRIATIC met its dual primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in both OS and PFS with durvalumab treatment versus placebo, with a clear and sustained separation of OS and PFS curves from 8 and 6 months, respectively. Compared with placebo, treatment with durvalumab also resulted in fewer PFS2 events and an improvement in PFS2 (HR: [redacted]), and a numerically greater improvement in cORR per Investigator ([redacted] with durvalumab versus [redacted] with placebo). In patients with PD-L1

expression, OS and PFS were consistent with those of the FAS, with improvements in OS and PFS observed for patients in the durvalumab group compared with placebo irrespective of PD-L1 expression. The PRO endpoints demonstrated that durvalumab resulted in no detriment in QoL, with stable or slight improvements while on treatment, and a trend towards a longer time to deterioration.

The results of ADRIATIC therefore demonstrate that, compared with placebo, treatment with durvalumab is associated with a significant and clinically meaningful improvement in OS and PFS, with no detrimental effect on QoL. Despite the high unmet needs in LS-SCLC, UK clinicians confirmed that the majority (90%) of patients who remain progression-free for 3–5 years following CRT can be deemed to have achieved functional cure.[17] Through significantly improving outcomes in patients with a very poor prognosis, durvalumab would therefore establish a new SoC in this underserved LS-SCLC population, representing a paradigm shift in disease management.

B.2.7 Subgroup analysis

Pre-planned subgroup analyses of OS and PFS included disease status, receipt of PCI, primary tumour location, time 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, WHO/ECOG PS, and PD-L1 status. Pre-planned subgroup analysis of ORR was also performed for PD-L1 status only.

Please see Sections B.2.6.1.1.2 and B.2.6.1.2.2 for the pre-defined subgroup analyses for the OS and PFS primary endpoints, respectively. Results for the OS, PFS, and ORR endpoints in patients with PD-L1 expression are presented in Appendix N, with the corresponding results for OS, PFS, and ORR in PD-L1 expression subgroups presented in Appendix E.

A treatment effect in favour of durvalumab was observed for OS and PFS endpoints across the majority of subgroups analysed; however, a greater proportion of patients in the placebo group had confirmed ORR in both the full PD-L1 analysis set and high PD-L1 expression subgroup compared with the durvalumab group (Appendix E).

B.2.8 Meta-analysis

ADRIATIC is the only Phase 3 randomised controlled trial (RCT) that has evaluated and reported on the efficacy and safety of durvalumab in adult patients with LS-SCLC who have not progressed following cCRT. A meta-analysis was therefore not required.

B.2.9 Indirect and mixed treatment comparisons

Comparative clinical efficacy for durvalumab was available from one Phase 3 RCT versus placebo (ADRIATIC). As the only relevant comparator in the Final Scope was stated as active monitoring (i.e. placebo) (Table 1), and no further studies that were deemed relevant to the decision problem were identified in the SLR, an indirect or mixed-treatment comparison was not required.

B.2.10 Adverse reactions

Summary of safety results from the ADRIATIC trial

- **Durvalumab treatment was well tolerated in adult patients with LS-SCLC, with a manageable safety profile consistent with the established safety profile in patients with lung cancer who have received prior cCRT, and no new safety findings identified**
- **AEs of any grade occurred in a similar proportion of patients (94.3% with durvalumab vs 88.3% with placebo):**
  - Radiation pneumonitis was the most common AE reported in ≥20% of patients in both treatment groups (22.9% with durvalumab vs 23.4% with placebo)
  - AEs of Grade 3 or 4 were experienced by 64 (24.4%) patients in the durvalumab group and 64 (24.2%) patients in the placebo group
- **SAEs were reported by 78 (29.8%) patients in the durvalumab group and 64 (24.2%) patients in the placebo group:**
  - Radiation pneumonitis was the most common SAE reported in both groups ([redacted] patients [redacted] with durvalumab vs [redacted] patients [redacted] with placebo)

- **There was a low incidence of treatment-emergent ADA and nAb, with AEs reported in durvalumab ADA-positive patients similar and broadly comparable to those who were durvalumab-negative:**
  - imAEs were higher in the durvalumab group compared with placebo (32.1% vs 10.2%), with imAEs of pneumonitis occurring in [redacted] in the durvalumab group and [redacted] in the placebo group
- **Discontinuation of treatment due to AEs was reported in 43 (16.4%) patients in the durvalumab group and 28 (10.6%) patients in the placebo group:**
  - Radiation pneumonitis was the most frequent AE leading to discontinuation in the durvalumab group ([redacted] patients; [redacted])
- **A total of 8 AEs leading to death were reported ([redacted] [redacted] patients with durvalumab vs [redacted] [redacted] patients with placebo)**

Adverse event data were recorded in the ADRIATIC trial at the IA and are presented from the 15th January 2024 DCO (PFS IA and OS IA1), which represents the most recent DCO for ADRIATIC. Data for the SAS (see Table 11 for population definition), which included 262 durvalumab-treated patients and 265 placebo-treated patients, is presented in this section.

B.2.10.1.1 Treatment exposure

A summary of the extent of exposure to durvalumab and placebo is presented in Table 26. The median duration of durvalumab treatment was [redacted] (mean [redacted]) and the median duration of placebo treatment was [redacted] (mean [redacted]).

The median actual treatment duration for durvalumab (total treatment duration excluding the total duration of dose interruptions and cycle delays; [redacted]) was similar to the median total treatment duration ([redacted]), reflecting the short duration of interruptions and cycle delays (Table 26). Similarly, the median actual treatment duration for placebo (total treatment duration excluding the total duration of dose interruptions and cycle delays; [redacted]) was the same as the median total treatment duration ([redacted]), again reflecting the short duration of interruptions and cycle delays (Table 26).

Table 26: Summary of durvalumab and placebo exposure (SAS)

Outcomes	Durvalumab (n=262)	Placebo (n=265)
Number of infusions received		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Total duration of treatment, weeks†		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]
Actual duration of treatment, weeks‡		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]
Number of treatment cycles received		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Number of treatment cycles received, n (%)§		
≥1	[redacted]	[redacted]
≥2	[redacted]	[redacted]
≥3	[redacted]	[redacted]
≥4	[redacted]	[redacted]
≥12	[redacted]	[redacted]
≥18	[redacted]	[redacted]
≥24	[redacted]	[redacted]

†Total treatment duration defined as number of days from first dose date of study drug to the earliest of "last dose date of study drug + 27 days" or death date or DCO (divided by 7 to convert to weeks). ‡Actual treatment duration defined as total treatment duration excluding total duration of dose interruptions and cycle delays. §Rows are cumulative and patients are included if they had taken treatment up to and including that number of cycles. Percentages are based on n (number of patients who received at least one dose).
Abbreviations: SAS, safety analysis set; SD, standard deviation.
Source: ADRIATIC interim CSR, Table 14.3.1.1.

B.2.10.1.2 Overview of adverse events

A summary of AEs in ADRIATIC is provided in Table 27 for all patients in the SAS. Of 527 patients in the safety population for the durvalumab (n=262) and placebo (n=265) groups, 247 (94.3%) and 234 (88.3%) experienced at least one AE, respectively.[2] The majority of patients in both treatment groups ([redacted] with durvalumab vs [redacted] with placebo) experienced AEs with a maximum severity of Grade 1 or 2, with AEs of Grade 3/4 severity experienced by a similar proportion of

patients in both groups (24.4% with durvalumab vs 24.2% with placebo). Discontinuations due to AEs occurred in a similar proportion of patients in both groups (16.4% with durvalumab vs 10.6% with placebo). Serious AEs (SAEs) were reported by 29.8% of the durvalumab group and 24.2% of the placebo group. The occurrence of imAEs was higher in the durvalumab group compared with placebo (32.1% vs 10.2%),[2] and 7 patients experienced an AE that led to death in the durvalumab group compared with no patients in the placebo group; however, only 2 (0.8%) of the AEs that led to death were possibly attributed to durvalumab treatment (Table 27).

Table 27: Overview of AEs in ADRIATIC (SAS)

Adverse events, n (%)	Durvalumab (n=262)	Placebo (n=265)
Any AE	**247 (94.3)**	**234 (88.3)**
Any AE possibly related to treatment‡	176 (67.2)	129 (48.7)
Any AE of any CTCAE Grade 3 or 4	[redacted]	[redacted]
Any AE of any CTCAE Grade 3 or 4, possibly related to treatment	[redacted]	[redacted]
Any AE with a maximum CTCAE Grade 3 or 4	64 (24.4)	64 (24.2)
Any AE possibly related to treatment, with a maximum CTCAE Grade 3 or 4‡,§	23 (8.8)	16 (6.0)
Any SAE (including events with outcome of death)	78 (29.8)	64 (24.2)
Any SAE (including events with outcome of death), possibly related to treatment‡	32 (12.2)	17 (6.4)
Any AE leading to discontinuation of treatment	43 (16.4)	28 (10.6)
Any AE leading to discontinuation of treatment, possibly related to treatment‡	[redacted]	[redacted]
Any AE leading to dose interruption¶	[redacted]	[redacted]
Immune mediated AEs††	84 (32.1)	27 (10.2)
Infusion reaction AEs‡‡	[redacted]	[redacted]
Any AE with outcome of death	7 (2.7)	5 (1.9)
Any AE with outcome of death possibly related to treatment‡	2 (0.8)	0 (0.0)

†Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. ‡As assessed by the Investigator. AEs are counted as related if related to any treatment (durvalumab, durvalumab placebo, or tremelimumab placebo) or missing response for any component. §Possibly related to treatment and further identified as maximum CTCAE Grade 3 or 4. ¶AEs on the AE eCRF form with Action taken = 'Drug interrupted'. Note that a drug interruption can either be a cycle delay beyond the protocol-specified window or an infusion interruption. ††imAEs are identified from AESIs and AEPIs using a programmatic approach. Excludes AESI group of infusion or hypersensitivity reaction. ‡‡As assessed by the Investigator.
Abbreviations: AE, adverse event; AEPI, adverse event of potential interest; AESI, adverse event of special interest; CTCAE, common terminology criteria for adverse events; eCRF, electronic case report form; imAE,

immune-mediated adverse event; SAE, serious adverse event; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Tables 14.3.2.1 and Table 14.3.6.4.1.A; ADRIATIC study publication Table 3.[2]

B.2.10.1.3 Most common adverse events by preferred term

The most frequently reported AEs (>5% of patients) are presented in Table 28. Radiation pneumonitis (60 patients; 22.9%), decreased appetite (44 patients; 16.8%), hyperthyroidism (42 patients; 16.0%), cough (40 patients; 15.3%), and pruritis (34 patients; 13.0%) were the most common in the durvalumab group. In the placebo group, the most common AEs were radiation pneumonitis (62 patients; 23.4%), headache (35 patients; 13.2%), decreased appetite (34 patients; 12.8%), fatigue (34 patients; 12.8%), and cough (32 patients; 12.1%) (Table 28).

The only AE reported in ≥20% of patients in both treatment groups was radiation pneumonitis (22.9% with durvalumab versus 23.4% with placebo), consistent with expectations in patients with LS-SCLC who have received prior cCRT (Table 28).

AEs occurring in more patients in the durvalumab group (>5 percentage points higher) compared with the placebo group were hypothyroidism (16.0% vs 3.8% patients), pruritis (13.0% vs 7.2%), and hyperthyroidism (10.3% vs 1.5%) (Table 28), consistent with the known safety profile of durvalumab.

Table 28: AEs reported for >5% of patients in ADRIATIC (SAS)

Adverse events, n (%)[†]	Durvalumab (n=262)	Placebo (n=265)
Any AE	**247 (94.3)**	**234 (88.3)**
Radiation pneumonitis	60 (22.9)	62 (23.4)
Decreased appetite	44 (16.8)	34 (12.8)
Hypothyroidism	42 (16.0)	10 (3.8)
Cough	40 (15.3)	32 (12.1)
Pruritus	34 (13.0)	19 (7.2)
Nausea	33 (12.6)	29 (10.9)
Dizziness	32 (12.2)	20 (7.5)
Fatigue	32 (12.2)	34 (12.8)
Diarrhoea	29 (11.1)	22 (8.3)
Pneumonia	29 (11.1)	20 (7.5)
Pneumonitis	28 (10.7)	16 (6.0)
Rash	28 (10.7)	16 (6.0)
Constipation	27 (10.3)	26 (9.8)

Adverse events, n (%)†	Durvalumab (n=262)	Placebo (n=265)
Hyperthyroidism	27 (10.3)	4 (1.5)
Asthenia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Headache	24 (9.2)	35 (13.2)
Anaemia	23 (8.8)	16 (6.0)
Weight decreased	[redacted]	[redacted]
Arthralgia	18 (6.9)	29 (10.9)
COVID-19	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]

†Number (%) of patients with AEs, sorted in decreasing frequency in the durvalumab monotherapy group.
Abbreviations: AE, adverse event; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Table 14.3.2.5; ADRIATIC study publication Table 3.[2]

B.2.10.1.4 Adverse events by severity

The number of patients in either treatment group who experienced at least one Grade ≥3 AE was similar, with a total of 69 patients (26.3%) experiencing at least one Grade ≥3 AE in the durvalumab group, and a total of 68 patients (25.7%) in the placebo group (Table 29). A summary of the most common Grade 3 or 4 AEs (excluding death) reported in ≥1% of patients in either treatment group is presented in Table 29.

Table 29: Most common Grade 3 or 4 AEs reported for >1% of patients in ADRIATIC (SAS)

Adverse events, n (%)†	Durvalumab (n=262)	Placebo (n=265)
Any Grade 3 or 4 AE	**64 (24.4)**	**64 (24.2)**
Any Grade 3 or higher AE	[redacted]	[redacted]
Pneumonia	7 (2.7)	9 (3.4)
Diarrhoea	5 (1.9)	0 (0.0)
Lipase increased	5 (1.9)	4 (1.5)
Pulmonary embolism	5 (1.9)	3 (1.1)
Amylase increased	3 (1.1)	0 (0.0)

Adverse events, n (%)†	Durvalumab (n=262)	Placebo (n=265)
Anaemia	3 (1.1)	3 (1.1)
Hyperglycaemia	3 (1.1)	0 (0.0)
Hypertension	3 (1.1)	0 (0.0)
Pneumonitis	3 (1.1)	2 (0.8)
Radiation pneumonitis	3 (1.1)	5 (1.9)
Chronic obstructive pulmonary disease	[redacted]	[redacted]
Fatigue	1 (0.4)	4 (1.5)

†Number (%) of patients with AEs, sorted in decreasing frequency in the durvalumab monotherapy group.
Abbreviations: AE, adverse event; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Tables 14.3.2.4.2 and 14.3.2.8.2; ADRIATIC study publication Table 3.[2]

B.2.10.1.5 Adverse events leading to dose modifications (interruptions or delays)

The proportions of patients with AEs leading to dose modifications (cycle delays or infusion interruptions) of study treatment were 34.7% in the durvalumab group and 28.7% in the placebo group (Table 30). The most frequently reported AEs leading to dose modification were radiation pneumonitis ([redacted] with durvalumab versus [redacted] with placebo) and pneumonitis ([redacted] with durvalumab versus [redacted] with placebo) (Table 30). Except for radiation pneumonitis and pneumonitis, AEs leading to dose modification were similar between treatment groups (Table 30).

A summary of the most common AEs leading to dose interruption reported in ≥2% of patients in either treatment group is presented in Table 30.

Table 30: Most common AEs leading to dose interruption for >2% of patients in ADRIATIC (SAS)

Adverse events, n (%)†	Durvalumab (n=262)	Placebo (n=265)
Any AE leading to dose interruption‡	**91 (34.7)**	**76 (28.7)**
Radiation pneumonitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]

Adverse events, n (%)†	Durvalumab (n=262)	Placebo (n=265)
Alanine aminotransferase increased	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Immune-mediated lung disease	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]

†Number (%) of patients with AEs leading to dose interruption, sorted by decreasing frequency in the durvalumab monotherapy group, then placebo group. Patients may have had more than one AE leading to dose interruption.
‡AEs on the AE eCRF form with Action taken = 'Drug interrupted'.
Abbreviations: AE, adverse event; eCRF, electronic case report form; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Table 14.3.2.11.

B.2.10.1.6 Adverse events of special interest, adverse events of potential interest, and immune-mediated adverse events

Consistent with the MoA of durvalumab, a higher frequency of imAEs was reported for the durvalumab group (84 patients; 32.1%) compared with the placebo group (27 patients; 10.2%); this was driven by hypothyroid ([redacted] vs [redacted]) and pneumonitis events ([redacted] vs [redacted]) (Table 31). The majority of imAEs were of maximum Grade 1 or 2, with Grade 3 or 4 imAEs reported for [redacted] and [redacted] of patients in the durvalumab and placebo groups, respectively. Similarly, a higher number of serious imAEs were reported for patients in the durvalumab group compared with placebo ([redacted] vs [redacted]) (Table 31). ImAEs that led to discontinuation of study treatment occurred in a higher proportion of patients in the durvalumab group compared with the placebo group ([redacted] vs [redacted]), and [redacted] imAE (pneumonitis) in the durvalumab group resulted in death (Table 31). Overall, the imAEs in the durvalumab group were consistent with the established safety profile for durvalumab, and the imAEs were generally tolerable and manageable.

An overview of AESIs (including AEPIs) and imAEs is presented in Table 31.

Table 31: AESIs, AEPIs, and imAEs in any category (SAS)

Adverse events, n (%)	Durvalumab (n=262)		Placebo (n=265)	
	AESI	imAE	AESI	imAE
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Any AE possibly related to any treatment†	[redacted]	[redacted]	[redacted]	[redacted]
Any AE possibly related to durvalumab/ placebo†	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of maximum CTCAE Grade 3 or 4‡	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of maximum CTCAE Grade 3 or 4, possibly related to any treatment†,‡	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of maximum CTCAE Grade 3 or 4 possibly related to durvalumab/ placebo†,‡	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE possibly related to any treatment†	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE possibly related to durvalumab/ placebo†	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE with outcome of death§	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE with outcome death, possibly related to any treatment†,§	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE with outcome death, possibly related to durvalumab/ placebo†,§	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation of any treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation of durvalumab/ placebo	[redacted]	[redacted]	[redacted]	[redacted]
Received therapy				
Systemic corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]
≥40 mg prednisone equivalent steroids	[redacted]	[redacted]	[redacted]	[redacted]
Other immunosuppressants	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine therapy	[redacted]	[redacted]	[redacted]	[redacted]
AE outcome§,¶				
Resolved	[redacted]	[redacted]	[redacted]	[redacted]
Not resolved	[redacted]	[redacted]	[redacted]	[redacted]

Note: AESIs also include AEPIs; imAEs do not include the AESI group of infusion or hypersensitivity reactions. The table includes AEs with an onset date or that worsen on or after the date of first dose and up to and including 90 days following the date of last dose of treatment, or up to the day prior to start of subsequent cancer therapy, whichever comes first.
Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
†Possibly related is defined as reasonable possibility that the AE was caused by treatment, as assessed by Investigator. ‡Grade 3: severe, Grade 4: life-threatening. §If a patient had multiple events within a specific AE type then the outcome of the event with the worst outcome was counted. Outcomes from worst to best are death, not resolved, resolved. ¶Reasons of not recovered/not resolved, recovering/resolving, unknown map to an outcome of Not Resolved. Reasons of recovered/resolved,
recovered/resolved with sequelae map to an outcome of Resolved.
Abbreviations: AE, adverse event; AEPI, adverse event of potential interest; AESI, adverse event of special interest; CTCAE, common terminology criteria for adverse events; imAE, immune-mediated adverse event; SAE,

serious adverse event; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Table 14.3.6.4.1.A.

B.2.10.1.7 AEs in ADA-positive patients

There was a low incidence of treatment-emergent ADA and nAb, with the AEs reported in patients positive for durvalumab ADA similar and broadly comparable to those reported in patients who were negative for durvalumab (Table 32). There were no new events or events clearly suggestive or indicative of immune complex disease suggesting the presence of ADAs had no apparent effect on the safety of durvalumab.

A summary of AEs in ADA-positive patients in the durvalumab group is presented in Table 32.

Table 32: AEs in any category, by durvalumab ADA category (SAS)

Adverse events, n (%)†	**Durvalumab (n=262)**			
	ADA to durvalumab			
	TE-ADA+‡	**nAb+**	**ADA+§**	**ADA-¶**
Number of durvalumab ADA evaluable patients	[redacted]	[redacted]	[redacted]	[redacted]
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Any AE possibly related to treatment††	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of any CTCAE Grade 3 or 4	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of any CTCAE Grade 3 or 4, possibly related to treatment††	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of maximum CTCAE Grade 3 or 4	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of maximum CTCAE Grade 3 or 4, possibly related to treatment††	[redacted]	[redacted]	[redacted]	[redacted]
Any AE with outcome of death	[redacted]	[redacted]	[redacted]	[redacted]
Any AE with outcome of death, possibly related to treatment††	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE (including events with outcome of death)	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE (including events with outcome of death), possibly related to treatment††	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation of treatment, possibly related to treatment††	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to dose interruption‡‡	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events, n (%)†	Durvalumab (n=262)			
	ADA to durvalumab			
	TE-ADA+‡	nAb+	ADA+§	ADA-¶
Any AESI or AEPI	[redacted]	[redacted]	[redacted]	[redacted]
Any AESI or AEPI, possibly related to treatment††	[redacted]	[redacted]	[redacted]	[redacted]
Immune mediated AEs§§	[redacted]	[redacted]	[redacted]	[redacted]
Infusion reaction AEs§§	[redacted]	[redacted]	[redacted]	[redacted]

†Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. ‡Treatment-emergent ADA-positive is defined as either treatment-induced (post-baseline ADA-positive only) or treatment-boosted ADA (baseline positive ADA titer that was boosted to ≥4-fold during the study period). §ADA-positive i.e., positive ADA result at any time, baseline or post-baseline. ¶ADA-negative includes patients without any ADA-positive results at baseline or post-baseline against durvalumab. ††As assessed by the Investigator. AEs are counted as related if related to any treatment (durvalumab, tremelimumab or placebo) or missing response for any component. ‡‡AEs on the AE eCRF form with Action taken = Drug interrupted. Note that a drug interruption can either be a cycle delay beyond the protocol-specified window or an infusion interruption. §§As assessed by the Investigator. Abbreviations: ADA anti-drug antibody(ies); AE, adverse event; AEPI, adverse event of potential interest; AESI, adverse event of special interest; CTCAE, common terminology criteria for adverse events; eCRF, electronic case report form; nAb, neutralising antibody(ies); SAE, serious adverse event; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Table 14.2.17.3.

B.2.10.1.8 SAEs

Serious AEs were reported for 78 (29.8%) patients in the durvalumab group and 64 (24.2%) patients in the placebo group (Table 33), with the majority of SAEs in both treatment groups assessed by the Investigator as not related to study treatment.[2] The most commonly reported SAEs in both the durvalumab and placebo treatment groups were radiation pneumonitis ([redacted] patients; [redacted] vs [redacted] patients; [redacted]), pneumonia ([redacted] patients; [redacted] vs [redacted] patients; [redacted]), and pneumonitis ([redacted] patients; [redacted] vs [redacted] patients; [redacted]), and no SAEs occurred in a notably higher proportion of patients (>5 percentage points higher) in the durvalumab group compared with the placebo group (Table 33).

A summary of SAEs reported in ≥1% of patients in any treatment group is presented in Table 33.

Table 33: SAEs reported in ≥1% of patients in ADRIATIC (SAS)

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

Adverse event, n (%)†	Durvalumab (n=262)	Placebo (n=265)
Immune-mediated lung disease	[redacted]	[redacted]
Pneumonia bacterial	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]

†Number (%) of patients with SAEs, sorted by decreasing frequency in the durvalumab group, then placebo group.
Abbreviations: SAE, serious adverse event; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Table 14.3.4.1.1; ADRIATIC study publication.[2]

B.2.10.1.9 Discontinuations

Adverse events leading to discontinuation of study treatment were reported in 43 (16.4%) patients in the durvalumab group and 28 (10.6%) patients in the placebo group (Table 34).[2] Maximum CTCAE Grade 3 or 4 AEs leading to discontinuation of study treatment were similar between treatment groups ([redacted] patients [redacted] with durvalumab vs [redacted] patients [redacted] with placebo); however, more patients in the durvalumab group had maximum CTCAE Grade 2 events leading to discontinuation of study treatment ([redacted] patients [redacted] with durvalumab vs [redacted] patients [redacted] with placebo), indicating that the higher number of AEs leading to discontinuation in the durvalumab group was largely driven by maximum CTCAE Grade 2 events.

The most commonly reported AEs leading to discontinuation in the durvalumab group were radiation pneumonitis ([redacted] patients; [redacted]), pneumonitis ([redacted] patients; [redacted]), immune-mediated lung disease ([redacted] patients; [redacted]), and pneumonia ([redacted] patients; [redacted]). Each AE occurred in a numerically higher number of patients in the durvalumab group compared with the placebo group; however, the difference in each case was [redacted] percentage points (Table 34).

A summary of AEs leading to discontinuation reported in ≥1% of patients in any treatment group is presented in Table 34.

Table 34: AEs leading to treatment discontinuation reported in ≥1% of patients in ADRIATIC (SAS)

Adverse event, n (%)†	Durvalumab (n=262)	Placebo (n=265)
Any AE leading to discontinuation‡	**43 (16.4)**	**28 (10.6)**
Radiation pneumonitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]

Adverse event, n (%)†	Durvalumab (n=262)	Placebo (n=265)
Immune-mediated lung disease	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

†Number (%) of patients with AEs leading to discontinuation of treatment, sorted by decreasing frequency in the durvalumab group, then placebo group. ‡Action taken of any treatment permanently stopped.
Abbreviations: SAE, serious adverse event; SAS, safety analysis set.
Source: ADRIATIC interim CSR, Table 14.3.5.1.1; ADRIATIC study publication.[2]

B.2.10.1.10 Deaths

Overall, deaths occurred in 43.6% of patients in the durvalumab group and in 54.9% of patients in the placebo group, with the majority of deaths in both treatment groups attributed to the disease, as determined by the Investigator: ([redacted] deaths with durvalumab versus [redacted] deaths with placebo) (Table 35).

Deaths due to both disease and an AE were reported for [redacted] ([redacted]) patients in the durvalumab group and [redacted] patients in the placebo group. AEs with an outcome of death only were reported for [redacted] ([redacted]) patients in the durvalumab group and [redacted] ([redacted]) patients in the placebo group (Table 35).

Table 35: Summary of deaths in ADRIATIC (FAS)

Category, n (%)†	Durvalumab (n=264)	Placebo (n=266)
Total number of deaths	115 (43.6)	146 (54.9)
Death related to disease under investigation only†	[redacted]	[redacted]
Death related to disease under investigation† and an AE with outcome of death‡	[redacted]	[redacted]
AE with outcome of death only‡	[redacted]	[redacted]
Death after end of safety follow up period and not due to AE or disease under investigation§	[redacted]	[redacted]
Unknown reason for death¶	[redacted]	[redacted]

†Death related to disease under investigation is determined by the Investigator. ‡Includes AEs with an onset date, or pre-treatment AEs that increase in severity, on or after the date of first dose and up to and including 90 days following the date of last dose of treatment or up to the date of initiation of the first subsequent systemic anti-cancer therapy (whichever occurred first). §Death not due to disease progression or a treatment-emergent AE. ¶Such patients may have an SAE recorded as unknown death.
Abbreviations: AE, adverse event; FAS, full analysis set.
Source: ADRIATIC interim CSR, Table 14.3.3.1.1.

B.2.10.1.11 Other significant AEs

B.2.10.1.11.1 Pneumonitis or radiation pneumonitis (Grouped term)

Pneumonitis or radiation pneumonitis was reported for 100 (38.2%) patients in the durvalumab group and for 80 (30.2%) patients in the placebo group. Maximum

CTCAE Grade 3 or 4 pneumonitis or radiation pneumonitis were reported for 3.1% of patients in the durvalumab group and 2.6% in the placebo group. Pneumonitis or radiation pneumonitis events leading to discontinuation of study treatment were reported for 8.8% of patients in the durvalumab group and 3.0% in the placebo group, and one patient in the durvalumab group had a fatal pneumonitis or radiation pneumonitis event.

As of the DCO, of the [redacted] patients with events in the durvalumab group, events were resolved in [redacted] patients with the median time to resolution for pneumonitis or radiation pneumonitis of [redacted] (range: [redacted]). Of the [redacted] patients with events in the placebo group, the events were resolved in [redacted] patients with the median time to resolution of [redacted] (range: [redacted]).

B.2.10.2 Additional studies

There are no additional studies that report adverse reactions for durvalumab besides those that are presented in Section B.2.2.

B.2.10.3 Safety overview

Durvalumab treatment was well tolerated in adult patients with LS-SCLC, with a manageable safety profile consistent with the established safety profile in patients with lung cancer who have received prior cCRT, and no new safety findings identified. Adverse events of any grade occurred in a similar proportion of patients (94.3% with durvalumab vs 88.3% with placebo), with radiation pneumonitis the most common AE reported in ≥20% of patients in both treatment groups (22.9% with durvalumab vs 23.4% with placebo). Similarly, AEs of Grade 3 or 4 were experienced by 64 (24.4%) patients in the durvalumab group and 64 (24.2%) patients in the placebo group.

Serious AEs were reported by 78 (29.8%) patients in the durvalumab group and 64 (24.2%) patients in the placebo group, with radiation pneumonitis again reported as the most common SAE in both groups ([redacted] patients [redacted] with durvalumab vs [redacted] patients [redacted] with placebo).

There was a low incidence of treatment-emergent ADA and nAb, with AEs reported in durvalumab ADA-positive patients similar and broadly comparable to those who were durvalumab negative. However, imAEs were higher in the durvalumab group

compared with placebo (32.1% vs 10.2%), with imAEs of pneumonitis occurring in [redacted] in the durvalumab group and [redacted] in the placebo group.

Discontinuation of treatment due to AEs was reported in 43 (16.4%) patients in the durvalumab group and 28 (10.6%) patients in the placebo group, with radiation pneumonitis reported as the most frequent AE leading to discontinuation in the durvalumab group ([redacted] patients; [redacted]). A total of [redacted] AEs leading to death were reported in the trial ([redacted] [redacted] patients with durvalumab vs [redacted] [redacted] patients with placebo).

B.2.11 Ongoing studies

Using model-based predictions, the durvalumab and placebo arms from ADRIATIC were predicted to have the required number of events for the planned second OS interim analysis which is anticipated to occur approximately in [redacted]. Please note, as this is an event-driven read-out, these timelines may be subject to change.

There are no other ongoing studies for durvalumab in the indication relevant to this appraisal that will report in the next 12 months.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

B.2.12.1.1 Summary of efficacy evidence

ADRIATIC demonstrated that durvalumab is the first and only immunotherapy to show survival benefit for the first-line treatment of LS-SCLC following cCRT, delivering statistically significant and clinically meaningful improvements compared with placebo in patients whose disease has not progressed after platinum-based cCRT. Current treatment options for patients with LS-SCLC are limited to platinum-based chemotherapy, delivered concurrently with twice-daily radiotherapy[18, 19] that offer limited survival and disease progression benefits.[14-16] There have been no new therapies approved for the first-line management of patients with LS-SCLC for several decades. Despite the poor prognosis for patients with LS-SCLC, UK clinicians confirmed that the majority (90%) of patients who remain progression-free for 3–5 years following CRT can be deemed to have achieved functional cure, highlighting the curative potential of durvalumab in these patients.[17]

ADRIATIC met its dual primary endpoint of demonstrating a statistically significant improvement in both OS and PFS compared with placebo. At the time of the IA (DCO: 15th January 2024) treatment with durvalumab resulted in a statistically significant, clinically meaningful, and sustained improvement in OS versus placebo, with a HR of 0.73 (98.321% CI: 0.54, 0.98; p=0.01), corresponding to a 27% reduction in the overall risk of death. There was a clear and sustained separation in the OS KM curves from 8 months, with an estimated improvement in median OS of 22.5 months with durvalumab versus placebo (55.9 months vs 33.4 months, respectively).

Improvements in OS for durvalumab over placebo were broadly consistent across prespecified subgroups (based on demographics, geographical region, primary tumour location, disease status, WHO/ECOG PS, and PD-L1 status). Two subgroups demonstrated an OS HR point estimate ≥1: patients with a time of ≥84 days from last dose of radiotherapy to randomisation in this study (HR: [redacted]); and patients with TNM Stage I or II based on IVRS (HR: [redacted]). However, it is important to note that the study was not sized for any of the individual subgroup evaluations and the lower number of patients and events across the individual subgroups may lead to greater uncertainty in the point estimates, and wider CIs.

Treatment with durvalumab also resulted in a statistically significant, clinically meaningful, and sustained improvement in PFS compared with placebo (HR: 0.76; 97.195% CI: 0.59, 0.98; p=0.02), corresponding to a 24% reduction in the overall risk of disease progression or death. A sustained separation of KM curves was seen from 6 months post-treatment initiation, with an estimated improvement in median PFS of 7.4 months with durvalumab versus placebo (16.6 months vs 9.2 months, respectively). In addition, treatment with durvalumab resulted in an improvement in PFS2 (HR: [redacted]), with a longer estimated median PFS2 compared with placebo.

Analysis of additional outcomes demonstrated that patients receiving durvalumab experienced a similar ORR as those receiving placebo (30.3% vs 32.0%; difference in proportion: -1.2%; 95% CI: -11.0, 8.5), with a longer median DoR observed in the durvalumab group (33.0 vs 27.7 months). Furthermore, for patients with PD-L1

expression status, an OS and PFS benefit was also observed for patients in the durvalumab group compared with placebo irrespective of PD-L1 expression. Finally, there was an improvement in TTDM with durvalumab treatment, with a HR of [redacted]), representing a [redacted] reduction in the overall risk TTDM with durvalumab treatment compared with placebo.

Extending OS and prolonging PFS to avoid disease progression to ES-SCLC is important for patients and are important indicators of treatment efficacy and success. The statistically significant improvement in median OS and PFS achieved with durvalumab should therefore be considered in the context of the current short life expectancy for patients with LS-SCLC of 2–3 years.[14-16]

B.2.12.1.2 Summary of QoL and safety evidence

Patient-reported outcome secondary endpoints (EORTC QLQ-C30 and EORTC QLQ-LC13) demonstrated there were no clinically meaningful differences observed between treatment groups. Treatment with durvalumab resulted in no detriment in QoL, with stable or slight improvements while on treatment, and a trend towards a longer time to deterioration. Avoiding disease progression and worsening health states, as well as preserving HRQoL, is important for patients, with HRQoL considered a major endpoint when investigating the clinical benefit of new therapeutic strategies for patients, and an important indicator of treatment efficacy as well as safety and tolerability.[49]

Treatment with durvalumab was well tolerated, with the overall safety profile generally manageable and consistent with the established safety profile of durvalumab. Almost all patients across both treatment groups in ADRIATIC experienced AEs during the study, and the rates of CTCAE Grade 3 or 4 AEs were very similar between the durvalumab and placebo treatment groups. No new safety findings were identified beyond the known safety profile of durvalumab.

B.2.12.1.3 Discussion and conclusions on clinical evidence

Approximately 30% of patients with SCLC are diagnosed with LS-SCLC[11-13] which is associated with substantial disease-related symptoms and QoL burden, and where complete (R0) surgical resection followed by adjuvant chemotherapy is unfeasible.[18] Furthermore, ~75% of patients with locally advanced disease who receive initial

treatment with curative intent will experience disease recurrence within two years.[20] Current treatment for these patients is limited to chemotherapy delivered with radiotherapy,[18, 19] and there have been no innovations in the management of first-line LS-SCLC for several decades. Patients with LS-SCLC have a poor prognosis, with median OS of 2–3 years, estimated 5-year OS rate of 29–34%, and median PFS of 13.5–15.5 months with current treatment.[14-16] Therefore there is a substantial unmet need in this patient population for new therapies that extend OS and prolong disease progression, as confirmed by clinical experts who described the data from ADRIATIC as encouraging for both OS and PFS in all subgroups within an area of real unmet need.[17] Despite the high unmet needs and poor prognosis for patients with LS-SCLC, UK clinicians confirmed that the majority (90%) of patients who remain progression-free for 3–5 years following CRT can be deemed to have achieved functional cure, highlighting the curative potential of durvalumab in LS-SCLC.[17]

Durvalumab has demonstrated a statistically significant and clinically meaningful improvement in both OS and PFS versus placebo with a clear and sustained separation in OS and PFS KM curves from 8 and 6 months, respectively. Furthermore durvalumab was associated with a statistically significant improvement in median OS and PFS, which should be considered in the context of the current life expectancy for patients with LS-SCLC of 2–3 years.[14-16] It should be noted that median OS and OS HRs do not always fully capture the non-conventional survival dynamics such as delayed curve separation. This may result in a substantial loss of statistical power and lack of survival difference reported by treatment arms. However, despite a delayed separation in the KM curves, the associated log-log plot and p-value from fitting a time-dependent covariate did not indicate that the non-proportional assumption was violated. The delay in the separation of the OS and PFS curves between the durvalumab and placebo groups may reflect the continued impact of the prior cCRT received by patients in ADRIATIC. It is therefore important to look beyond the median OS and PFS and consider the clinical value captured by the long-term OS and PFS data (OS24, OS36, PFS18 and PFS24), which better demonstrate the potential for a long-term survival and disease progression benefit with durvalumab treatment. The importance of considering these types of data is reflected in the ESMO-Magnitude of Clinical Benefit Scale scoring system, which includes percentage increase in survival at landmark timepoint analyses. In the case

of ADRIATIC, the OS rate at two and three years for the durvalumab arm is higher than the placebo arm (OS24: 68.0% with durvalumab vs 58.5% with placebo; OS36: 56.5% with durvalumab vs 47.6% with placebo). Similar results were observed for PFS at both 18 and 24 months, with a higher rate of PFS for durvalumab compared with placebo (PFS18: 48.8% with durvalumab vs 36.1% with placebo; PFS24: 46.2% with durvalumab vs 34.2% with placebo). This clearly demonstrates the improved potential for a long-term survival benefit and durable OS benefit offered by durvalumab over placebo. Furthermore, use of durvalumab treatment resulted in no detriment in QoL and a manageable safety profile consistent with the established safety profile of durvalumab.

The anticipated licensed indication for durvalumab is for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy.[4] Expert clinical opinion confirmed that patients who receive sCRT for LS-SCLC are also expected to benefit from treatment with durvalumab,[17] with precedent from the PACIFIC-6 study where durvalumab demonstrated encouraging efficacy in NSCLC patients following sCRT,[35] and further supported by an ASCO recommendation for durvalumab in patients with LS-SCLC and ECOG PS 3–4 who have received sCRT.[36]

Durvalumab is therefore a suitable therapy option for all LS-SCLC patients who would otherwise receive active monitoring for disease progression following cCRT and prior to receiving second-line treatment for their disease. Biomarker testing in SCLC is not routinely carried out or recommended in current guidelines, owing to the absence of validated biomarkers with prognostic or predictive relevance that can be used for disease classification or to inform treatment decisions.[18] Neither PD-L1 nor tumour mutational burden testing is recommended in routine clinical practice;[18] consequently there is no requirement for PD-L1 testing among patients as PD-L1 is not a validated biomarker in SCLC. This highlights the importance of ensuring patient access to this first treatment option in several decades which provides the opportunity of extended survival for this underserved population who experience poor survival rates.

B.2.12.2 Strengths and limitations of the clinical evidence base for the technology

B.2.12.2.1 Internal validity

B.2.12.2.1.1 ADRIATIC trial design

ADRIATIC is a large, ongoing, multinational, well controlled and well conducted study. The study employed a randomised, double-blind, placebo-controlled design to minimise bias. All study personnel and the sponsor remained blinded to treatment allocation throughout the trial as described in Section B.2.3.1.6.2. Patients were stratified by disease stage (I/II vs III) based on TNM classification, and receipt of PCI (yes vs no).

An Independent Data Monitoring Committee (IDMC) composed of independent experts was convened to confirm the safety and tolerability assessments and make recommendations to continue, modify, or stop the study based on safety findings. The IDMC was also responsible for reviewing unblinded efficacy data.

Permitted concomitant medications were limited to those deemed necessary for prophylaxis, supportive care, or well-being; no other therapies for LS-SCLC were permitted, thereby reducing any possibility of distorting the perceived effects of durvalumab.

Eligibility criteria were selected to ensure enrolment of an appropriate patient population in the study, with baseline characteristics well balanced between treatment groups and no notable differences observed in demographics (age, sex, race, ethnicity, and smoking status), baseline disease characteristics (ECOG PS, tumour type) or prior treatments received.

Overall survival, which was one of the dual primary endpoints of ADRIATIC, is considered the most appropriate and reliable endpoint in randomised controlled oncology clinical studies as it is not subject to investigator bias.[48] PFS was the other primary endpoint assessed in ADRIATIC and is also considered a recognised endpoint in oncology trials as it is assessed prior to survival and therefore not subject to any potential confounding effect of subsequent therapy. As the study adopted a rigorous double-blind design, measurement of these endpoints was not subject to assessment bias.

The dropout rate for reasons other than disease progression or toxicity was low and balanced between the two treatment arms. Compliance with study treatments was assured as durvalumab and placebo were given as IV infusions administered by staff at the study centres.

B.2.12.2.1.2 Limitations

A consistent benefit with durvalumab compared with placebo was seen regardless of the previous thoracic radiotherapy schedule or the use of PCI. However, these data should be interpreted with caution as ADRIATIC was not powered for subgroup comparisons. Another limitation of ADRIATIC is the underrepresentation of Black people, among whom the risk of SCLC is lower than the risk among White people and for whom there is a need for more data on SCLC clinical care and outcomes.[2, 51]

B.2.12.2.2 External validity

The ADRIATIC study reflects the proposed indication and anticipated use of durvalumab in clinical practice in England.[4] Expert clinical opinion confirmed that the study design of ADRIATIC was appropriate and the most effective way to demonstrate the efficacy of durvalumab following CRT.[17]

Platinum-based chemotherapy delivered concurrently with twice-daily radiotherapy is the current SoC for the first-line treatment of patients with LS-SCLC.[18, 19] Following cCRT, patients undergo active monitoring for disease progression prior to initiating second-line treatments for disease recurrence. Despite the poor prognosis for patients with LS-SCLC, UK clinicians confirmed that the majority (90%) of patients who remain progression-free for 3–5 years following CRT can be deemed to have achieved functional cure, highlighting the curative potential of durvalumab in these patients.[17] Durvalumab is therefore a suitable therapy option for all LS-SCLC patients who would otherwise receive active monitoring for disease progression following cCRT and prior to receiving second-line treatment for disease progression. Placebo is therefore considered to be the only appropriate comparator, as patients with LS-SCLC who have first received first-line cCRT would then receive active monitoring for their disease. The enrolment criteria for ADRIATIC were consistent with the expected population that will use durvalumab in UK clinical practice, i.e. those with good performance status.

In ADRIATIC, patients received durvalumab or placebo for up to 4 cycles, after which chemotherapy was discontinued and patients continued to receive durvalumab or placebo until clinical progression, or unless there was unacceptable toxicity, consent was withdrawn, or the patient discontinued for another reason. The use of durvalumab for up to 4 cycles is in line with previous trials investigating the efficacy and safety of durvalumab and is consistent with UK clinical practice in other indications.[4]

In accordance with OS being considered the most appropriate and reliable endpoint in randomised controlled oncology clinical studies,[48] OS was included and evaluated as a dual primary endpoint in ADRIATIC as median OS in patients with LS-SCLC is typically 2–3 years.[14-16] Progression-free survival was the other dual primary endpoint assed in ADRIATIC, and was assessed alongside ORR as they are also both considered as recognised endpoints in oncology trials. Secondary efficacy endpoints were evaluated either per BICR or Investigator-assessed using RECIST version 1.1, which is a well-recognised international standard for measuring tumour burden.[52]

The impact of treatment on various aspects of HRQoL was assessed using several recognised, reliable, and validated tools, including the cancer-specific EORTC QLQ-C30 and lung cancer-specific EORTC QLQ-LC13 questionnaires. The EORTC scales include many of the key LS-SCLC symptoms and impacts, such as appetite loss, chest pain, cough, dyspnoea, fatigue, and physical functioning, and are therefore considered relevant to patients' experience of the disease.

B.3 Cost effectiveness

B.3.1 Summary of the economic analysis

- **The Phase 3 ADRIATIC met its dual primary endpoint, with durvalumab demonstrating a statistically significant and clinically meaningful improvement in both OS (55.9 months vs 33.4 months) and PFS (16.6 months vs 9.2 months) versus placebo**
- **A 3-state partitioned survival model was developed to assess the cost-effectiveness of durvalumab in patients with LS-SCLC who have not progressed following CRT**
- **The health states include progression-free, progressed disease, and death**
- **The economic analysis uses data from the ADRIATIC trial (time-to-event outcomes, health state utilities, and AEs), which is the most relevant and representative dataset for this submission**
- **In the deterministic base case economic analysis, treatment with durvalumab compared with "watch and wait" was associated with an increase in life years ([redacted] years per patient), increased quality-adjusted life years (QALYs; [redacted] per patient), and an incremental cost of [redacted] per patient. This produced an incremental cost per QALY gained (ICER) of £21,285**
- **The probabilistic analyses were consistent with the deterministic analyses, with a corresponding cost per QALY of £21,564**
- **ICERs ranged between £17,228 and £25,464 in scenario analyses (Section B.3.12.3)**
- **Key drivers of the model identified by the deterministic sensitivity analysis (DSA) were the parameters related to the proportion of patients receiving subsequent treatments as well as the cost associated with the subsequent treatments**

B.3.2 Published cost-effectiveness studies

A SLR was conducted to identify relevant economic evaluations of treatments for patients with LS-SCLC. Detailed descriptions of the review methodology and results are provided in Appendix G. All database searches were conducted between 7th May and 17th June 2024. In total, two studies reporting on the cost-effectiveness of treatments for LS-SCLC were identified, neither of which were conducted from a UK perspective or evaluated the cost-effectiveness of systemic consolidation therapy following CRT. A summary of these studies is presented in Table 36.

Table 36: Summary list of published cost-effectiveness studies in LS-SCLC

Study	Year	Population	Country	Model structure	Total costs, USD	QALY	ICER, USD/ QALY
Chien et al[53]	2014	Patients with LS-SCLC	Taiwan	Population-based propensity-score matched analysis	• CRT arm: $42,439 • Chemotherapy arm: $28,357	NR	NR
Qu et al[54]	2017	Patients with LS-SCLC	US	State transition Markov model	• HA-PCI: $9,846 • C-PCI: $4,986	• HA-PCI: 1.85 • C-PCI: 1.75	$47,107

Abbreviations: C-PCI, Conventional prophylactic cranial irradiation; CRT, chemoradiotherapy; HA-PCI, Hippocampal avoidance prophylactic cranial irradiation; ICER, incremental cost-effectiveness ratio; LS-SCLC, limited-stage small-cell lung cancer; NR, not reported; QALY, quality-adjusted life year; US, United States; USD, United States Dollar.

Neither of the studies identified in the SLR were considered relevant to inform selection of the most appropriate model structure for this submission. Relevant appraisals assessing treatments for ES-SCLC or relapsed SCLC were therefore identified in a targeted literature review of previous NICE TA submissions. In total, five appraisals were identified; two of which were identified where a partitioned survival model (PSM) structure was used, and which was well received by NICE. A summary of the appraisals is presented in Table 37.

Table 37: Summary list of published cost-effectiveness studies in SCLC

Study	Year	Country	Population	Model structure	Health states
NICE TA638: Atezolizumab + carboplatin and etoposide[45]	2020	UK	Adult patients with untreated ES-SCLC	Partitioned Survival Analysis	• Progression-free • Progressed disease • Death
NICE TA184: Topotecan[39]	2009		Adult patients with relapsed SCLC	Partitioned Survival Analysis	• Relapsed SCLC • Progressive Disease • Death

Abbreviations: ES-SCLC, extensive-stage small-cell lung cancer; NICE, National Institute for Health and Care Excellence; SCLC, small-cell lung cancer; TA, technology appraisal; UK, United Kingdom.

Durvalumab for maintenance treatment of unresectable NSCLC after platinum-based chemoradiation (TA798),[5] was also considered to be relevant as it used a partitoned survival analysis and included progression-free, progressed disease, and death health states.

For consistency with previous models used in NICE technology appraisals for SCLC, and to align with the modelling approach typically used in oncology submissions where OS and PFS are efficacy endpoints of interest, a PSM approach was used in this economic analysis for durvalumab.

B.3.3 Economic analysis

No published economic analyses of durvalumab for the treatment of patients with LS-SCLC were identified in the cost-effectiveness SLR (see Section B.3.2). A *de novo* model was therefore developed to assess the cost-effectiveness of durvalumab monotherapy in patients with LS-SCLC who have not progressed following CRT.

B.3.3.1 Patient population

The relevant population for the cost-effectiveness analysis is patients with LS-SCLC who have not progressed following CRT. The ITT population (full analysis set [FAS]) of the ADRIATIC trial (NCT03043872) was used to model the patient population.[55] A summary of patient baseline characteristics from ADRIATIC is summarised in Table 38.

Table 38: Summary of baseline characteristics from the ADRIATIC trial

Characteristic	Value	Reference
Baseline age, years†	61.50	ADRIATIC[1]
Body weight, kg	[redacted]	
Height, cm	[redacted]	
Proportion female, %	[redacted]	
Body surface area, m^2	[redacted]	Calculation[56]

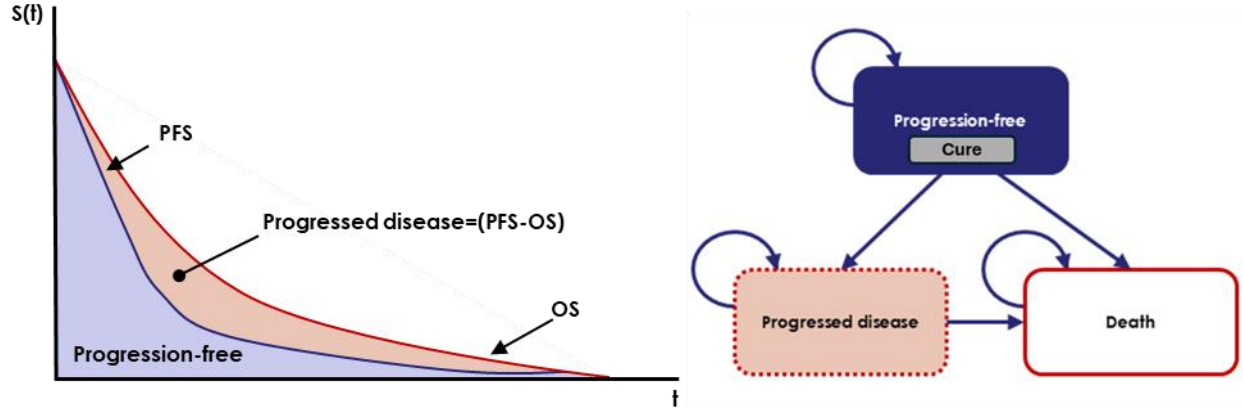
B.3.3.2 Model structure

A three-state area under the curve (AUC) model, also known as a PSM, was developed in Microsoft® Excel to assess the cost-effectiveness of durvalumab. The three distinct and mutually exclusive health states are progression-free (PF), progressed disease (PD) and death. The model structure was selected based on the following:

- The structure directly leverages the time-to-event endpoints collected in the ADRIATIC study, namely OS and PFS, demonstrating the model accurately reflects disease progression and the observed survival profile of patients treated with durvalumab
- The structure is consistent with approaches adopted in the majority of economic analyses submitted to HTA bodies for treatments in SCLC (see Section B.3.2)
- As noted in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19,[57] partitioned survival modelling is well understood, intuitive, and easy to communicate

An illustration of the model schematic is presented in Figure 16.

Figure 16: Model schematic



Abbreviations: OS, overall survival; PFS, progression-free survival; S(t), survival; t, time (months).

All patients enter the model in the PF health state and receive treatment. Within this health state patients can then transition to PD or Death. Patients in the PD health state are also at risk of transitioning to Death, which is an absorbing state. The three states are mutually exclusive and fully exhaustive, meaning that patients must occupy one of the states at any given time.

The PFS outcomes from the ADRIATIC study align with the opinion of UK clinicians that functional cure is currently achieved in most patients who remain progression-free for 3–5 years after CRT treatment[17]. This is suggested by plateauing of the Kaplan-Meier curves in both the treatment and placebo arms. Therefore, the model structure also considered a functional cure. The functional cure assumption reflects the time point at which patients are deemed cured and the proportion of patients assumed to be cured at this time. Patients who are assumed cured face the same mortality risk as the general population and will not experience progression for the remainder of the model. Cured patients were assigned the same utility values as the general population and no treatment costs or health state costs were applied to cured patients. The functional cure assumption was applied to both the treatment arms (see Section B.3.4.2).

As outlined in the DSU review of partitioned survival analysis (TSD19),[57] the model estimates the proportion of the cohort in each state based upon parametric survival models fit separately to the OS and PFS curves. The proportion occupying the PF state is estimated directly from the cumulative survival probabilities for PFS, while the proportion occupying the PD state is estimated from the cumulative survival of

OS minus the cumulative survival of PFS. The proportion occupying the death state are calculated as one minus the OS curve.

The health state occupancy calculations are:

- Progression-free: PF
- Progressed disease: OS – PF
- Death: 1 – OS

Extrapolated survival curves were adjusted for general population mortality, informed by life tables for the UK[58] to ensure that the disease-specific probability of death never falls below that of the general population (see Section B.3.4.3).

While PFS was used to model patient survival and progression, clinical data on time on treatment was also necessary to estimate the treatment-related costs, including treatment acquisition and administration costs. Time to treatment discontinuation (TTD) data from the ADRIATIC trial were therefore used to estimate durvalumab treatment-related costs (see Section B.3.4.4).

B.3.3.3 Features of the economic analysis

In the base case analysis, to align with NICE guidance,[59] costs and health outcomes were modelled over a lifetime horizon. Based on the ADRIATIC trial, the starting age of patients in the model is 61.5 years. The model time horizon was therefore assumed to be 39 (38.5) years, which was considered sufficient to capture all patient outcomes because after this timepoint <1% of the patient population remained alive in the model. As the starting age in the model was sourced from the ADRIATIC trial, there is consistency between the evidence sources used to inform the patient characteristics and the modelled time-to-event outcomes. A scenario analysis considering a 20-year time horizon was explored and is presented in Section B.3.12.3.

A 4-week cycle length was adopted in the model, which aligned with the frequency of administration over the time period patients could receive durvalumab in ADRIATIC.[55] This approach is consistent with prior NICE TAs in SCLC, where the cycle length was aligned with the frequency of drug administration, most notably in TA184 where the model's cycle length was 21 days and topotecan was administered

for 5 consecutive days in 21-day cycles.[39] Half-cycle correction was applied in the base case.

Following the first year of the model, an annual 3.5% discount rate was applied to both costs and health outcomes, as per NICE guidelines.[59] Alternative discount rates were explored in scenario analyses, as shown in Section B.3.12.3.

In line with NICE guidelines, the model adopts a UK National Health Service and personal social services healthcare payer perspective.[59] As such, societal costs were not considered in the base case analysis.

The key features of the economic analysis, and a comparison with previous NICE TAs are summarised in Table 39. NICE TA638,[45] TA184,[39] and TA798[5] were considered the only comparable submissions and were therefore used to validate the model inputs where appropriate.

Table 39: Features of the economic analysis

Factor	Previous evaluations			Current evaluation	
	TA638	TA184	TA798	Chosen values	Justification
Model structure	PSM	PSM	PSM	PSM	Aligned with the previous economic models
Perspective on costs	UK NHS and PSS healthcare payer	UK NHS and PSS healthcare payer	UK NHS and PSS healthcare payer	UK NHS and PSS healthcare payer	As per NICE guidelines[59]
Perspective on outcomes					
Time horizon	Lifetime (20 years)	Lifetime (5 years)	Lifetime (40 years)	Lifetime (39 years)	
Discount rate	3.5% for costs and health outcomes	3.5% for costs and health outcomes	3.5% for costs and health outcomes	3.5% for costs and health outcomes	
Outcome measure	• QALYs • LYs	• QALYs • LYs • Mean and median PFS, TTD and OS	• QALYs • LYs • Mean and median PFS, TTD and OS	• QALYs by health states (PF and PD) • LYs by health states (PF, PD) • Mean and median PFS, TTD and OS	As per the NICE final scope

Factor	Previous evaluations			Current evaluation	
	TA638	TA184	TA798	Chosen values	Justification
Treatment waning effect	No waning but treatment benefit capped at 5 years after diagnosis	No waning	No waning (waning effect after 10 years explored in scenario analysis)	No treatment waning will be applied	Aligned with the previous economic models
Source of utilities	IMpower133 trial, EQ-5D individual patient level data	EQ-5D during the RCT	EQ-5D-5L data collected in PACIFIC and mapped to 3L	• Health-state utility values derived from the ADRIATIC trial • Disutilities for AEs from published literature	As per NICE guidelines[59]
Source of costs	• NHS reference costs • eMIT	• NHS reference costs • BNF	• NHS reference costs • PSSRU • MIMS • eMIT	• NHS reference cost collection • PSSRU • BNF • eMIT	As per NICE guidelines[59] and aligned with previous economics evaluations

Abbreviations: AE, adverse event; BNF, British National Formulary; eMIT, electronic market information; EQ-5D, EuroQol- 5 Dimension; LS-SCLC, limited-stage small-cell lung cancer; LY, life year; NICE, National Institute of Health and Care Excellence; NHS, national health service; NR, not reported; OS, Overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; PSM, partitioned survival model; PSSRU, Personal Social Services Research Unit; QALY, Quality-adjusted life years; RCT, randomised controlled trial; TA, technology appraisal; TTD, time to treatment discontinuation.

B.3.3.4 Intervention technology and comparators

The intervention considered in the economic analysis is durvalumab monotherapy. As per the ADRIATIC trial, durvalumab is administered intravenously at a dose of 1,500 mg every 4 weeks until disease progression, intolerable toxicity, or a maximum of 24 months, whichever occurs first.

The European Society for Medical Oncology (ESMO)[18] and National Comprehensive Cancer Network (NCCN)[60] guidelines recommend concurrent (cCRT) or sequential (sCRT) CRT as treatment for LS-SCLC, with cCRT recommended for patients with better performance status (0–1 in ESMO guidelines; 0–2 in NCCN v2 2024 guidelines). NCCN guidelines recommend 4 cycles of chemotherapy for patients receiving cCRT. Patients who respond to CRT can receive PCI to reduce the risk of

brain metastases.[60] However, to date, as per ESMO and NCCN guidelines, there is no consolidation treatment specifically recommended for patients with LS-SCLC after CRT.[18, 60]

Due to the lack of available consolidation therapy for LS-SCLC, the modelled comparator was a “watch and wait” strategy, represented by the placebo arm of the ADRIATIC trial. The model utilised data from the ADRIATIC trial to inform clinical efficacy of durvalumab and placebo for the comparator arm.

B.3.4 Clinical parameters and variables

The baseline patient characteristics, efficacy, and AE data used in the economic analysis were taken from the ADRIATIC trial and are outlined in sections B.3.4.1 to B.3.4.6. A summary of the baseline characteristics is presented in Section B.3.3.1 (Table 38).

B.3.4.1 Efficacy

The ADRIATIC trial was conducted to assess the efficacy and safety of durvalumab monotherapy and durvalumab plus tremelimumab as consolidation treatments for patients with LS-SCLC who have not progressed after cCRT. The durvalumab monotherapy group is the primary focus in this submission as these patients received durvalumab monotherapy, in line with the proposed licensed indication for durvalumab.

At the time of the first interim analysis of OS and PFS (data cut-off date: January 15th, 2024), the ADRIATIC study met the dual primary endpoints for OS and PFS for the comparison of durvalumab monotherapy versus placebo.[61] The secondary endpoint of OS for the durvalumab plus tremelimumab versus placebo comparison did not meet the boundary for statistical significance. The durvalumab plus tremelimumab arm remains blinded and continues to be observed for the next planned analysis. This submission therefore focuses on the durvalumab monotherapy arm of the ADRIATIC trial using first interim analysis data (see Sections B.2.3.1.5 and B.2.4.4.1) available at the time of this submission. Data from the placebo arm of the ADRIATIC trial was used to inform the “watch and wait” comparator in the economic analysis.

B.3.4.1.1 Survival analysis and extrapolations

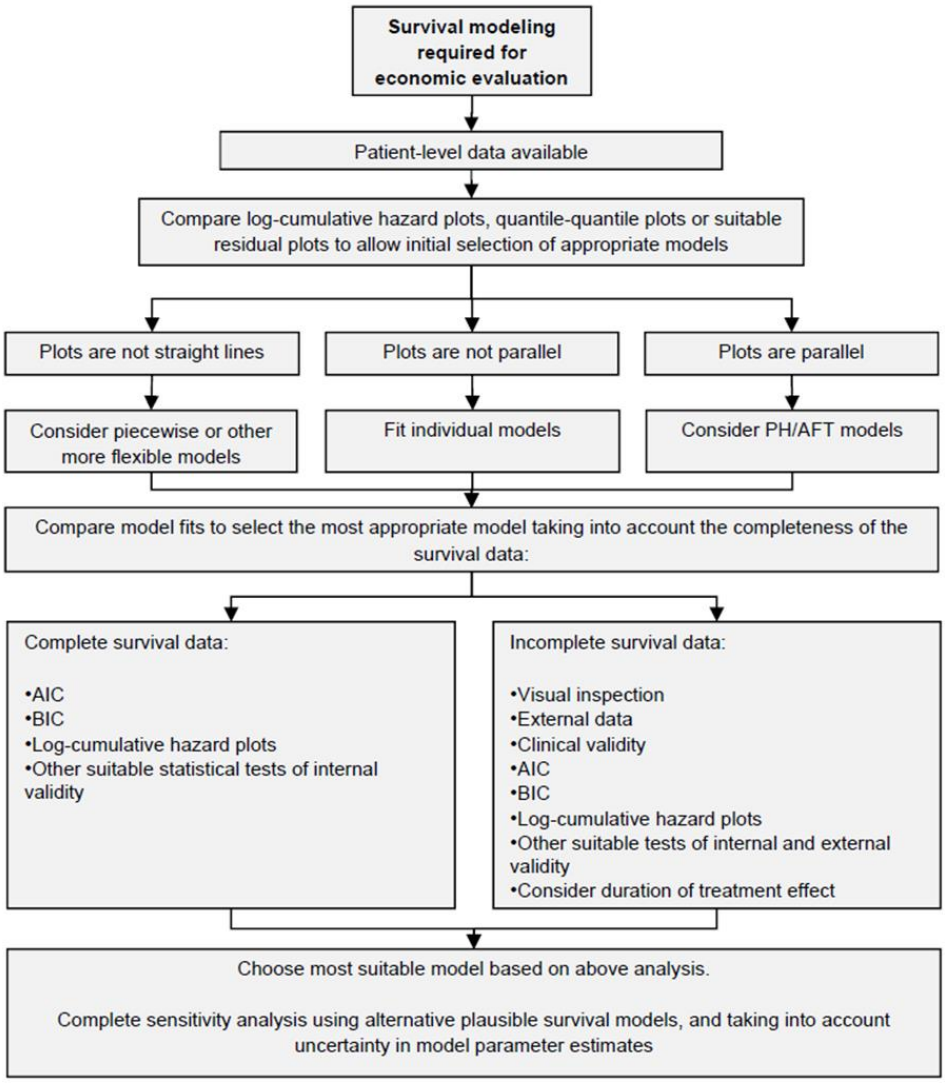
Survival analyses were conducted and assessed through five main steps, which are aligned with the survival model selection process algorithm described in NICE DSU TSD 14[62] (see Figure 17) and NICE DSU TSD 21:[63]

- Assessment of the proportional hazards assumption (PHA):
  - The PHA was primarily assessed based on log-cumulative hazard plots (LCHP), with additional formal statistical methods (such as Schoenfeld residual test) considered to further confirm the validity of proportional hazards. If the PHA holds (LCHP curves are parallel and do not cross, or Schoenfeld's residuals p-value is >0.05 indicating no autocorrelation among residuals at 95% confidence interval) dependent models should be selected. In this case, parametric models should be fitted for one treatment and a proportional treatment effect used to generate the other treatment curve. If the PHA does not hold (LCHP curves cross or are not considered parallel, or Schoenfeld's residuals p-value is significant), then independent models or more flexible models, such spline-based models, should be selected, which permit capturing different shapes of the hazards
- Statistical goodness of fit (Akaike Information Criterion [AIC]/ Bayesian Information Criterion [BIC]):
  - The statistical fit of each curve was assessed by considering the ranking of AIC and BIC values
- Visual fit to Kaplan-Meier (KM) plots:
  - The goodness of fit of the parametric curves to the KM data for durvalumab and placebo was visually assessed, with consideration given to the entire trial period for which data were available
- Assessment of hazard functions:
  - The hazards within the trial period and hazards beyond the trial using a 10-year time horizon for each distribution were assessed. For the within-trial period, the trial hazard was visually compared with the model-predicted hazards. Hazards over a 10-year timeframe were also considered to confirm that the extrapolated hazards for the chosen base case curve is clinically plausible. Consideration of the extrapolated hazards was important as some hazard predictions were

overly influenced by the events occurring at the end of follow-up due to small patient numbers at the end of follow-up in ADRIATIC

- External validation to understand the suitability of the extrapolated curves:
  - The clinical plausibility of long-term projections was assessed by clinical expert opinion and comparisons with medium to long-term data from clinical trials within a similar treatment indication.

Figure 17: NICE DSU recommendations for the analysis of survival data



Abbreviations: AFT, accelerated failure time; AIC, Akaike Information Criterion; BIC Bayesian Information Criterion; PH, proportional hazards.

In the model, PFS was capped to ensure it does not exceed OS, maintaining the logical sequence of events where PFS aligns under OS. This methodological choice ensures that the curve selection process is not impacted by inconsistencies,

reflecting a realistic scenario where patients who progress ultimately contribute to OS events. This approach is especially applicable in settings with curative intent, such as LS-SCLC, representing a subset of patients achieving functional cure from the primary disease (see Section B.3.4.2 for further details). In these cases, PFS and OS curves may eventually converge, indicating a group of patients who achieve a functional cure from the primary disease.

B.3.4.1.2 Progression-free survival

Progression-free survival was defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. The primary analysis of PFS was assessed by BICR using RECIST, version 1.1. Median time to PFS is presented in Table 40.

Table 40: PFS time to event data

Treatment	Total number of events, n (%)	Median time to event, months (95% CI)
Intervention (n=264)	139 (52.7)	16.6 (10.2, 28.2)
Placebo (n=266)	169 (63.5)	9.2 (7.4, 12.9)

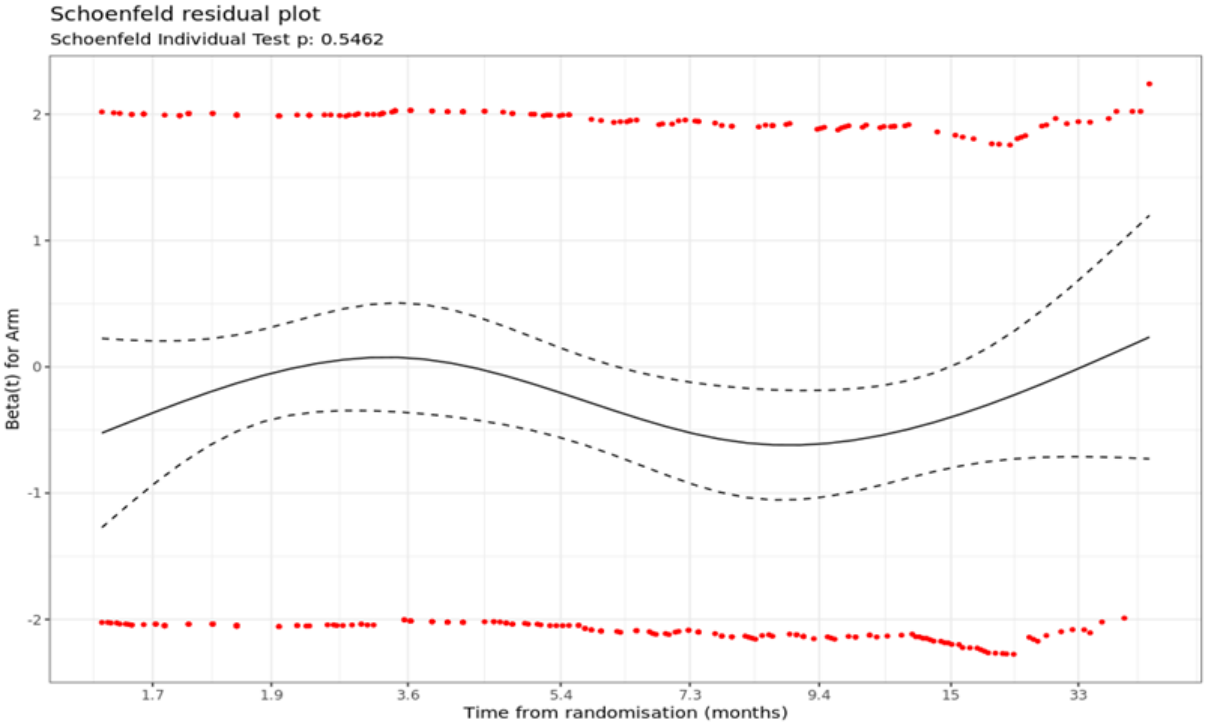
Abbreviations: CI, confidence interval; PFS, progression-free survival.

To determine whether dependent models could be used (i.e., predict the survival of both durvalumab and “watch and wait” with the same survival function using a treatment effect covariate), the PHA was tested. Inspection of Schoenfeld residuals and the log cumulative hazard plot were conducted to test the PHA and determine whether independent survival models were required.

The Schoenfeld residual and log-cumulative hazard plots for PFS are presented in Figure 18 and Figure 19, respectively. The Grambsch-Therneau test result was p=0.5462, which failed to reject the PHA. However, the Schoenfeld residual plot showed some evidence of non-proportional hazards, (i.e., a non-horizontal line), although there was no clear pattern or trend in the treatment effect over time. In addition, the log-cumulative hazard plot showed minor departures from PHA with the trend lines diverging and being non-parallel. These departures from PHA may be reflective of the delayed separation (at approximately 6 months) of the PFS KM

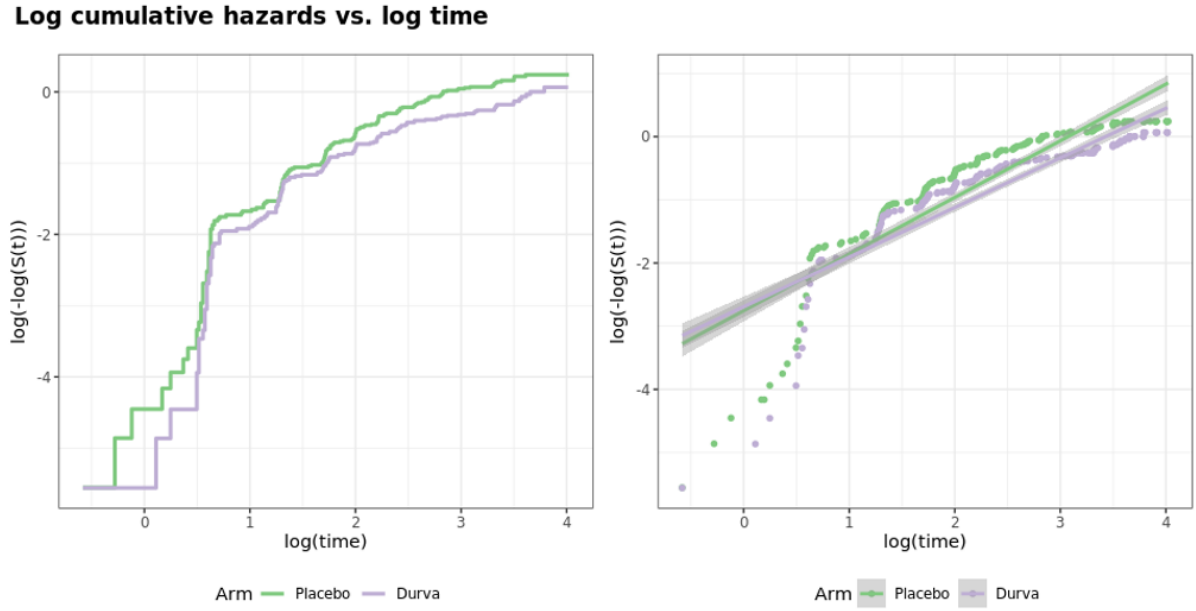
curves (Figure 20). Consequently, methods for non-proportional hazards analysis were explored and independent models were selected for the extrapolation of PFS.

Figure 18: PFS Schoenfeld residual plot



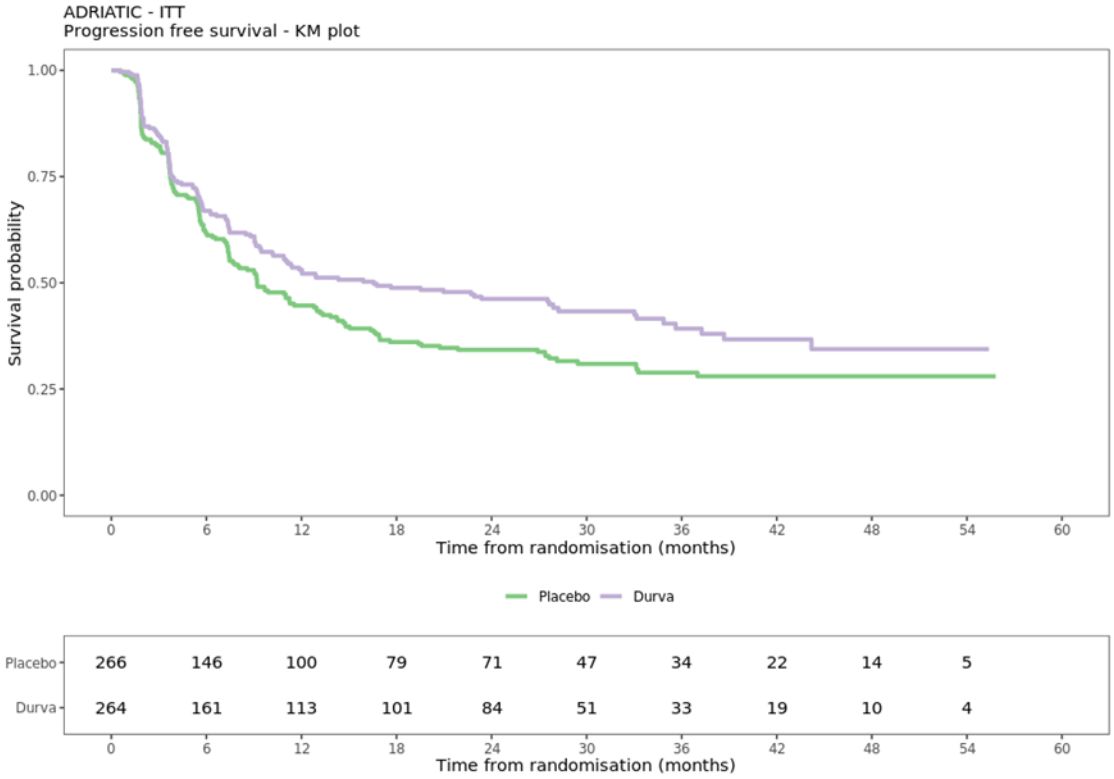
Abbreviations: PFS: progression-free survival; t, time (months).

Figure 19: Log cumulative hazard plots for PFS



Abbreviations: Durva, durvalumab; PFS: progression-free survival; S(t), survival.

Figure 20: PFS Kaplan-Meier plot



Abbreviations: Durva, durvalumab; ITT, intention to treat; KM, Kaplan-Meier; PFS, progression-free survival.

In accordance with NICE DSU TSD 14[62] and NICE DSU TSD 21,[63] seven standard parametric distributions (exponential, gamma, generalised gamma, log-normal, log-logistic, Weibull, Gompertz), along with flexible spline-based models (up to 3 knots), were fitted to the observed PFS data from the ADRIATIC trial.

Flexible parametric models were considered due to their ability to accommodate hazard functions with complex shapes (NICE DSU TSD 21, Section 2.1.2).[63] The assessment of hazard functions for PFS in both treatment arms of the ADRIATIC trial supported the consideration of such models. For the spline-based approach, Royston-Parmer models were used and fitted with up to 3 knots. Spline knot locations were chosen as equally spaced quantiles of the uncensored survival times, for example, at the median with 1 knot or at the 33.3% and 66.7% quantiles for 2 knots. Boundary knots are chosen as the minimum and maximum event times.

B.3.4.1.2.1 Durvalumab progression-free survival

Statistical goodness of fit

The goodness of fit statistics based on AIC and BIC for the survival models for the durvalumab arm are presented in Table 41. The 2-knot spline normal model was

considered the best fit according to the AIC rank, followed by 3-knot spline odd and 3-knot spline hazard models. According to the BIC rank, generalised gamma was the best fit, 1-knot spline normal was ranked second, and 2-knot spline normal was ranked third.

Table 41: AIC/BIC for durvalumab PFS

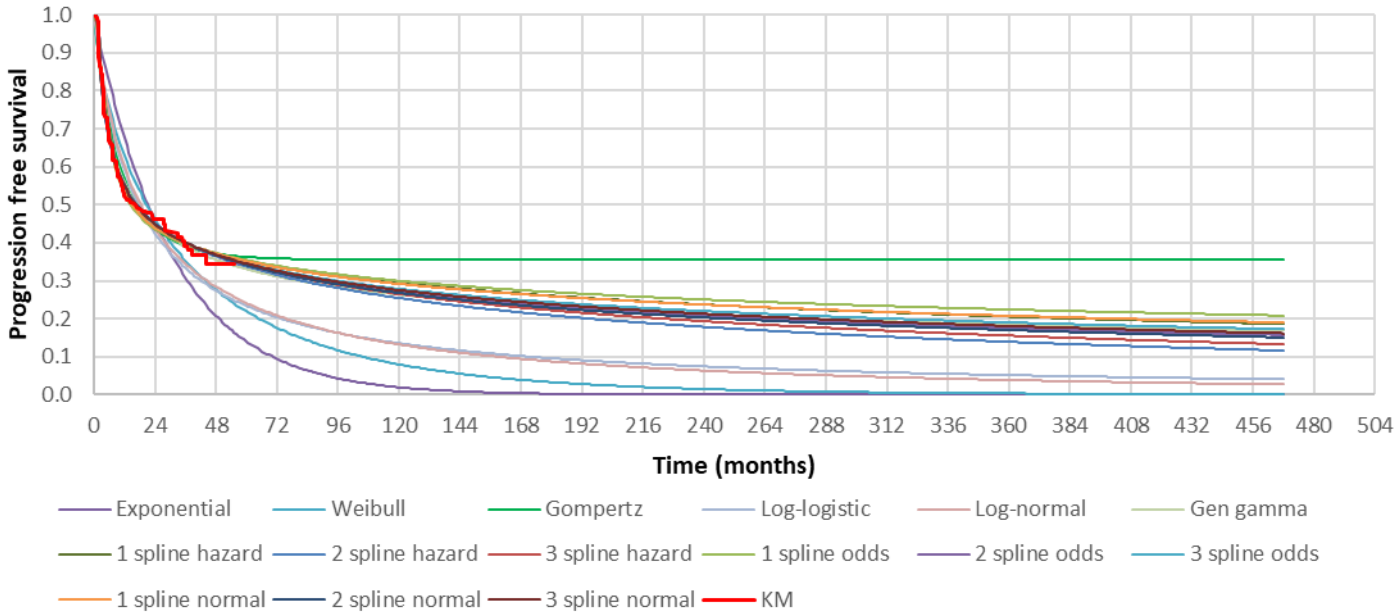
	Durvalumab			
Model	**AIC**	**AIC rank**	**BIC**	**BIC rank**
Exponential	1230.50	16	1234.10	16
Weibull	1211.40	14	1218.50	14
Gompertz	1179.00	12	1186.10	12
Log-logistic	1190.90	13	1198.00	13
Log-normal	1177.80	11	1184.90	11
Gen gamma	1138.60	6	1149.40	1
Gamma	1218.20	15	1225.40	15
1-knot spline hazard	1147.70	10	1158.40	10
2-knot spline hazard	1138.70	7	1153.00	5
3-knot spline hazard	1137.50	3	1155.30	7
1-knot spline odds	1144.60	9	1155.30	7
2-knot spline odds	1138.20	5	1152.60	4
3-knot spline odds	1137.20	2	1155.10	6
1-knot spline normal	1138.80	8	1149.50	2
2-knot spline normal	1136.70	1	1151.00	3
3-knot spline normal	1137.60	4	1155.50	9

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Visual fit to KM plot

The PFS extrapolation curves for each distribution were plotted together with the KM durvalumab data from the ADRIATIC trial and are presented in Figure 21.

Figure 21: PFS extrapolations – Durvalumab



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

Based on the PFS extrapolations presented in Figure 21, the spline-based models provided the best visual fit to the observed survival data for durvalumab. While the generalised gamma distribution also provided a reasonable visual fit, the other standard parametric distributions generally exhibited a poorer fit to the observed data; tending to overestimate survival initially and underestimating it towards the end of the follow-up period (except for the Gompertz distribution). These trends were also observed when comparing the predicted PFS between 1–3 years with the KM survival probabilities, generalised gamma and Gompertz showed PFS that more consistently align with the ADRIATIC KM survival probabilities for the durvalumab arm. Additionally, all spline-based models also aligned well with the 1–3-year KM survival data.

The spline models not only provided a strong visual fit to the observed PFS KM data but also several of them achieved a superior statistical fit compared to the generalised gamma model, according to the AIC ranking (Table 41). These models

preserved the pattern captured by the generalized gamma distribution while offering enhanced flexibility and precision, making them the best fitting models for the data.

Assessment of hazard function

The raw hazard plot for both durvalumab and “watch and wait”, showing that the hazards change over the course of the trial, is presented in Figure 22. Durvalumab initially displayed a trend of [redacted], as illustrated in Figure 35. The smoothed hazards are presented in Figure 23 which helps to display how the trial hazard changes over time in the durvalumab arm (i.e., [redacted]).

Figure 22: PFS hazard plot (raw) – Durvalumab and “watch and wait”

[redacted]

Abbreviations: BICR; Blinded Independent Central Review; Durval, durvalumab; PFS, progression-free survival.

Figure 23: PFS smoothed hazard plot (kernel method) – Durvalumab and "watch and wait"

Abbreviations: BICR; Blinded Independent Central Review; Durval, durvalumab; PFS, progression-free survival.

The PFS hazard plots for all parametric curves were extrapolated over a 10-year (120-month) time horizon to confirm clinical plausibility of the base case curve in the long-term. The PFS hazard plots for the standard parametric curves are presented in Figure 24.

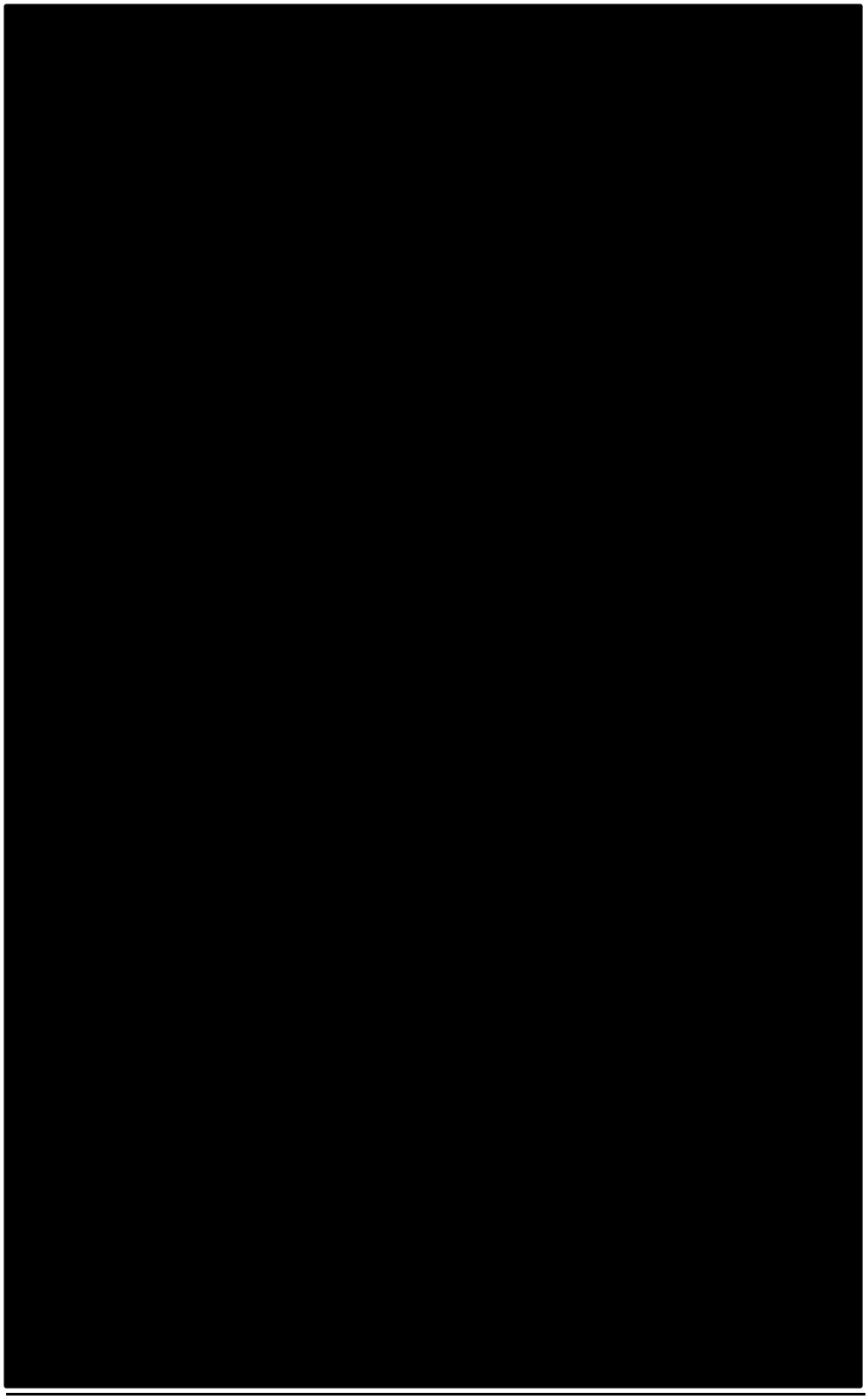
Only the generalised gamma and Gompertz distributions were able to capture the overall change in the trial hazard in the durvalumab arm. The other standard parametric distributions did not accurately fit the trial hazard, and therefore were not considered appropriate to model PFS in the durvalumab arm.

Figure 24: PFS extrapolated hazard plots for standard parametric distributions – Durvalumab and "watch and wait"

Abbreviations: BICR; Blinded Independent Central Review; Durva, durvalumab; ITT, intention-to-treat; PFS, progression-free survival.

The PFS hazard plots for all spline models that were extrapolated over a 10-year (120-month) time horizon is presented in Figure 25. All spline models were able to capture the general trend of trial hazard in the durvalumab arm. However, the spline models with 1 knot appeared to best fit the initial decline in hazards compared with their 2-knot and 3-knot counterpart models. For all scales, increasing the number of knots overestimated the initial trial hazard before it begins to decline.

Figure 25: PFS extrapolated hazard plots for spline models – Durvalumab and "watch and wait"



Abbreviations: BICR; Blinded Independent Central Review; Durva, durvalumab; ITT, intention-to-treat; PFS, progression-free survival.

External validation

Clinical expert opinion was sought during an advisory board on 11th October 2024 to ensure that the best-fitting model provided a clinically plausible extrapolation beyond the trial data.[17] All seven standard parametric models with PFS predictions from 1 to 15 years were presented to the clinical experts. Table 42 presented the 10- and 15-year PFS predictions associated with each standard parametric distribution for the durvalumab arm.

Table 42: Estimated 10- and 15-year PFS for durvalumab standard parametric distributions

Trial	10-year PFS rate, %	15-year PFS rate, %
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gen gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviaitons: KM, Kaplan-Meier; PFS, progression-free survival

When reviewing the standard parametric extrapolations in the durvalumab arm, clinical experts all agreed that based on 5-year KM data of 34.9% the generalised gamma distribution provided the most clinically plausible 10-year PFS rate of [redacted]%.

As the spline models produced extrapolations similar to those of the generalised gamma model (see Table 50 and Table 51), which clinical experts considered a reasonable fit, additional validation of the spline models by clinical experts was not required. Spline models were preferred over standard parametric models due to their flexibility in capturing complex hazard functions, with single-knot models favoured for their superior fit. Therefore, the 1-knot spline normal, which had the best statistical fit, was selected for the base case.

Table 43: Estimated 10- and 15-year PFS for durvalumab spline models

Trial	10-year PFS rate, %	15-year PFS rate, %
1-knot spline hazard	[redacted]	[redacted]
2-knot spline hazard	[redacted]	[redacted]
3-knot spline hazard	[redacted]	[redacted]
1-knot spline odds	[redacted]	[redacted]

Trial	10-year PFS rate, %	15-year PFS rate, %
2-knot spline odds	[redacted]	[redacted]
3-knot spline odds	[redacted]	[redacted]
1-knot spline normal	[redacted]	[redacted]
2-knot spline normal	[redacted]	[redacted]
3-knot spline normal	[redacted]	[redacted]

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

B.3.4.1.2.2 Watch and wait progression-free survival

Statistical goodness of fit

The goodness of fit statistics, based on AIC and BIC for the survival models for the watch and wait arm, are presented in Table 44. The 3-knot spline odds and 3-knot spline normal models were considered the best fit according to AIC ranking followed by 3-knot spline hazard and 1-knot spline normal. The 1-knot spline normal model was the best fit according to the BIC ranking, followed by generalised gamma, and 1-knot spline odds ranked second and third, respectively.

Table 44: AIC/BIC for watch and wait PFS

	"Watch and wait"			
Model	**AIC**	**AIC rank**	**BIC**	**BIC rank**
Exponential	1400.90	16	1404.50	16
Weibull	1380.70	14	1387.90	14
Gompertz	1331.80	11	1338.90	11
Log-logistic	1345.00	13	1352.10	13
Log-normal	1335.00	12	1342.10	12
Gen gamma	1298.00	5	1308.70	2
Gamma	1390.30	15	1397.50	15
1-knot spline hazard	1302.10	10	1312.90	6
2-knot spline hazard	1302.00	9	1316.30	10
3-knot spline hazard	1295.80	3	1313.70	8
1-knot spline odds	1301.10	7	1311.90	3
2-knot spline odds	1301.80	8	1316.10	9
3-knot spline odds	1294.80	1	1312.70	4

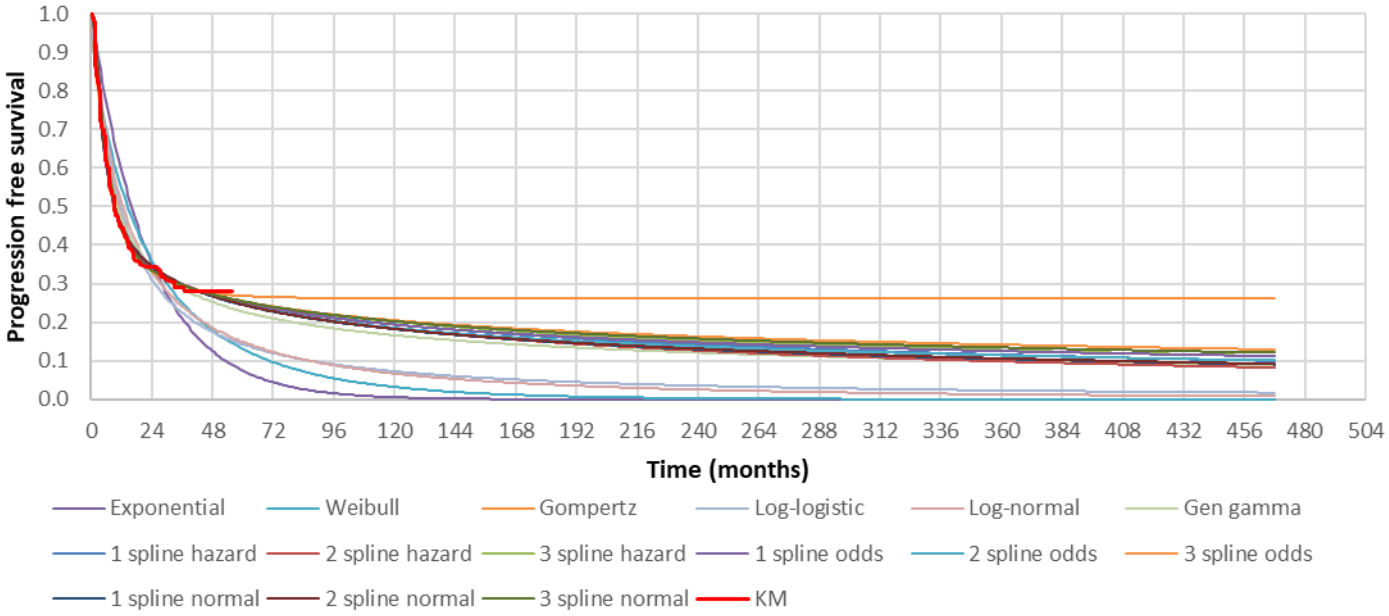
	“Watch and wait”			
1-knot spline normal	1297.60	4	1308.40	1
2-knot spline normal	1299.20	6	1313.50	7
3-knot spline normal	1294.80	1	1312.70	4

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Visual fit to KM plot

The PFS extrapolation curves for each distribution were plotted together with the KM placebo data from the ADRIATIC trial and are presented in Figure 26.

Figure 26: PFS extrapolations – Watch and wait



Abbreviations: PFS, progression-free survival.

The generalised gamma and Gompertz distributions provided a reasonable fit to the KM curve; however, after approximately 72 months, the Gompertz curve plateaus providing an unrealistic long-term curve. One clinician noted that where the PFS curve flattens, it would likely represent patients who are cured. Similar to that observed in the durvalumab arm, the other standard parametric distributions appeared to initially overestimate PFS and then underestimate PFS in the “watch and wait” arm after approximately 30 months. The spline models appeared to show a better visual fit to the KM data compared with some of the standard parametric

distributions, such as the exponential, Weibull, log-logistic, and log-normal distributions. The spline models produced similar curves to the generalised gamma curve.

Assessment of hazard function

The change in trial hazard for the "watch and wait" arm are presented in Figure 23 and Figure 24, and demonstrate a trend of [redacted].

The hazard plots for PFS standard parametric curves in the "watch and wait" arm are presented in Figure 24. The generalised gamma and Gompertz distributions captured the general trend of the trial hazard; however, the generalised gamma distribution appeared to better capture the change in trial hazard that occurred between [redacted]. Furthermore, the tail of the Gompertz distribution appeared to plateau after 48 months.

As presented in Figure 25, the 1-knot and 2-knot spline models on all scales appear to capture the general trend of the trial hazard in the "watch and wait" arm. In contrast, the 3-knot models show an increase in the trial hazard at approximately 12 months, which is not reflected in the general trends shown in Figure 23 and Figure 24. On the hazard and odds scale, increasing the number of knots increases the initial trial hazard before it starts to decline, whereas only the 3-knot model on the normal scale appears to increase the initial trial hazard. Therefore, the normal scale was considered to best capture the trial hazard, with the 1-knot model being the best-fitting.

External validation

To assess the clinical plausiblity of extrapolations, the predicted PFS from the parametric distributions for the "watch and wait" arm were compared with landmark PFS reported from previous clinical trials of CRT with longer-term follow-up than the ADRIATIC trial. The CONVERT[14, 16] and CALGB 3061[15] trials were identified from the clinical SLR (Section B.2.1 and Appendix D) and considered relevant, as patients with LS-SCLC were randomised to receive either once-daily or twice-daily radiotherapy (RT) concurrently with platinum-etoposide chemotherapy in both trials,

as per prior therapy in the ADRIATIC trial. Although another trial which reported 5-year outcomes from concurrent CRT was identified in the review (NCCTG 89-20-52),[64] the CONVERT and CALGB 3061 trials were considered more appropriate to validate predicted long-term outcomes for the ADRIATIC placebo arm. This is because the results of NCCTG 89-20- 52 were published two decades ago, during which time significant advancements have been made in oncology treatment, RT techniques, and supportive care. The results of NCCTG 89-20- 52 are therefore unlikely to reflect current standards or treatment pathways.

In both the CONVERT and CALGB 3061 trials, 5-year OS and PFS landmarks have been reported (CONVERT median follow-up for surviving cohort was 81.2 months;[16] CALGB 3061 median follow-up was 4.7 years).[15] The long-term outcomes from the CONVERT and CALGB 3061 trials have therefore been used to validate the predicted long-term outcomes for the “watch and wait” comparator in the model.

The predicted PFS landmarks associated with each parametric model and the KM PFS data, as well as the 5-year PFS reported in the CONVERT and CALGB 3061 trials, are presented in Table 45. The 5-year PFS rates from CONVERT and CALGB 3061 are reported as ranges in Table 45, reflecting the two different RT regimens used in each trial arm. In CONVERT, patients received either 45 or 66 Gy RT, while in CALGB 3061, they received either 45 or 70 Gy RT. The PFS range in each trial represents the 5-year PFS from each respective radiotherapy arm.

Table 45: Long-term PFS (5-year) for Placebo extrapolation curves and published literature

Trial	PFS rate, ‘Watch and wait’ (Placebo), %
CONVERT	28–31
CALGB 3061	24–25
ADRIATIC trial	
KM data	27.99
Exponential	[redacted]
Weibull	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Gen gamma	[redacted]
Gamma	[redacted]

Trial	PFS rate, 'Watch and wait' (Placebo), %
1-knot spline hazard	[redacted]
2-knot spline hazard	[redacted]
3-knot spline hazard	[redacted]
1-knot spline odds	[redacted]
2-knot spline odds	[redacted]
3-knot spline odds	[redacted]
1-knot spline normal	[redacted]
2-knot spline normal	[redacted]
3-knot spline normal	[redacted]

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

The Gompertz and all spline-based models predicted 5-year PFS that were between the highest and lowest values of the two ranges combined of the 5-year PFS ranges reported in the CONVERT and CALGB 3061 trials (24–31%).

Clinical expert opinion was also sought to assess which distribution provided a clinically plausible extrapolation beyond the trial data. Based on the observed 5-year PFS data, the clinical experts noted that they would expect the 5-year PFS to fall between 20% and 25%, rather than the observed 27.99%. Table 46 presents the with from 10- and to 15-year PFS predictions associated with the seven standard parametric models.

Table 46: Estimated 10-year PFS for placebo standard parametric extrapolation curves

	10-year PFS rate, %	15-year PFS rate, %
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gen gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviaitons: PFS, progression-free survival.

For the 10-year predicted PFS, all experts agreed that the Weibull and exponential models were unsuitable, as they did not initially align with the Kaplan-Meier curve and could not reliably predict future outcomes. Some clinicians initially favoured the Gompertz model, attributing the curve's flattening at around 2 years to the

assumption that some patients were cured. However, other clinicians felt that the Gompertz model underestimated future deaths, suggesting that the generalised gamma model offered a more accurate estimation of PFS at 10 years. This view was ultimately supported by the majority of the clinical experts.

As mentioned in Section B.3.4.1.2.1, the spline models were not validated by clinical experts, as they produced extrapolations similar to those of the preferred standard parametric model (generalised gamma), which clinical experts considered a reasonable fit (see Table 47). Spline models were preferred over standard parametric models due to their flexibility in capturing complex hazard functions, with single-knot models favoured for having the most accurate fit. Furthermore, the 1-knot spline normal model had the closest 10- and 15-year predictions to the values the clinicians deemed the most reasonable (generalised gamma). Therefore, the 1-knot spline normal, which had the best statistical fit, was selected for the base case.

Table 47: Estimated 10- and 15-year PFS for placebo ("watch & wait") spline models

	10-year PFS rate, %	15-year PFS rate, %
1-knot spline hazard	[redacted]	[redacted]
2-knot spline hazard	[redacted]	[redacted]
3-knot spline hazard	[redacted]	[redacted]
1-knot spline odds	[redacted]	[redacted]
2-knot spline odds	[redacted]	[redacted]
3-knot spline odds	[redacted]	[redacted]
1-knot spline normal	[redacted]	[redacted]
2-knot spline normal	[redacted]	[redacted]
3-knot spline normal	[redacted]	[redacted]

Abbreviaitons: KM, Kaplan-Meier; PFS, pregression-free survival.

B.3.4.1.2.3 Summary of choice of progression-free survival distributions for base case and scenario analyses

Independent models for extrapolating PFS were used for both treatment arms, as Section B.3.4.1.2 highlighted evidence of non-proportionality in the log cumulative hazard plots. Flexible parametric spline models were preferred over standard models because they can accommodate complex hazard functions, as supported by the hazard function assessment of the ADRIATIC trial data (see Figure 23).

The 1-knot spline normal model's 5-year PFS prediction in the "watch and wait" arm aligned with the CONVERT and CALGB 3061 trials (24–31%). Although clinical experts validated the generalised gamma model as plausible, the 1-knot spline normal model was considered more appropriate for the "watch and wait" arm due to its flexibility and superior fit. In the durvalumab arm, the 1-knot spline normal model was preferred for its ability to capture subtle trends while remaining simpler than multi-knot spline models.

Therefore, the 1-knot spline normal model was selected for both arms in the base case, based on its strong statistical fit to the observed KM data: it ranked 2nd by BIC in the durvalumab arm and 1st by BIC in the "watch and wait" arm. Moreover, the model provided clinically plausible extrapolations and offered flexibility to the hazard function in both arms. Full details of the choice are described in Section B.3.4.1.2.1 and B.3.4.1.2.2. Consistent modelling across arms was also preferred by NICE (DSU TSD 21),[63] ensuring comparability and avoiding variability from model structure.

As clinical experts considered the generalised gamma model to be a plausible distribution and it ranked highly according to the BIC in both arms, a scenario analysis was conducted to extrapolate PFS using this model (see Section B.3.12.3).

B.3.4.1.3 Overall survival

OS was defined as the time from the date of randomisation until death due to any cause. At the time of the first interim analysis, 115 and 146 OS events had occurred in the durvalumab and placebo arms, representing 43.6% and 54.9% maturity in each arm, respectively.[2] The OS time to event data is presented in Table 48.

Table 48: OS time to event data

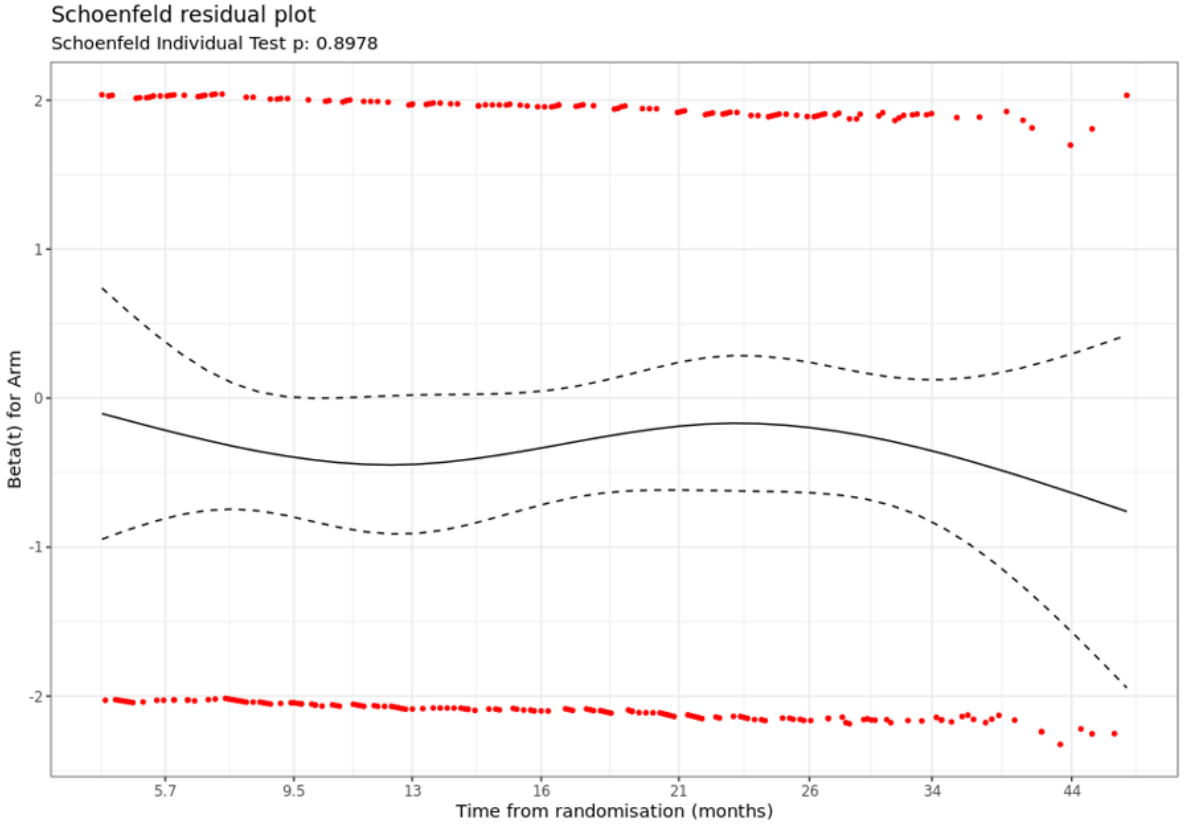
Treatment	Total number of events, n (%)	Median time to event, months (95% CI)
Intervention (n=264)	115 (43.6)	55.9 (37.3, NR)
Placebo (n=266)	146 (54.9)	33.4 (25.5, 39.9)

Abbreviations: CI, confidence interval; NR, not reported; OS, overall survival.

To assess whether dependent models could be used, the PHA was tested via inspection of Schoenfeld residuals and the log cumulative hazard plot. The Schoenfeld residual test for OS (Figure 27) showed no clear violation of the PHA (Grambsch-Therneau test result p=0.8978), however the non-horizontal line in the

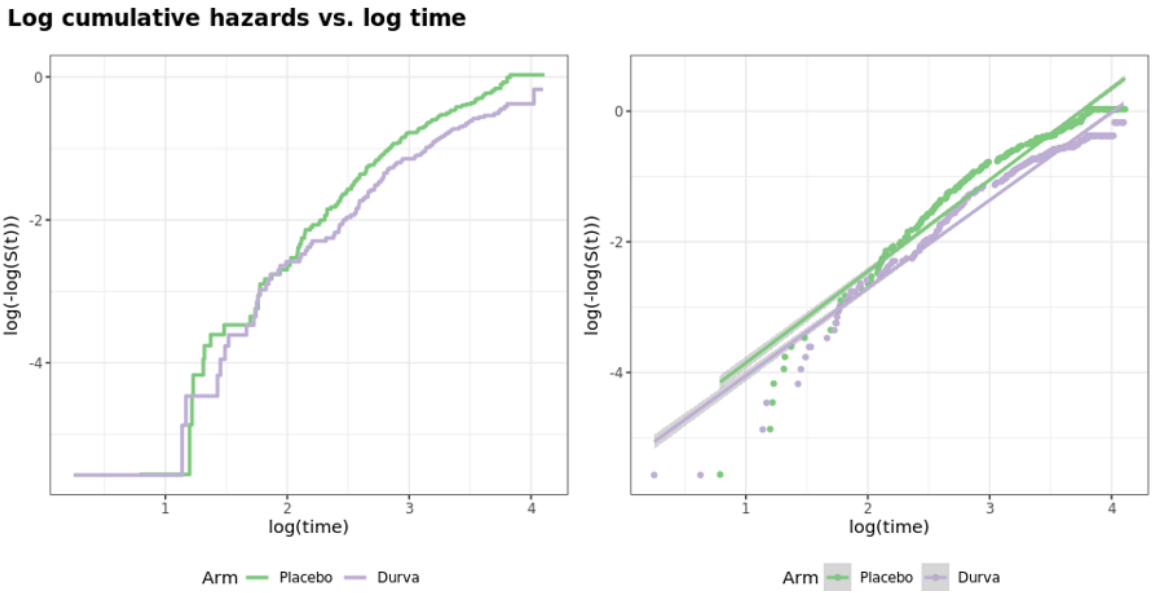
Schoenfeld residual plot provides evidence of non-proportionality. Furthermore, non-parallel lines were observed in the log cumulative hazard plot (Figure 28), further providing evidence of non-proportionality. These departures from the PHA may be reflective of the delayed separation (at approximately 8 months) of OS KM curves. Consequently, methods for non-proportional hazards analysis were explored and independent models were selected for extrapolation of OS.

Figure 27: OS Schoenfeld residual plot



Abbreviations: OS, overall survival; t, time (months).

Figure 28: Log cumulative hazard plots for OS



Abbreviations: Durva, durvalumab; OS, overall survival; S(t), survival.

As described in Section B.3.4.1.2, parametric models, including the seven standard parametric distributions and spline-based models were fitted separately to the OS data from both arms.

B.3.4.1.3.1 Durvalumab overall survival

Statistical goodness of fit

The goodness of fit statistics based on AIC and BIC for the survival models for the durvalumab arm are presented in Table 49. The 1-knot spline hazard model was considered the best fit according to the AIC statistic, followed by the 1-knot spline odds, and the 1-knot spline normal models. The BIC statistic ranked the log-normal distribution as the best fit with the 1-knot spline hazard model and 1-knot spline odds model ranked second and third, respectively.

Table 49: AIC/BIC for durvalumab

	Durvalumab			
Model	**AIC**	**AIC rank**	**BIC**	**BIC rank**
Exponential	1199.70	15	1203.30	11
Weibull	1196.60	14	1203.70	12
Gompertz	1201.60	16	1208.80	16
Log-logistic	1189.60	12	1196.70	6
Log-normal	1184.20	5	1191.30	1
Gen gamma	1184.20	5	1195.00	5

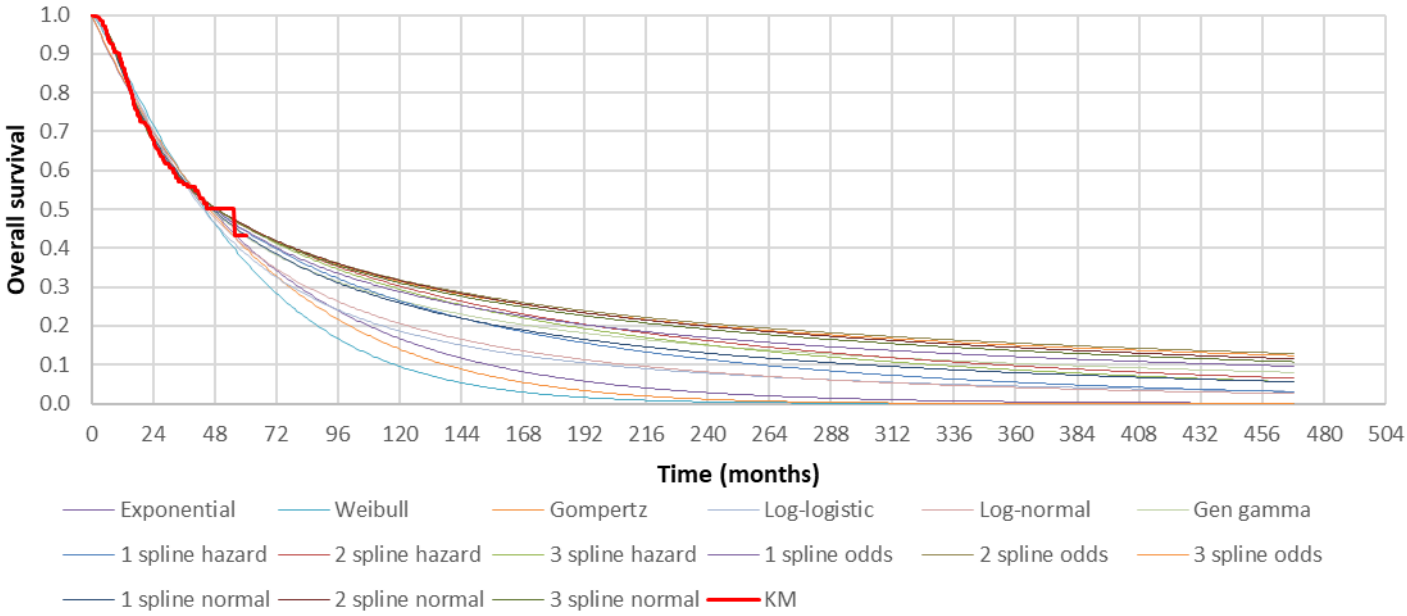
	Durvalumab			
Gamma	1194.50	13	1201.60	10
1-knot spline hazard	1182.80	1	1193.50	2
2-knot spline hazard	1184.30	7	1198.60	8
3-knot spline hazard	1186.20	10	1204.00	14
1-knot spline odds	1182.90	2	1193.60	3
2-knot spline odds	1184.40	8	1198.70	9
3-knot spline odds	1186.30	11	1204.20	15
1-knot spline normal	1183.90	3	1194.60	4
2-knot spline normal	1184.10	4	1198.40	7
3-knot spline normal	1186.10	9	1203.90	13

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian information criterion

Visual fit to KM plot

The OS extrapolation curves for each distribution are plotted together with the KM durvalumab data from the ADRIATIC trial and presented in Figure 29.

Figure 29: OS extrapolations – Durvalumab



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

The generalised gamma, log-normal, log-logistic, and all spline models each provided a reasonable fit to the observed KM data for the durvalumab arm. However, the log-normal and log-logistic distributions provided a more pessimistic view of the tail of the OS curves compared with the generalised gamma distribution. As presented in Figure 29, the generalised gamma distribution appeared to better capture the decrease in hazards from 24 months onwards, compared with the log-normal and log-logistic distributions.

Other standard parametric distributions did not fit the observed survival data and hazards as well, and tended to provide even more pessimistic predictions of the OS curve tails (with implications for PFS-OS curve crossing, as discussed in Section B.3.4.1.3.3). The spline models produced OS extrapolations that were closer to the generalised gamma distribution (as opposed to the log-normal and log-logistic distributions).

Assessment of hazard function

The raw hazard plots for both the durvalumab and “watch and wait” arms are presented in Figure 30, illustrating the changes in hazards over the course of the trial. In the durvalumab arm, the hazards appear to [redacted]. Although the number of patients at risk was low at later timepoints, the trend exhibited a [redacted]. This pattern may suggest that a subset of patients achieved long-term survival or were potentially cured. Figure 30 also shows that there is a [redacted]. The smoothed hazards plots, presented in Figure 31, further depict these changes over time (i.e., [redacted]).

Figure 30: OS hazard plot (raw) – Durvalumab and “watch and wait”

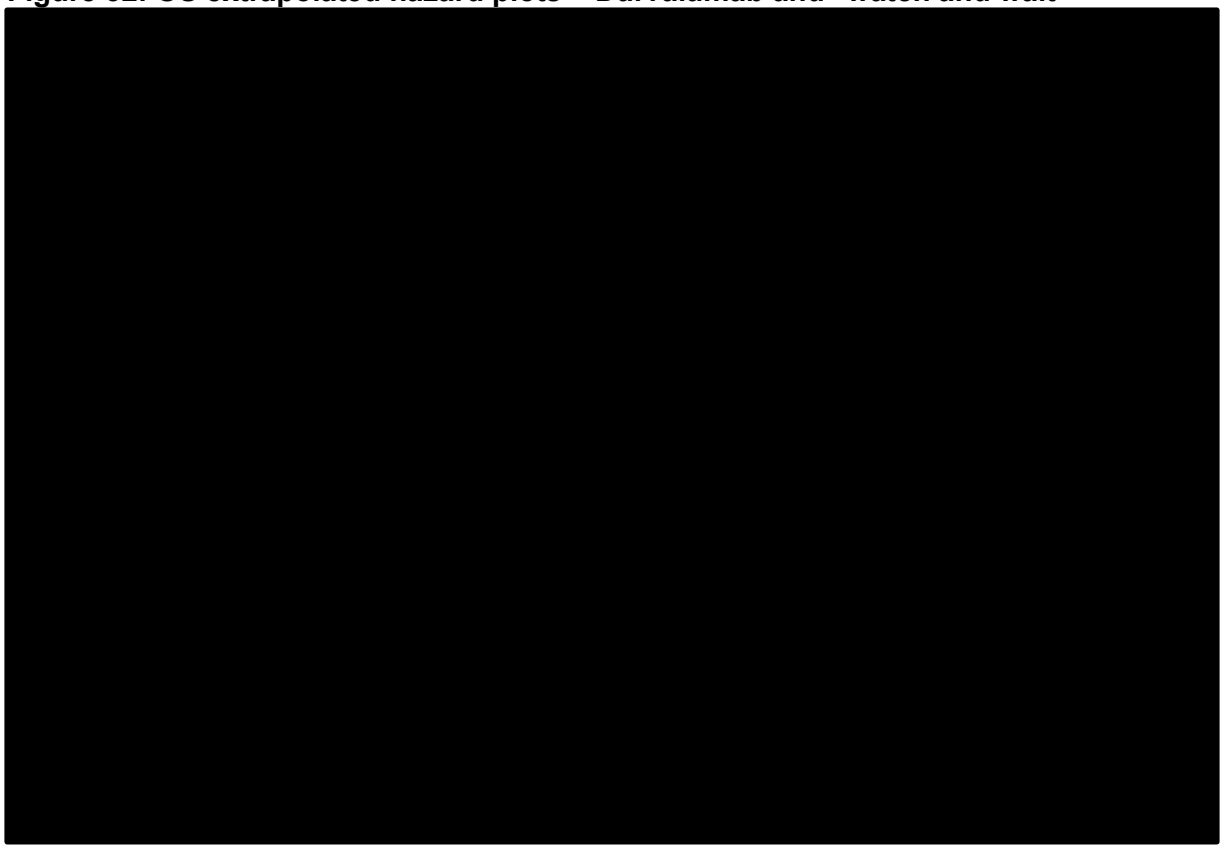
Abbreviations: Durva, durvalumab; OS, overall survival.

Figure 31: OS smoothed hazard plot (kernel method) – Durvalumab and "watch and wait"

Abbreviations: Durva, durvalumab; OS, overall survival.

The OS hazard plots for all parametric curves were extrapolated over a 10-year time horizon to confirm clinical plausibility of the base case curve in the long-term. The OS hazard plots for the standard parametric curves in both the durvalumab and "watch and wait" arm are presented in Figure 32. The exponential, Weibull, Gompertz, and gamma distributions failed to capture the general trend of the trial hazard, particularly the , and were therefore not considered appropriate. The generalised gamma distribution appears to best capture the trial hazards, which initially increase and then decrease at a slower rate of decline. The log-normal and log-logistic distributions do not appear to capture the magnitude of the decrease in the trial hazards and are therefore not considered appropriate for the base case analyses.

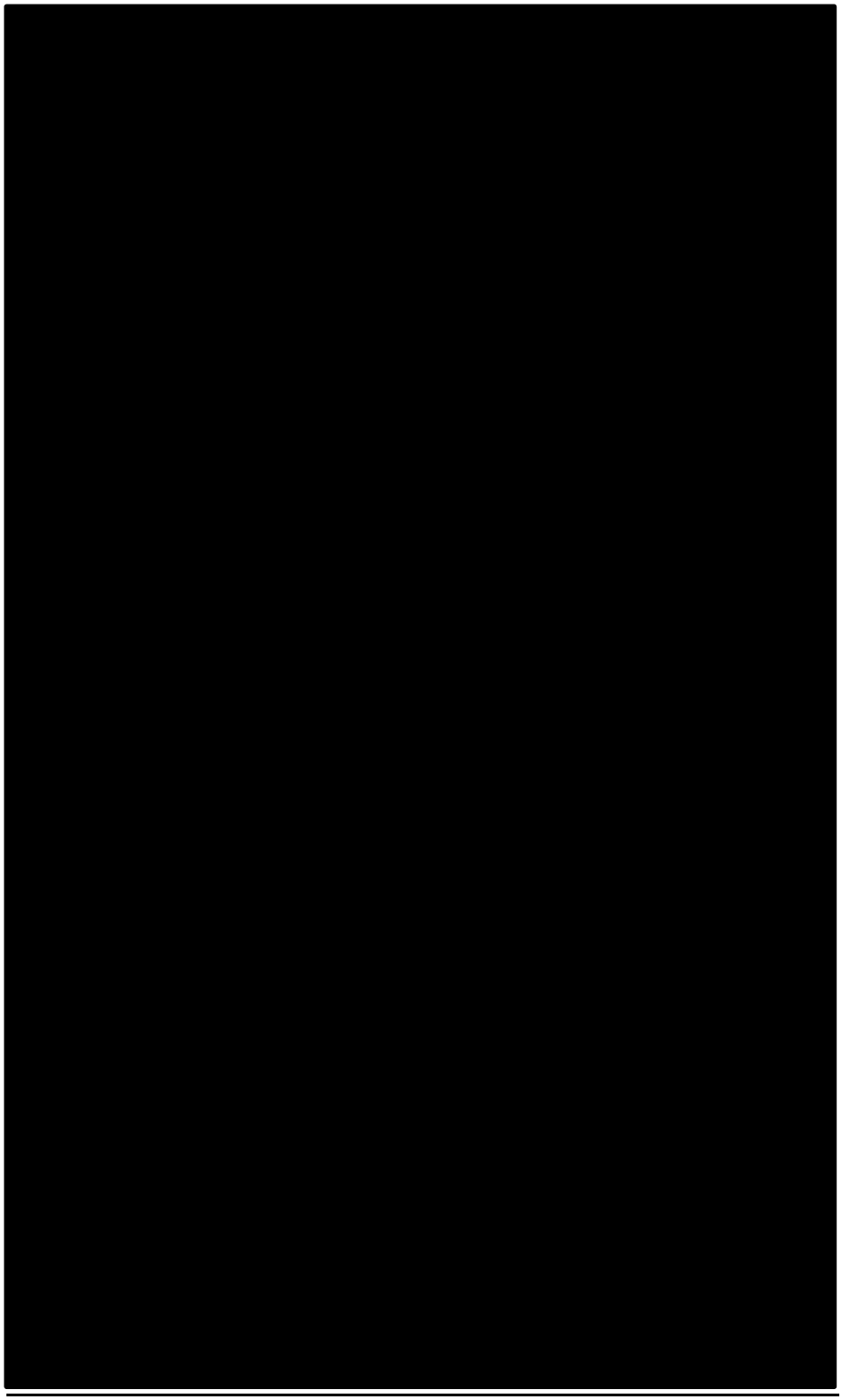
Figure 32: OS extrapolated hazard plots – Durvalumab and "watch and wait"



Abbreviations: Durva, durvalumab; ITT, intention-to-treat; OS, overall survival

The OS hazard plots for the spline models which have been extrapolated over a 10-year time horizon are presented in Figure 33. Unlike most of the standard parametric models, all spline models successfully captured the general hazard trend in the durvalumab arm, specifically the [redacted]. The 1-knot model on all scales appeared to overestimate the decline in trial hazard compared with their 2-knot and 3-knot model counterparts. Models with more than 1-knot on the odd scale increased the [redacted] in the trial hazard seen at approximately [redacted].

Figure 33: OS extrapolated hazard plots for spline models – Durvalumab and "watch and wait"



Abbreviations: Durva, durvalumab; OS, overall survival.

External validation

Clinical expert opinion was sought during an advisory board on 11th October 2024 to ensure that the best-fitting model provides a clinically plausible extrapolation beyond the trial data.[17] All seven standard parametric models with OS predictions from 1 to 15 years were presented to the clinical experts, as shown in Table 50.

Table 50: Estimated 10- and 15-year OS for durvalumab standard parametric distributions

	10-year OS rate, %	15-year OS rate, %
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gen gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviaitons: KM, Kaplan-Meier; OS, overall survival.

Based on the 5-year OS and PFS KM data in the durvalumab arm (50.32%), clinicians indicated that they would expect between 27% and 33% of patients to be alive at 120 months and 19% to 27% to be alive at 180 months. The generalised gamma and gamma distributions aligned best with the OS predictions, as the other standard parametric models tended to underestimate OS in the durvalumab arm.

The OS hazard function observed in the durvalumab arm of the ADRIATIC trial exhibited a changing trend over time that standard parametric models could not adequately capture (see Figure 30 and Figure 31). Therefore, following guidance in NICE DSU TSD 14 and 21,[62, 63] flexible spline-based models (with up to 3 knots) were utilised. These models were presented to clinicians in follow-up questions post-advisory board to gather their opinions on the OS predictions from 12 to 180 months. The 10- and 15-year OS rates predicted by each spline model in the durvalumab arm are presented in Table 51.

Table 51: Estimated 10- and 15-year OS for durvalumab spline models

	10-year OS rate, %	15-year OS rate, %
1-knot spline hazard	[redacted]	[redacted]
2-knot spline hazard	[redacted]	[redacted]
3-knot spline hazard	[redacted]	[redacted]

	10-year OS rate, %	15-year OS rate, %
1-knot spline odds	[redacted]	[redacted]
2-knot spline odds	[redacted]	[redacted]
3-knot spline odds	[redacted]	[redacted]
1-knot spline normal	[redacted]	[redacted]
2-knot spline normal	[redacted]	[redacted]
3-knot spline normal	[redacted]	[redacted]

Abbreviaitons: KM, Kaplan-Meier; OS, overall survival.

All spline models, apart from 1-knot spline normal and 1-knot spline hazard, predicted 120-month and 180-month OS rates that aligned with those expected by clinicians in the main advisory board.

Although there was no clear consensus among clinicians in the post-advisory board responses regarding the spline models, the majority deemed those with 2 or 3 knots to be the most clinically plausible for the durvalumab arm. Therefore, the 2-knot spline model, which demonstrated a better statistical fit based on AIC and BIC statistics (specifically, the 2-knot spline normal), was deemed the most appropriate for the base case.

In addition, one clinician noted that, where the hazard function changes over time (Figure 31), the knots in spline models allowed for greater flexibility, capturing how hazard risks evolve at various time points and better reflecting the disease's natural progression in response to treatment. Compared with standard parametric models, spline models offer a more adaptable approach to representing underlying survival patterns that might not be fully captured by standard models. Therefore, spline models were preferred for the base case analyses.

B.3.4.1.3.2 Watch and wait overall survival

Statistical goodness of fit

The goodness of fit statistics based on AIC and BIC for the survival models for the “watch and wait” arm are presented in Table 52. The 1-knot spline hazard model and the 1-knot spline odds model were considered the best fit according to the AIC statistic, followed by 1-knot spline normal and generalised gamma distribution. The log-normal distribution was considered the best fit, according to the BIC statistic, and the 1-knot spline hazard and 1-knot spline odds were ranked joint second.

Table 52: AIC/BIC for "watch and wait"

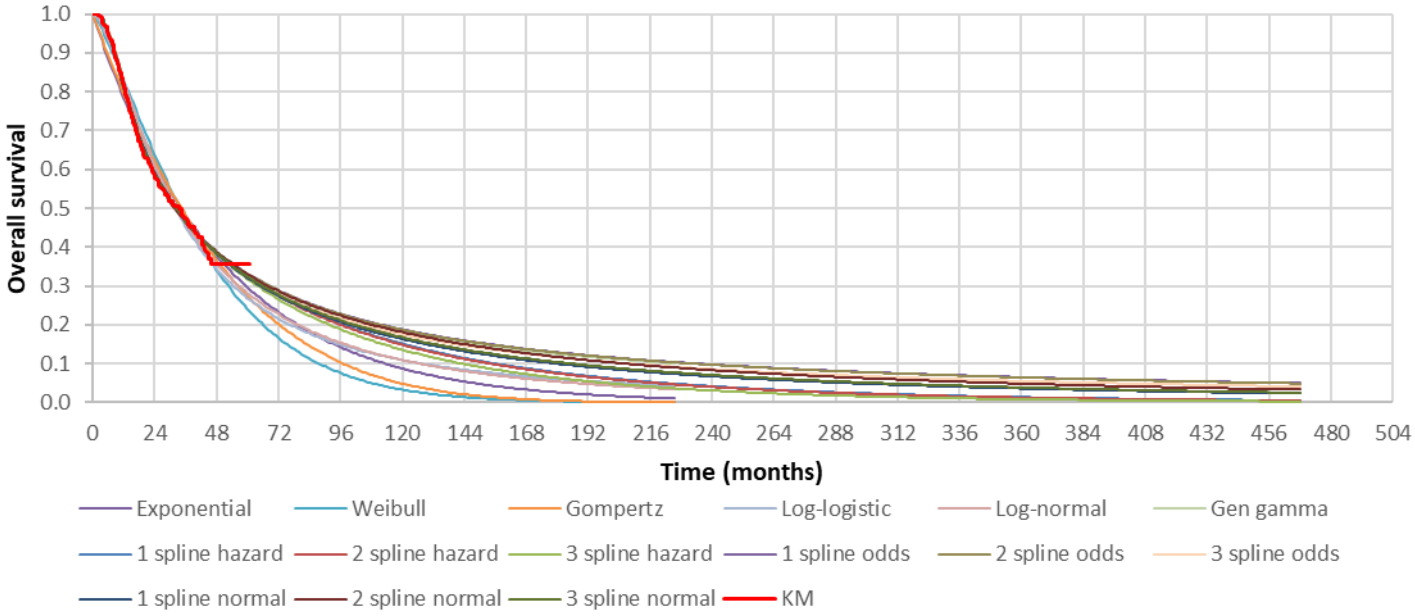
	"Watch and wait"			
Model	**AIC**	**AIC rank**	**BIC**	**BIC rank**
Exponential	1432.00	15	1435.60	15
Weibull	1424.60	14	1431.80	14
Gompertz	1433.40	16	1440.60	16
Log-logistic	1412.30	12	1419.50	9
Log-normal	1405.10	9	1412.30	1
Gen gamma	1402.20	4	1413.00	5
Gamma	1420.60	13	1427.80	13
1-knot spline hazard	1401.80	1	1412.50	2
2-knot spline hazard	1403.90	6	1418.20	7
3-knot spline hazard	1405.50	11	1423.40	11
1-knot spline odds	1401.80	1	1412.50	2
2-knot spline odds	1403.90	6	1418.20	7
3-knot spline odds	1405.40	10	1423.40	11
1-knot spline normal	1401.90	3	1412.70	4
2-knot spline normal	1403.50	5	1417.80	6
3-knot spline normal	1405.00	8	1422.90	10

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian information criterion.

Visual fit to KM plot

The OS extrapolation curves for each distribution are plotted together with the KM placebo data from the ADRIATIC trial and are presented in Figure 34.

Figure 34: OS extrapolations – Watch and wait



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

As observed in the durvalumab arm, the generalised gamma, log-normal, log-logistic and all spline models provided a reasonable fit to the observed data for “watch and wait” arm (Figure 34). The log-normal and log-logistic distributions provided a more pessimistic view of the tail of the OS curves compared with the generalised gamma distribution. The other parametric distributions had poorer fit to the observed survival data, providing a more pessimistic views of the OS curve tails.

The spline models appeared to fit the observed OS data reasonably well and provided a more pessimistic view of long-term OS compared with the generalised gamma, log-normal, and log-logistic models.

Assessment of hazard function

The change in the OS trial hazard for the “watch and wait” arm is presented in Figure 30 and Figure 31. The trial hazards in the “watch and wait” arm, displaying an [redacted], are presented in Figure 30. Thereafter, the trial hazard

[redacted]. The smoothed hazards, presented in Figure 31, shows the trial hazards [redacted].

[redacted].

The hazard plots for OS standard parametric curves in the “watch and wait” arm are presented in Figure 32. The exponential, Weibull, Gompertz, and gamma distributions were unable to capture the turning point in the trial hazard, and therefore were not considered appropriate. The other standard parametric distributions were able to capture the overall change in the trial hazard; however, the log-normal and log-logistic distributions appeared to overestimate more than the generalised gamma distribution. The generalised gamma was therefore considered more appropriate based on the extrapolated hazard plots.

The 10-year extrapolated hazard plots for the spline models in the “watch and wait” arm are shown in Figure 33. All the spline models capture the turning point whereby the trial hazards begin to decline after 12 months. The extrapolations for the spline models on the hazard scale and odds scale were similar. However, on all scales, applying 3-knot models overestimated the initial increase in the trial hazard; 1- and 2-knot models were therefore preferred for the base case.

External validation

As stated in Section B.3.4.1.2.2, 5-year survival data reported in the CONVERT and CALGB 3061 trials were used to validate the clinical plausibility of OS extrapolations in the “watch and wait” arm. The predicted OS landmarks associated with each parametric model and the KM OS data, as well as the 5-year OS reported in the CONVERT and CALGB 3061 trials, are presented in Table 53. As described in Section B.3.4.1.2.2, the results from the CONVERT and CALGB 3061 trials in Table 53 are presented as ranges to reflect both radiotherapy arms in each trial.

Table 53: Long-term OS (5-year) for Placebo extrapolation curves and published literature

Trial	OS rate, 'Watch and wait' (Placebo), %
CONVERT	32–34
CALGB 3061	29–32
ADRIATIC trial	
KM data from ADRIATIC	35.70
Exponential	[redacted]
Weibull	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Gen gamma	[redacted]
Gamma	[redacted]
1-knot spline hazard	[redacted]
2-knot spline hazard	[redacted]
3-knot spline hazard	[redacted]
1-knot spline odds	[redacted]
2-knot spline odds	[redacted]
3-knot spline odds	[redacted]
1-knot spline normal	[redacted]
2-knot spline normal	[redacted]
3-knot spline normal	[redacted]

Abbreviations: KM, kaplan-meier; OS, overall survival.

The CONVERT trial reported a 5-year OS of 32–34% and CALGB 3061 reported a 5-year OS of 29–32%.[15, 16] Compared with published outcomes from the CONVERT and CALGB 3061 trials, the generalised gamma and all spline models predicted 5-year OS for the ADRIATIC placebo arm that were consistent with the combined range of 5-year OS reported from CONVERT and CALGB 3061 (29–34%). The log-normal and log-logistic, however, tended to underestimate 5-year OS for the ADRIATIC placebo arm when compared with the CONVERT and CALGB 3061 trials.

Clinical expert opinion was also sought to determine which distribution provided the most clinically plausible extrapolation beyond the trial data (presented in Table 54).

Table 54: Estimated 10- and 15-year OS for placebo (“watch & wait”) standard parametric distributions

	10-year OS rate, %	15-year OS rate, %
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gen gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviaitons: KM, Kaplan-Meier; OS, overall survival.

Based on the observed 5-year OS and PFS data from the ADRIATIC trial, clinical experts concluded that, among the standard parametric distributions, the generalised gamma distribution provided the most reasonable 10- and 15-year OS predictions, at [redacted] and [redacted], respectively.[17]

Due to the change in hazard function observed in the 'watch and wait' arm of the ADRIATIC trial, and in accordance with NICE DSU TSD 14 and 21,[62, 63] flexible spline-based models (with up to 3 knots) were presented to clinicians in follow-up questions post-advisory board to gather their opinions on OS predictions from 12 to 180 months.

Table 55: Estimated 10- and 15-year OS for placebo (“watch & wait”) spline models

	10-year OS rate, %	15-year OS rate, %
1-knot spline hazard	[redacted]	[redacted]
2-knot spline hazard	[redacted]	[redacted]
3-knot spline hazard	[redacted]	[redacted]
1-knot spline odds	[redacted]	[redacted]
2-knot spline odds	[redacted]	[redacted]
3-knot spline odds	[redacted]	[redacted]
1-knot spline normal	[redacted]	[redacted]
2-knot spline normal	[redacted]	[redacted]
3-knot spline normal	[redacted]	[redacted]

Abbreviaitons: KM, Kaplan-Meier; OS, overall survival.

In the follow-up responses, there was a lack of consensus among clinical experts regarding which spline model provided the best long-term OS estimate in the “watch

and wait arm".[17] However, the majority selected splines with 2 or 3 knots, leading to a preference for these models for the base case. The 2-knot spline normal model was selected as the most suitable choice for the "watch and wait" arm in the base case analyses. This decision was based on its OS predictions, which closely matched the clinicians' expectations for 10-year and 15-year overall survival rates ([redacted] and [redacted], respectively) as discussed in the main advisory board.

As stated in the Section B.3.4.1.3.1, spline models provide greater flexibility compared to standard parametric models, allowing them to effectively capture the evolution of hazard risks at different time points throughout the ADRIATIC trial. This approach received approval from clinicians, leading to the preference for spline models in the base case analyses.

B.3.4.1.3.3 Summary of choice of overall survival distributions for base case and scenario analyses

Section B.3.4.1.3 highlighted non-proportionality in the log cumulative hazard plots, showing delayed separation of OS curves in the ADRIATIC trial. As a result, independent models were used to extrapolate OS. The hazard plots in Figure 30 and Figure 31 show changes in hazard rates over time, supporting the use of flexible spline models, which better represent evolving risk dynamics. A clinical expert noted that "the knots allow flexibility to capture the natural pattern of the disease."

In the durvalumab arm, although 1-knot spline models ranked high statistically (see Table 49), they overestimated hazard decline compared to 2- and 3-knot models (Figure 32). Expert feedback favoured the 2- or 3-knot models, and the 2-knot spline normal model was chosen for its strongest statistical fit.

For the "watch and wait" arm, 1-knot spline models also performed well statistically (see Table 52) but both the 1- and 2-knot models were considered more appropriate than the 3-knot models which overestimated the [redacted]. 5-year OS predictions from spline models aligned with data from CONVERT and CALGB 3061 (29–34%), and clinical experts validated 10- and 15-year OS predictions ([redacted] and [redacted] respectively). The 2-knot spline normal model was deemed the most appropriate for the base case as it best aligned with these clinician expectations.

For these reasons, the 2-knot spline normal model was chosen for both arms in the base case with full detail provided in Sections B.3.4.1.3.1 and B.3.4.1.3.2. In addition, a scenario analysis was conducted using the 2-knot spline odds model for OS extrapolation for both arms to explore another clinically plausible alternative. The results of this scenario are presented in Section B.3.12.3.

B.3.4.2 Cure assumption

The OS and PFS curves for both treatment arms were adjusted to reflect the cure assumption, with patients considered to be functionally cured. During an advisory board, clinical experts explained that patients who remain disease-free for 3–5 years following CRT treatment are generally considered functionally cured. Plateauing of the PFS Kaplan-Meier curves in both the treatment and placebo arms suggests that the outcomes the ADRIATIC study are aligned with the opinion of UK clinicians. A proportion of patients alive at 5 years were therefore assumed to be cured, which was adopted as the cure timepoint in the base case.[17] Since 5 years represents the upper value of the range provided by clinicians, this approach was considered conservative.

Clinical experts estimated that 90% of patients who are progression-free at 5 years would have a low risk of recurrence and would achieve functional cure.[17] As a result, the model base case assumed a cure fraction of 90% in both the durvalumab and “watch and wait” arms.

After the cure timepoint, cured patients were modelled to follow general population survival rates, while the remaining patients continued along the extrapolated PFS trajectory. In the model, cured patients no longer incurred treatment or health state costs, however they did incur end of life (EOL) costs. Additionally, cured patients were assumed to have the same utility as the age- and sex-matched general population. This approach in consistent with previous NICE appraisals in lung cancer.[5, 65]

A scenario with a 3-year cure timepoint was considered in Section B.3.12.3 to reflect the lower range of the clinical experts' cure timepoint assumption. A scenario analysis, which assumed a cure fraction of 80% in both treatment arms was used to assess parameter uncertainty in the model, is also provided in Section B.3.12.3.

B.3.4.3 General population mortality

Background population mortality was used to cap the OS and PFS of patients in each treatment arm, such that the hazard of death (or of progression/death, in the case of PFS) in each cycle would not be lower than the hazard of death of the general population (age- and gender-matched). Background mortality adjustments were made using general population mortality data from the lifetables published by the Office of National Statistics for England and Wales,[58] as per NICE recommendations.[59]

B.3.4.4 Time to discontinuation

The model used the time to treatment discontinuation (TTD) curves from the ADRIATIC trial for estimating the proportion of patients receiving durvalumab in each cycle.

At the time of the ADRIATIC interim analysis, all patients had had the opportunity to receive the maximum 24 months of treatment, and no patients were ongoing with study treatment at the time of the data cut-off date. Extrapolation of TTD was therefore not conducted due to the availability of fully mature TTD data from ADRIATIC. Instead, the observed TTD data for the durvalumab arm was used directly in the model to estimate the proportion of patients in each model cycle who were still on treatment with durvalumab and who therefore incurred durvalumab treatment-related costs (drug acquisition and administration). The TTD data for durvalumab is presented in Figure 35. While there are TTD data for the placebo arm of ADRIATIC, these are not considered relevant as there were no treatment-related costs for the “watch-and-wait” arm.

Figure 35: TTD Kaplan-Meier curve for durvalumab

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

B.3.4.5 Adverse events

Adverse events (AEs) were included in the model to reflect the healthcare costs and loss of health-related quality of life (HRQoL) due to toxicities associated with AEs. The ADRIATIC trial was used as the source for the AEs to include in the model and the AE event rates. The AEs included in the model were those that were Grade 3 to 4 (any cause) that occurred in ≥2% patients in either treatment arm. Similar selection criteria have been used in previous economic evaluations, including TA638[45] and TA184,[39] and other durvalumab indications (TA798).[5]

Pneumonia was the only Grade 3 or 4 AE which occurred at a frequency ≥2% in either arm of the ADRIATIC trial. The AEs included in the model are presented in Table 56.

Table 56: Treatment-related adverse events

Adverse event	Durvalumab (n=262), n (%)	Watch and wait (n=265), n (%)
Pneumonia	7 (2.7%)	9 (3.4%)

B.3.4.6 Base case efficacy summary

A summary of the main clinical parameters and variables applied in the base case analysis is presented in Table 57.

Table 57: Summary of clinical model parameters and variables used in the economic model base case

Parameter	Value	Rationale	Section
Baseline characteristics	As presented in Table 38 informed by the ADRIATIC trial	Aligned to the observed efficacy in ADRIATIC and considered generalisable to UK practice	
PFS models	Independent models • Durvalumab: 1-knot spline normal • "Watch and wait": 1-knot spline normal	The selection of OS and PFS curves was based on an assessment of PHA, statistical and visual fit to observed data, hazard function evaluation, and validation of the clinical plausibility of long-term projections	B.3.4.1.2
OS models	Independent models • Durvalumab: 2-knot spline normal • "Watch and wait": 2-knot spline normal		B.3.4.1.3
TTD models	• Durvalumab: TTD KM data from the ADRIATIC trial • "Watch and wait": No TTD assumed	• Extrapolation of TTD data not required due to the availability of fully mature TTD data from the ADRIATIC trial. • TTD not required for the "watch and wait" arm as no treatment related costs were included in this arm	B.3.4.4
Adverse events	Grade 3 to 4 AEs (any cause) that occurred in ≥2% of patients in either treatment arm	Considered to reflect the main AEs experienced by patients and those that could impact the economic analysis	B.3.4.5

Abbreviations: AE, adverse events; KM, Kaplan-Meier; PFS, progression-free survival; PHA, proportional hazards assumption; OS, overall survival; TTD, time to treatment discontinuation; UK, United Kingdom.

B.3.5 Measurement and valuation of health effects

B.3.5.1 Health-related quality of life data from clinical trials

In ADRIATIC, HRQoL outcomes were measured using the following questionnaires:

- European Organisation for Research and Treatment of Cancer quality of life (EORTC QLQ)-C30 and EORTC QLQ-LC13
- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
- Patient Global Impressions scale (PGIS)

- European Quality of Life 5-dimension-5 level (EQ-5D-5L)

EQ-5D-5L was collected as part of an exploratory analysis to compare health-state utility for durvalumab monotherapy versus placebo treatment. EQ-5D-5L data was initially collected at Week 0 (i.e. first study treatment visit) and then every 8 weeks relative to a patient's randomisation until second disease progression (PFS2) or death.

Patients from the ITT population were included in the analysis. In total, 4,528 EQ-5D-5L observations were available from 503 patients. Of these, 3,545 observations were recorded pre-progression, 747 were recorded post-progression and 236 were recorded after censoring for progression.

After mapping the EQ-5D-5L responses to EQ-5D-3L (see Section B.3.5.2), mixed models for repeated measures (MMRM) were used to estimate the statistical relationship between utilities and health states (i.e., defined by progression or treatment status). This method accounts for the correlation in utility score across repeated measurements for each subject and provides valid results where utility data are missing at random. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period that had an unknown/missing health status were omitted from the analysis.

The correlation of repeated utility measurements within subjects over time was captured via the specification of covariance structures for the MMRM. Univariate and multivariate analyses were conducted by fitting models which include the following covariates:

- Treatment (durvalumab, placebo)
- Progression status (progression-free, post-progression)
- Treatment * Progression status

The MMRM considered in the analysis are presented in Table 58.

Table 58: Summary of clinical model parameters and variables used in the economic model base case

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	$Utility = \beta_0 + \beta_1 \cdot Treatment + \beta_2 \cdot Progression\ Status + \beta_3 \cdot \text{Treatment} * Progression\ Status$

Abbreviations: MMRM, mixed models for repeated measures

The 'marginal' mean utility score by health and/or treatment status (i.e., treatment and/or progression state) was calculated from each MMRM. The marginal ('least square') mean provided a model-based estimate of utility score that was averaged over observations with adjustment for repeated measures. The coefficients and standard errors associated with each MMRM are presented in Table 59. The relative statistical fit of each model was assessed in terms of the AIC and BIC score (Table 59). The models with the lowest AIC and BIC were judged to best fit the trial data.

Table 59: Mixed models for repeated measures point estimates

Parameter	Equation 1 [standard error]	Equation 2 [standard error]	Equation 3 [standard error]	Equation 4 [standard error]
Intercept	[redacted] p< 0.001)	[redacted] (p< 0.001)	[redacted] (p< 0.001)	[redacted] (p <0.001)
Treatment (Durvalumab)	[redacted] (p= 0.158)	-	[redacted] (p= 0.160)	[redacted] (p= 0.143)
Progression status (Post-progression)	-	[redacted] (p< 0.001)	[redacted] (p< 0.001)	[redacted] (p= 0.007)
Treatment * progression status (Durvalumab: post-progression)	-	-	-	[redacted] (p= 0.782)
AIC score	-5866.2	-5881.2	-5877.5	-5871.2
BIC score	-5731.4	-5746.4	-5742.7	-5736.4

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian information criterion.

The model including progression status only (Equation 2) was associated with the lowest AIC and BIC scores. Furthermore, the inclusion of treatment status (either as the only model covariate or with progression status) did not have a significant impact

(p>0.05) on utility estimates. The utility values included in the model were therefore based on progression status alone, with the same utility values used for the durvalumab and placebo arms. The equations below demonstrate how marginal mean utility values for the PFS and PD health state were calculated:

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

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

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

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

The impact of AEs on utility (which is treatment-specific) is modelled separately through AE disutilities (Section B.3.5.4).

B.3.5.2 Mapping

The EQ-5D-5L responses collected in ADRIATIC were mapped to EQ-5D-3L using the mapping function developed by the NICE DSU and in line with the reference case analysis recommended in the NICE health technology evaluations manual.[59, 66, 67]

A tabulated summary of the EQ-5D-5L mapped to EQ-5D-3L utility values used in the model is presented in Table 60.

Table 60: Health utility values

Health state	Number of observations	Mean (95% CI)
PF	3,545	[redacted]
PD	747	[redacted]

Abbreviations: CI, confidence interval; PD, progressed disease; PF, progression-free

B.3.5.3 Health-related quality of life studies

A SLR was conducted to identify relevant studies reporting HRQoL or utility data for patients with LS-SCLC. All database searches were conducted between 7th May and 17th June 2024. A total of 22 studies were identified which reported humanistic burden (HRQoL or HSUV). Only three studies reported EQ-5D data; however, none of the studies were considered appropriate for the economic analysis.

Table 61: Health utility values

Author (year)	Country	Population (n)	Utility value (95% CI)	Reason for exclusion
Ganti et al (2022)[68]	US	Patients with LS-SCLC (417)	• QD arm: −0.04 • BID arm: 0.03	• US patient population • Mean worsening reported rather than HSUV
Kuehne et al (2022)[30]	Canada	Historic diagnosis of SCLC (111, 40 with LS-SCLC diagnosis)	• Stable: 0.775 (0.74–0.81) • Progressing: 0.674 (0.61–0.74)	• Canadian patient population • Majority of patients did not have LS-SCLC
Yang et al (2019)[69]	Taiwan	Patients with lung cancer	• Age <65 years: 0.79 (0.06) • Age ≥65 years: 0.78 (0.09)	• Taiwan patient population • Not specific to LS-SCLC population • Only utility values by age reported for LS-SCLC

Abbreviations: BID, twice daily; HSUV, health state utility value; LS-SCLC, limited-stage small-cell lung cancer; QD, once daily; US, United States.

B.3.5.4 Adverse reactions

AE-related QALY decrements, defined as the disutility adjusted for the duration of the AE, were applied as a one off-decrement in the first model cycle, based on the frequency reported in Section B.3.4.1.3.

Pneumonia was assumed to last for 28 days (1 model cycle). This assumption is consistent with NHS information on usual time taken to recover from pneumonia (2–4 weeks).[70] The disutility associated with pneumonia was sourced from Mehra et al. 2021,[71] as presented in Table 62, and was also used for pneumonia in TA798.[5]

Table 62: Disutility per adverse event

AE	Disutility	Source	Duration (days)	Source
Pneumonia	-0.0735	Mehra et al. 2021[71]	28	Assumption

Abbreviations: AE, adverse event.

Section B.3.12.3 considers a scenario which excludes disutility associated with pneumonia.

B.3.5.5 Health-related quality of life data used in the cost-effectiveness analysis

The base case health state utility values were derived from ADRIATIC. This was considered the most robust and applicable source of utility data for this population as data were directly collected from patients with LS-SCLC who have not progressed following CRT. The values measure the health states using EQ-5D-5L mapped to EQ-5D-3L which is the preferred method outlined in the NICE reference case.

As per the NICE reference case,[59] age-based utility multipliers were applied in the base case. Age-specific utilities were extracted from UK Utility Norms (2022), based on data from the 2014 wave of the Health Survey for England, the most recent wave including EQ-5D-3L.[72] If the utilities associated with each health state were greater than the general population utility, the general population utility was applied. Section B.3.12.3 presents a scenario analysis which does not consider age-adjusted utilities.

The HSUVs used in the model base case are presented in Table 63.

Table 63: Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)	95% CI	Reference in submission	Justification
PF	[redacted]	[redacted]	B.3.5.2	Based on MMRM using data derived from ADRIATIC trial
PD	[redacted]	[redacted]		

Abbreviations: CI, confidence interval; MMRM, mixed models for repeated measures; PD, progressed disease; PF, progression-free.

The utility value for PFS was derived from HRQoL data collected in the ADRIATIC trial and was considered to capture the HRQoL of patients in this early-stage disease setting who have a good performance status at baseline. However, it is acknowledged that the utility values derived from the trial data may be relatively high compared to clinical practice. Therefore, several scenario analyses were conducted in Section B.3.12.3, varying the PFS and PD health state utility values.

To assess the impact of the PF HSUV, a scenario analysis was conducted assuming the PF utility value to be equal to the age- and gender-matched utility value of the UK population. In this scenario, the PD utility is based on difference between the base case PF and PD ([redacted]).

Alternative utility values for PD were also explored in scenario analyses based on published literature on the impact of progression on utility in SCLC. One scenario used EQ-5D data from the durvalumab CASPIAN indication (where PF in first-line ES-SCLC is assumed to represent a proxy for the PD health state for LS-SCLC).[73] Another scenario analysis assumed the PD health state utility was based on the difference between 'Stable' and 'Progressing' health states reported in Kuehne et al. 2022 (-0.101).[30]

B.3.6 Cost and healthcare resource use identification, measurement and valuation

B.3.6.1 Intervention and comparators' costs and resource use

The following costs were included in the model:

- Drug acquisition
- Drug administration
- Monitoring costs associated with disease management by progression state
- Adverse events
- End-of-life care
- Subsequent treatment

Costs inputs for the base case economic analysis were sourced from the most recent NHS reference costs,[74] electronic market information tool (eMIT), and the British National Formulary (BNF).[75] Additional sources, such as published NICE TAs, and other published literature were used to supplement these inputs, where applicable.

B.3.6.1.1 Drug acquisition costs

The list price for durvalumab was obtained from the BNF (£2,446.00).[75] Durvalumab has an approved confidential commercial discount of [redacted], resulting in a net price of [redacted] per 500 mg vial. No treatment-related costs were assumed in the "watch-and-wait" arm. The unit drug costs associated with the durvalumab and "watch and wait" arm are presented in Table 64.

Table 64: Unit costs associated with the technology in the economic model

Treatment	Strength (mg) per vial/cap	Vials/caps per pack	Cost per vial/cap (with commercial arrangement)	Source
Durvalumab	500	1	£2,446 ([redacted])	BNF 2024[75]
Watch and wait	0	0	£0	Assumption

Abbreviations: BNF, British National Formulary.

Vial sharing was considered in the base case analysis, as this is what is seen in NHS clinical practice, however Section B.3.12.3 presents a scenario which excludes vial sharing.

B.3.6.1.2 Dosing schedules

The dosing schedule for durvalumab was taken from the ADRIATIC trial where patients received durvalumab 1,500 mg via intravenous (IV) infusion every four weeks.

The model base case assumed the relative dose intensity (RDI) was 100%. This assumption was made as in clinical practice the RDI of durvalumab is generally high, as it is typically maintained through dose delays or therapy discontinuations rather than dose reductions. This approach reflects durvalumab's tolerability profile and clinical management strategies, where maintaining full-dose administration is prioritized to maximise therapeutic efficacy.

The model used the TTD curve as shown in Section B.3.4.4 to estimate the proportion of patients receiving durvalumab in each cycle.

The dosing schedule and cost per treatment cycle based on both the durvalumab list price and its price with commercial arrangement are presented in Table 65.

Table 65: Dosing schedules and cost per treatment cycle (using durvalumab list price)

Drug	Dose per administration	Number of administrations per model cycle	Treatment cycle length	RDI	Administration frequency	Total dose per treatment cycle	Total cost per model cycle (with commercial arrangement)
Durvalumab	1,500 mg	1	28 days	100%	1	1,500 mg	£7,398. ([redacted])

Abbreviations: RDI, relative dose intensity.

B.3.6.1.3 Administration costs

The cost of delivering IV infusion therapy was sourced from the NHS reference costs 2022/23, as presented in Table 66.

Table 66. Drug administration unit costs

Treatment setting	Code	Description	Cost	Source
IV infusion	SB12Z	Deliver Simple Parenteral Chemotherapy at First Attendance - Outpatient	£411.99	NHS reference costs 2022/23[74]

Abbreviations: IV, intravenous; NHS, National Health Service.

B.3.6.2 Health state unit costs and resource use

The model base case assumes that healthcare resource use utilisation and costs are dependent on a patient's health state (PF and PD). This approach aligns with recent submissions to NICE, including TA798[5] and TA638.[45]

In addition to a lack of prior NICE appraisals in LS-SCLC to inform resource use, as described in Section B.3.2, there is also a lack of resource use data in other SCLC appraisals, such as ES-SCLC. For example, it was noted in TA638 that NHS resource use data was unavailable for ES-SCLC due to a lack of prior NICE appraisals in this condition and that no published studies of relevance were found that could help inform healthcare resource use reflecting current NHS practice in SCLC.[45] To address the limited evidence available for LS-SCLC, the model includes both the resources used and their frequencies with appraisals in analogous settings, such as NSCLC, as it is assumed there would be limited difference between SCLC and NSCLC in terms of resources used.

The model adopted the approach used in TA798 which utilised PACIFIC trial data to assess durvalumab versus best supportive care for the treatment of adults with locally advanced, unresectable NSCLC, ≥1% PD-L1 without progression after concurrent platinum-based chemoradiation.[5] While the disease settings are not the same, the treatment regimens are aligned and ESMO recommendations for follow-up are similar between LS-SCLC and early NSCLC. The costs associated with resource use were obtained from NHS reference costs 2022/23. The health state costs associated with the PF and PD health states are presented in Table 67 and Table 68, respectively.

Table 67: Progression-free health state costs

Cost item	Resource use per annum			Unit cost	Costs source
	Durvalumab (on treatment)	Durvalumab (off treatment)	Watch and wait		
Outpatient oncologist visit: Year 1	0.00	5.00	5.00	£233.95	NHS reference costs 2022/23 [370][74]
Outpatient oncologist visit: Year 2	0.00	3.00	3.00	£233.95	
Outpatient oncologist visit: Year 3–5	0.00	2.00	2.00	£233.95	
Chest X-ray: Year 1	0.00	2.00	2.00	£41.23	NHS reference costs 2022/23 [DAPF][74]
Chest X-ray: Year 2	0.00	0.00	0.00	£41.23	
Chest X-ray: Year 3–5	0.00	2.00	2.00	£41.23	
CT scan (chest): Year 1	2.00	3.00	3.00	£172.26	NHS reference costs 2022/23 [RD26Z][74]
CT scan (chest): Year 2	2.00	3.00	3.00	£172.26	
CT scan (chest): Year 3–5	2.00	0.00	0.00	£172.26	
Blood test	24.00	0.00	0.00	£2.75	NHS reference costs 2022/23 [DAPS05][74]

Abbreviations: CT, computed tomography; ECG, electrocardiogram; GP, General practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 68: Progressed disease health state costs

Cost item	Resource use per annum	Unit cost	Source
Outpatient oncologist visit	9.61	£233.95	NHS reference costs 2022/23 [370][74]
Chest X-ray	6.79	£41.23	NHS reference costs 2022/23 [DAPF][74]
CT scan (chest)	0.62	£172.26	NHS reference costs 2022/23 [RD26Z][74]
CT scan (other)	0.36	£172.26	
ECG	1.04	£296.02	NHS reference costs 2022/23 [EY50Z][74]
Community nurse visit	8.70	£82.00	PSSRU 2022/23 [1 hour Band 8a of patient-related work][76]
Clinical nurse specialist	12.00	£82.00	

Cost item	Resource use per annum	Unit cost	Source
GP surgery	12.00	£42.00	PSSRU 2022/23 [10 minutes, including direct care][76]
Blood test	0.00	£2.75	NHS reference costs 2022/23 [DAPS05][74]

Abbreviations: CT, computed tomography; ECG, electrocardiogram; GP, General practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

The resource use and costs associated with the PFS and PD heath states (Table 67 and Table 68, respectively) were presented to clinical experts at an advisory board who agreed which the approach taken in the base case.[17]

As stated in Section B.3.4.2, no costs (except EOL costs) were applied to patients that were assumed to be cured.

B.3.6.2.1 End-of-life costs

End-of-life costs were included in the base case and were applied as a one-off cost at the time of death. End-of-life costs were assumed to be the same for patients across both treatment arms and were sourced from TA638, the most recent NICE HTA in SCLC.[45] In TA638 the end-of-life costs were leveraged from TA484[77] and inflated to 2018 costs (i.e., £3,739).[45, 77] As this approach was well-accepted by the Evidence Review Group, the base case economic analysis utilised the same approach, inflating to 2024 costs using the Consumer Price Inflation (CPI) for health from the Office for National Statistics.[78] This produced an end-of-life cost of £4,703.66.

Patients assumed to be cured were assumed to incur the end-of-life costs when they subsequently died.

B.3.6.3 Adverse reaction unit costs and resource use

Unit costs associated with the management of pneumonia are presented in Table 69 and were sourced from NHS reference costs 2022/23.[74] Adverse event costs were applied as a one-off total cost in the first model cycle. This cost was calculated by multiplying the percentage of patients experiencing the adverse events (outlined in Section B.3.4.1.3) by the cost per event.

Table 69: List of adverse reactions and summary of costs in the economic model

Adverse reactions	Cost per event	Source
Pneumonia	£4,649.55	NHS reference costs 2022/23 [DZ11N – DZ11Q][74]

Abbreviations: NHS, National Health Service.

B.3.6.4 Miscellaneous unit costs and resource use

B.3.6.4.1 Subsequent treatment costs

In the model, patients who experience disease progression may receive subsequent therapy (or best supportive care; "watch and wait"). These subsequent therapies only impact costs in the model, as post-progression survival is already captured within the clinical data from ADRIATIC that is used in the model.

To align with the source of efficacy data, the types and proportions of subsequent therapies were derived from data in ADRIATIC and then validated and adjusted through clinical expert opinions to ensure alignment with real-world clinical practice.

Following an advisory board, the proportion of patients receiving subsequent therapy after progression was presented to clinical experts. These proportions were calculated based on the number of patients receiving any subsequent anticancer therapy (n=[redacted] for the durvalumab arm and n=[redacted] for the "watch and wait" arm) and the total number of progressed patients in each arm (n=126 for the durvalumab arm and n=158 for the "watch and wait" arm). As a result, [redacted]% and [redacted]% of patients in the intervention and "watch and wait" arms, respectively, were assumed to require subsequent treatment.

Subsequent therapies included those received by ≥5% of patients in either arm of the ADRIATIC study. These treatments were single-agent chemotherapy (n=[redacted] for the intervention arm and n=[redacted] for the "watch and wait" arm), platinum-doublet chemotherapy (n=[redacted] for the intervention arm and n=[redacted] for the "watch and wait" arm), and immune-oncology (IO) therapies combined with chemotherapy (n=[redacted] for the intervention arm and n=[redacted] for the "watch and wait" arm).

The proportion of patients receiving each type of subsequent therapy was calculated based on the relative proportions of these treatments, excluding less frequently used options. The individual regimens for these different types of subsequent therapy and

the distribution of patients receiving these regimens (and best supportive care; "watch and wait") in each arm of ADRIATIC are outlined in Table 70.

Table 70: Distribution of patients across subsequent treatments based on ADRIATIC

Treatment	From		Source
	Durvalumab	"Watch and wait"	
BSC ("watch and wait")	[redacted]	[redacted]	Assumption: Not all patients who progress will receive active subsequent therapy. Estimation based on the difference in the ADRIATIC trial between the number of patients with a PFS event = progression and the number of patients receiving subsequent anticancer therapy
Topotecan (oral)	[redacted]	[redacted]	Topotecan was the most common single agent chemotherapy regimen received in ADRIATIC, and is recommended by NICE for patients with relapsed SCLC (NICE TA184) Estimated from ADRIATIC; based on the number of patients receiving 'Cytotoxic Chemotherapy Single Agent' as subsequent anticancer therapy
Etoposide + cisplatin	[redacted]	[redacted]	Estimated from ADRIATIC; based on the number of patients receiving 'Cytotoxic Chemotherapy Platinum Doublet' as subsequent anticancer therapy and % cisplatin vs carboplatin in the CASPIAN trial
Etoposide + carboplatin	[redacted]	[redacted]	Estimated from ADRIATIC; based on the number of patients receiving 'Cytotoxic Chemotherapy Platinum Doublet' as subsequent anticancer therapy and % cisplatin vs carboplatin in the CASPIAN trial
Durvalumab + etoposide + cisplatin	[redacted]	[redacted]	Estimated from ADRIATIC; based on the number of patients receiving 'Durvalumab' under category 'Chemotherapy + Immunotherapy' as subsequent anticancer therapy, % cisplatin vs carboplatin in the CASPIAN trial

Treatment	From		Source
	Durvalumab	"Watch and wait"	
Durvalumab + etoposide + carboplatin	[redacted]	[redacted]	Estimated from ADRIATIC; based on the number of patients receiving 'Durvalumab' under category 'Chemotherapy + Immunotherapy' as subsequent anticancer therapy, % cisplatin vs carboplatin in the CASPIAN trial
Atezolizumab + etoposide + carboplatin	[redacted]	[redacted]	Estimated from ADRIATIC; based on the number of patients receiving 'Atezolizumab' under category 'Chemotherapy + Immunotherapy' as subsequent anticancer therapy

Abbreviations: BSC, Best supportive care; NICE, National Institute of Health and Care Excellence; PFS, progression-free survival; SCLC, small-cell lung cancer; TA, technology appraisal.

In both arms, clinical experts stated they would not treat patients with a durvalumab regimen (durvalumab + etoposide + cisplatin or durvalumab + etoposide + carboplatin) as durvalumab is awaiting approval in patients with ES-SCLC. The proportion of patients with a durvalumab regimen were therefore instead assumed to be treated with atezolizumab + etoposide + carboplatin. This treatment approach was confirmed by the clinicians.

Clinical experts also stated that they provide etoposide + cisplatin to no more than 5% of patients. Therefore, the remaining patients treated with etoposide + cisplatin in both arms were assumed to receive BSC.

The BlueTeq criteria states that patients with SCLC cannot receive anti-PD-1/PD-L1 therapy prior to treatment with atezolizumab.[79] Therefore, it was assumed that patients in the durvalumab arm who received atezolizumab + etoposide + carboplatin should instead receive etoposide + carboplatin.

Additionally, clinical experts disagreed with the proportion of patients receiving topotecan in both arms, noting this was overestimated and did not account for the current shortage of topotecan in the UK. Clinical experts anticipated that no more than 10% of patients would receive topotecan as a subsequent treatment due to this shortage; this assumption was applied in the base case. The remaining patients treated with topotecan in the "watch and wait" arm were therefore assumed to receive atezolizumab + etoposide + carboplatin. As patients in the durvalumab arm

cannot receive atezolizumab, the remaining patients instead received chemotherapy (etoposide + carboplatin).

The distribution of patients receiving subsequent therapy regimens used in the model base case and informed by clinical input is presented in Table 71.

Table 71: Distribution of patients across subsequent treatments based on clinical input

Treatment	From	
	Durvalumab	**"Watch and wait"**
BSC ("watch and wait")	28.5%	22.6%
Topotecan (oral)	10.0%	10.0%
Etoposide + cisplatin	5.0%	5.0%
Etoposide + carboplatin	56.5%	23.9%
Durvalumab + etoposide + cisplatin	0.0%	0.0%
Durvalumab + etoposide + carboplatin	0.0%	0.0%
Atezolizumab + etoposide + carboplatin	0.0%	38.5%

Abbreviations: BSC, Best supportive care; NICE, National Institute of Health and Care Excellence; PFS, progression-free survival.

A scenario analysis which utilises the subsequent treatments and distributions based on ADRIATIC (presented in Table 70) is also presented in Section B.3.12.3.

In each model cycle, subsequent treatment costs were applied as a one-off cost for the proportion of patients who experienced disease progression (i.e. entered the PD health state) in that cycle. This one-off cost was calculated as a weighted average based on the distribution of patients across the different subsequent treatments (Table 70) and the total cost associated with each treatment (Table 72). For the total cost of each treatment, the duration of therapy was based on the median number of doses/infusions reported from the pivotal trials for each treatment. For model simplicity, no-vial sharing was assumed for subsequent lines. The weighted one-off subsequent treatment costs were £4,895.83 and £13,793.50 for the durvalumab and "watch and wait" arms, respectively.

Drug administration costs were also included in the one-off cost for subsequent treatments and are shown in Table 73. No administration cost was applied for the

oral administration of topotecan. Adverse event costs were not included within subsequent treatment costs.

Table 72. Subsequent treatment acquisition costs

Regimen	Treatment	Dose per admin	Total # admin (treatment duration)	Relative dose intensity	Formulation per vial/cap, mg	Vials/caps per pack	Cost per vial/cap	Total cost per model cycle
BSC		0.00	0.00	0%	0	0	£0.00	£0.00
Topotecan (oral)		2.30 mg/m^2	20.00	100%	0.25	10	£7.50[80]	£3,000.00
Etoposide + cisplatin	Etoposide	100.00 mg/m^2	18.00	100%	100	1	£5.07[81]	£630.46
	Cisplatin	75.00 mg/m^2	6.00	100%	100	1	£37.34[81]	
Etoposide + carboplatin	Etoposide	100.00 mg/m^2	18.00	100%	100	1	£5.07[81]	£1,636.58
	Carboplatin	572.00 mg	6.00	100%	150	1	£60.59[82]	
Durvalumab + etoposide + cisplatin	Durvalumab	1500.00 mg	7.00	100%	500	1	[redacted] (when applying the commercial arrangement)	[redacted]
	Etoposide	100.00 mg/m^2	12.00	100%	100	1	£5.07[81]	
	Cisplatin	75.00 mg/m^2	4.00	100%	100	1	£37.34[81]	
Durvalumab + etoposide + carboplatin	Durvalumab	1,500.00 mg	7.00	100%	500	1	[redacted] (when applying the commercial arrangement)	[redacted]
	Etoposide	100.00 mg/m^2	12.00	100%	100	1	£5.07[81]	
	Carboplatin	572.00 mg	4.00	100%	150	1	£60.59[82]	
Atezolizumab + etoposide + carboplatin	Atezolizumab	1,200.00 mg	7.00	100%	1200	1	£3,807.69[82]	£27,744.88
	Etoposide	100.00 mg/m^2	12.00	100%	100	1	£5.07[81]	
	Carboplatin	572.00 mg	4.00	100%	150	1	£60.59[82]	

Abbreviations: BSC, Best supportive care.

Table 73: Subsequent treatment administration cost

Treatment	Unit cost	Cost per regimen†	Total admin cost per treatment cycle	Source
BSC ("watch and wait")	£0.00	£0.00	£0.00	Assumption
Topotecan (oral)		£0.00	£0.00	
Etoposide + cisplatin	£411.99	£823.98	£14,831.64	SB12Z, Deliver Simple Parenteral Chemotherapy at First Attendance - Outpatient NHS reference costs 2022/23 [SB12Z][74]
Etoposide + carboplatin		£823.98	£4,943.88	
Durvalumab + etoposide + cisplatin		£1,235.97	£1,235.97	
Durvalumab + etoposide + carboplatin		£1,235.97	£1,235.97	
Atezolizumab + etoposide + carboplatin		£1,235.97	£1,235.97	

†Cost per regime was calculated as the unit cost multiplied by the number IV treatments per treatment regimen.
Abbreviations: BSC, Best supportive care; NHS, National Health Service.

B.3.7 Severity

Patients with LS-SCLC have a poor prognosis, with a median OS of 25–30 months.[14-16] Despite treatment for LS-SCLC being given with curative intent, there is a high risk of disease relapse, with the majority of patients (~75%) with locally advanced disease experiencing disease recurrence within two years of treatment.[20]

The QALY shortfall calculator, developed by Schneider et al. 2021,[83] was used to generate absolute and proportional QALY shortfall estimates using the reference case HRQoL norms (MHV value set + HSE 2014 ALDVMM model, Hernandez Alava et al). Patient characteristics used in the analysis were consistent with those informing the base-case economic analysis as described in Table 38.

Durvalumab was found to not meet the criteria for a severity weight. Based on the expected total QALYs for the general population and the total QALYs for previously untreated patients with LS-SCLC, the absolute and proportional QALY shortfalls do not result in qualification for a severity weight (Table 74).

Table 74: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
[redacted] (calculated based on the average patient age (62 years†) and percentage female ([redacted]%) used in the model, using the calculator by Scheider et al. 2021[83]	3.88	• Absolute shortfall: 8.08 • Proportional shortfall: 67.55% • QALY weight: x1

Abbreviations: QALY, quality-adjusted life year.
† Please note that the QALY shortfall calculation rounds the patient's age to the nearest whole number (e.g., 61.5 years rounds to 62).

B.3.8 Uncertainty

Uncertainty in the model is explored in Section B.3.12. Uncertainty relating to the model parameters is assessed through probabilistic sensitivity analysis (PSA) in Section B.3.12.1 and deterministic sensitivity analysis (DSA) in Section B.3.12.2. Scenario analyses are also used to analyse the impact of uncertainty on model inputs and assumptions and are discussed in Section B.3.12.3.

B.3.9 Managed access proposal

Not applicable to this submission.

B.3.10 Summary of base-case analysis inputs and assumptions

B.3.10.1 Summary of base-case analysis inputs

A summary of the key variables included in the model are provided in Table 75.

Table 75: Summary of variables applied in the economic model

Variable	Value	Lower, upper bound (distribution)	Reference to section in submission
General setting			
Cycle length	4-week	N/A	B.3.3.3
Time horizon	39 years		
Discount rate	3.5%		
Population			
Starting age (years)	61.50	45.50, 81.32 (lognormal)	B.3.3.1
Body weight (kg)	[redacted]	[redacted] (lognormal)	
Height (cm)	[redacted]	[redacted] (lognormal)	
Proportion female	[redacted]		
Survival distributions			
PFS – durvalumab	1-knot spline normal	Variance-covariance matrices	B.3.4.1.2
PFS – "watch and wait"	1-knot spline normal	Variance-covariance matrices	
OS – durvalumab	2-knot spline normal	Variance-covariance matrices	B.3.4.1.3
OS – "watch and wait"	2-knot spline normal	Variance-covariance matrices	
Cure inputs - durvalumab			
Cure point (months)	60	54, 66 (lognormal)	B.3.4.2
Cure fraction	90%	72%, 100% (beta)	
Cure inputs – "watch and wait"			
Cure point (months)	60	54, 66 (lognormal)	B.3.4.2
Cure fraction	90%	72%, 100% (beta)	
Adverse events – durvalumab			
Pneumonia	2.7%	2.1%, 3.2% (beta)	B.3.4.5
Adverse events – "watch and wait"			
Pneumonia	3.4%	2.7%, 4.1% (beta)	B.3.4.5

Variable	Value	Lower, upper bound (distribution)	Reference to section in submission
Utilities			
PFS health state utility	[redacted]	[redacted] (beta)	B.3.5.5
OS health state utility	[redacted]	[redacted] (beta)	
Pneumonia disutility	-0.0735	-0.0882, -0.0588 (beta)	B.3.5.4
PFS resource use – durvalumab on treatment			
CT scan (chest): Year 1	6.00	4.80, 7.20 (gamma)	B.3.6.2
CT scan (chest): Year 2	6.00	4.80, 7.20 (gamma)	
CT scan (chest): Year 3–5	6.00	4.80, 7.20 (gamma)	
Blood test	24.00	19.20, 28.80 (gamma)	
PFS resource use – durvalumab off treatment and "watch and wait"			
Outpatient oncologist visit: Year 1	5.00	4.00, 6.00 (gamma)	B.3.6.2
Outpatient oncologist visit: Year 2	3.00	2.40, 3.60 (gamma)	
Outpatient oncologist visit: Year 3-5	2.00	1.60, 2.40 (gamma)	
Chest X-ray: Year 1	2.00	1.60, 2.40 (gamma)	
Chest X-ray: Year 2	0.00	0.00, 0.00 (gamma)	
Chest X-ray: Year 3–5	2.00	1.60, 2.40 (gamma)	
CT scan (chest): Year 1	3.00	2.40, 3.60 (gamma)	
CT scan (chest): Year 2	3.00	2.40, 3.60 (gamma)	
CT scan (chest): Year 3–5	0.00	0.00, 0.00 (gamma)	
PD resource use			
Outpatient oncologist visit	9.61	7.69, 11.53 (gamma)	B.3.6.2
Chest X-ray	6.79	5.43, 8.15 (gamma)	
CT scan (chest)	0.62	0.50, 0.74 (gamma)	
CT scan (other)	0.36	0.29, 0.43 (gamma)	
ECG	1.04	0.83, 1.25 (gamma)	
Community nurse visit	8.70	6.96, 10.44 (gamma)	
Clinical nurse specialist	12.00	9.60, 14.40 (gamma)	
GP surgery	12.00	9.60, 14.40 (gamma)	
PD resource use			
Outpatient oncologist visit	9.61	7.69, 11.53 (gamma)	B.3.6.2
Chest X-ray	6.79	5.43, 8.15 (gamma)	
CT scan (chest)	0.62	0.50, 0.74 (gamma)	

Variable	Value	Lower, upper bound (distribution)	Reference to section in submission
CT scan (other)	0.36	0.29, 0.43 (gamma)	
ECG	1.04	0.83, 1.25 (gamma)	
Community nurse visit	8.70	6.96, 10.44 (gamma)	
Clinical nurse specialist	12.00	9.60, 14.40 (gamma)	
GP surgery	12.00	9.60, 14.40 (gamma)	
Resource use costs			
Outpatient oncologist visit	£233.95	£187.16, £280.74 (gamma)	B.3.6.2
Chest X-ray	£41.23	£32.98, £49.48 (gamma)	
CT scan (chest)	£172.26	£137.81, £206.71 (gamma)	
CT scan (other)	£172.26	£137.81, £206.71 (gamma)	
ECG	£296.02	£236.82, £355.22 (gamma)	
Community nurse visit	£82.00	£65.60, £98.40 (gamma)	
Clinical nurse specialist	£82.00	£65.60, £98.40 (gamma)	
GP surgery	£42.00	£33.60, £50.40 (gamma)	
Blood test	£2.75	£2.20, £3.30 (gamma)	
Subsequent treatment total costs - durvalumab			
BSC	24.6%	19.7%, 29.5% (Dirichlet)	B.3.6.4.1
Topotecan (oral)	10.0%	8.0%, 12.0% (Dirichlet)	
Etoposide + cisplatin	18.8%	4.6%, 6.8% (Dirichlet)	
Etoposide + carboplatin	46.6%	37.3%, 55.9% (Dirichlet)	
Subsequent treatment total costs – "watch and wait"			
BSC	19.6%	15.7%, 23.5% (Dirichlet)	B.3.6.4.1
Topotecan (oral)	10.0%	8.0%, 12.0% (Dirichlet)	
Etoposide + cisplatin	8.0%	6.4%, 9.6% (Dirichlet)	
Etoposide + carboplatin	23.9%	19.2%, 28.7% (Dirichlet)	
Atezolizumab + etoposide + carboplatin	38.5%	30.8%, 46.2% (Dirichlet)	
Treatment acquisition costs			
Durvalumab	[redacted]	[redacted] (gamma) [Not varied in sensitivity analyses]	B.3.6.1.1
"Watch and wait"	£0.00	£0.00, £0.00 (gamma)	
Treatment administration costs			
Durvalumab	£411.99	£329.59, £494.39 (gamma)	B.3.6.1.3

Variable	Value	Lower, upper bound (distribution)	Reference to section in submission
"Watch and wait"	£0.00	£0.00, £0.00 (gamma)	
RDI			
Durvalumab	100%	80%, 100% (lognormal)	B.3.6.1.2
Subsequent treatment total costs			
BSC	£0.00	£0.00, £0.00 (gamma)	B.3.6.4.1
Topotecan (oral)	£3,000.00	£2,400.00, £3,600.00 (gamma)	
Etoposide + cisplatin	£630.46	£504.37, £756.55 (gamma)	
Etoposide + carboplatin	£1,636.58	£1,309.26, £1,963.89 (gamma)	
Durvalumab + etoposide + cisplatin	[redacted]	[redacted] (gamma)	
Durvalumab + etoposide + carboplatin	[redacted]	[redacted] (gamma)	
Atezolizumab + etoposide + carboplatin	£27,744.88	£22,195.90, £33,293.86 (gamma)	
Adverse event costs			
Pneumonia	£4,649.55	£3,719.64, £5,579.46 (gamma)	B.3.6.3
End-of-life costs			
End of life care costs	£4,703.66	£3,762.93, £5,644.39 (gamma)	B.3.6.2.1

Abbreviations: BSC, best supportive care; CT, computed tomography; ECG, electrocardiogram; GP, General practitioner; N/A, not applicable; NHS, National Health Service; OS, overall survival; PFS, progression-free survival.

B.3.10.2 Assumptions

A summary of all the model assumptions and justifications is provided in Table 76.

Table 76. Main model assumptions

Model input	Assumption	Rationale/ Justification
Perspective	NHS and PSS	NICE reference case
Discounting	3.5% per annum for costs and health outcomes	NICE reference case
Time horizon	39 years	A lifetime horizon consistent with NICE reference case. Fewer than 1% of the patient population remained alive in the model after 39 years
Cycle length	4-week	The cycle length is 4-weeks to aligned with the frequency of administration over the time period patients could receive durvalumab in the ADRIATIC trial

Model input	Assumption	Rationale/ Justification
Efficacy	Direct extrapolation of ADRIATIC efficacy endpoints (OS and PFS) for the base case.	Uses available data from a head-to-head randomised control trial. Validated by clinical experts as the preferred approach
	Independent models are fitted for OS and PFS	Inspection of the Schoenfeld residual and log-cumulative hazards plots indicate the proportional hazards assumption was systematically violated between the two treatment arms. Independent models capture different shapes of the hazards between the two arms
Cure assumption	90% of patients cured after 5 years in the durvalumab arm 90% of patients cured after 5 years in the "watch and wait" arm	Based on clinical expert opinion.
	Cured patients followed the general population survival rates and no longer incurred any treatment or health state costs	To align with previous NICE TAs that assume a cure point (TA761)
Utilities	Utility values are assumed to differ by health state, but not by treatment arm	A MMRM which considered progression status as a covariate was used to estimate the HSUV for PFS and PD based on its AIC and BIC rankings
Costs	Price of durvalumab is estimated using the commercial arrangement	To reflect the expected cost of durvalumab in UK clinical practice
Vial sharing	Vial sharing (no wastage) was assumed	Conservative assumption as durvalumab is associated with no wastage given the dosage is fixed at 1,500mg, and the vial size for 1 pack is 500 mg
Subsequent treatment	Patients in the durvalumab and "watch and wait" arm were eligible for subsequent treatment	The proportions are aligned with the clinical trial and UK clinical opinion
	Subsequent therapies only impact costs in the model	The post-progression survival data is assumed to already captured within the clinical data from the ADRIATIC trial
End-of-life care costs	Inclusion of end-of-life care cost	Inclusion of these costs reflects the additional care required in the months prior to death, borne by the NHS/PSS. End-of-life costs were applied as a one-off cost to all patients at the point of death

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; HSUV, health state utility value; MMRM, mixed models for repeated measures; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PSS, Personal Social Services; TA, technology appraisal; UK, United Kingdom.

B.3.11 Base-case results

B.3.11.1 Base-case incremental cost-effectiveness analysis results

The base case results are presented in Table 77 and Table 78. Clinical outcomes and the disaggregated results are presented in Appendix J.

All results presented in Sections B.3.11 and B.3.12 apply the commercial access arrangement for durvalumab. List prices are used for all other treatments, such as subsequent treatments. The base case results show that durvalumab is associated with an increase of [redacted] life years, and [redacted] QALYs compared with “watch and wait”. Durvalumab is associated with an increase in costs of [redacted] versus “watch and wait”, when applying the commercial access arrangement for durvalumab. This results in an ICER of £21,285 per QALY versus “watch and wait”.

The base case net health benefit at £20,000 and £30,000 willingness-to-pay thresholds (WTP) are shown in Table 78. The base case net health benefit shows a net health benefit (NHB) of -0.106 at the £20,000 WTP threshold, and a NHB of 0.478 at the £30,000 WTP threshold.

Table 77: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	-	-	-	-	-
"Watch and wait"	£22,938.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,285.22	£21,285.22

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 78: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Durvalumab	[redacted]	[redacted]	-	-	-	-
"Watch and wait"	£22,938.37	[redacted]	[redacted]	[redacted]	-0.106	0.478

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

B.3.12 Exploring uncertainty

B.3.12.1 Probabilistic sensitivity analysis

PSA was performed by varying all parameters in the model simultaneously by sampling from probability distributions. The ranges and the distributions assumed are shown in Table 75. For parameters where CIs and/or standard deviations/standard errors of the mean (SDs/SEs) were available, these are used to estimate parameter uncertainty. For variables where no CIs and/or SDs/SEs were available, the CIs are assumed arbitrarily to be +/-10% of the base case value, or other plausible maximum/minimum plausible ranges if +/-10% is implausible.

The results of the pairwise PSA are shown in Table 79 and Figure 36. These results were generated based on 1,000 simulations (convergence of the ICER was achieved by approximately the 350th simulation, as shown in Figure 37). The PSA results show durvalumab to be cost effective at the £30,000 WTP threshold. The ICER is £21,564.01 in the probabilistic analysis, and £21,285.22 in the deterministic analysis when compared with “watch and wait”.

Table 79: Probabilistic results

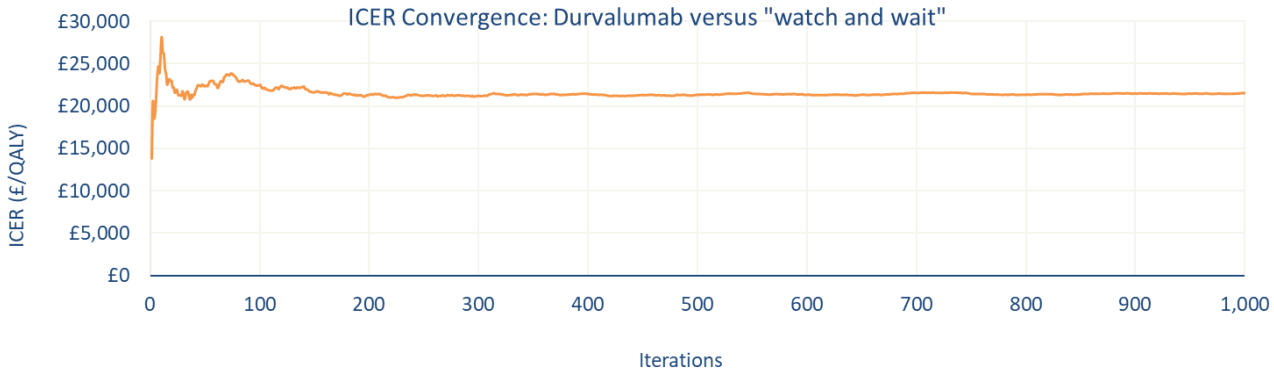
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	-	-	-	-	-
“Watch and wait”	£23,025.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,564.01	£21,564.01

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 36: Cost-effectiveness plane

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

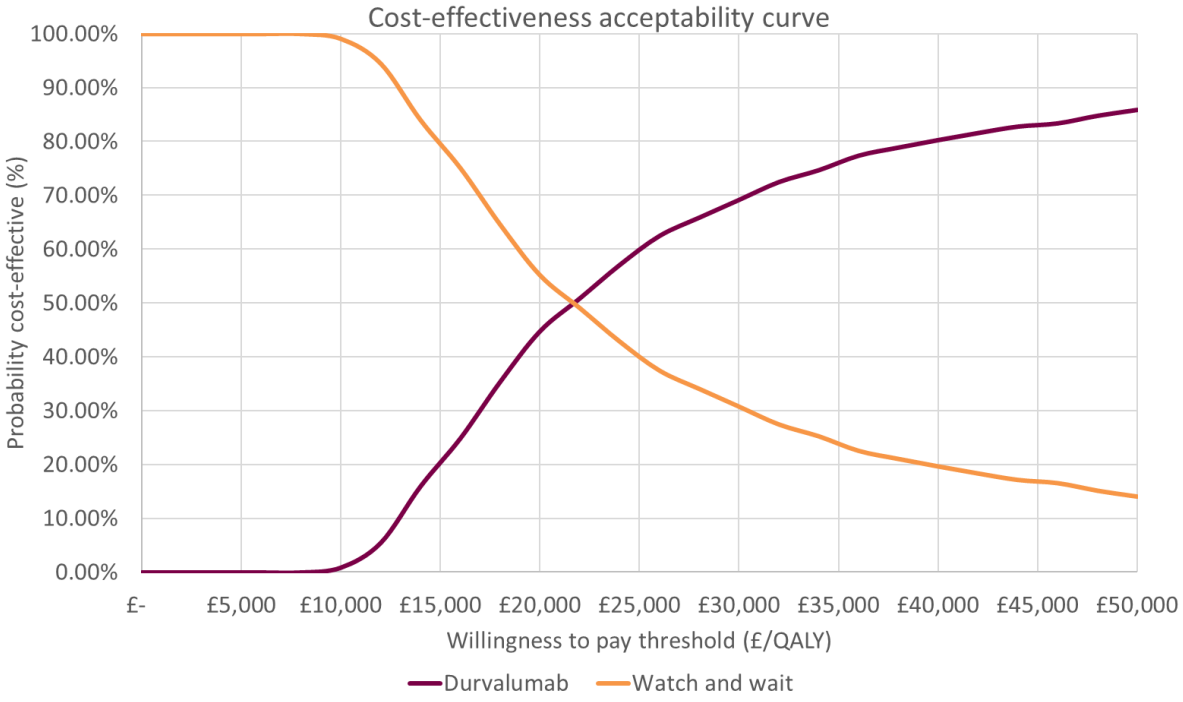
Figure 37: ICER convergence plot



Abbreviations: ICER, incremental cost-effectiveness ratio

The results were plotted in a cost-effectiveness acceptability curve (CEAC) which shows the probability of either treatment being the most cost-effective across a range of WTP thresholds (Figure 38). At a willingness to pay threshold of £30,000, durvalumab is associated with a 69.2% probability of being cost effective.

Figure 38: CEAC curve



Abbreviations: CEAC, cost-effectiveness acceptability curve; ICER, incremental cost-effectiveness

B.3.12.2 Deterministic sensitivity analysis

In the DSA, each input parameter was varied +/-10% (or other plausible maximum/minimum plausible ranges if +/-10% is implausible) to explore the impact

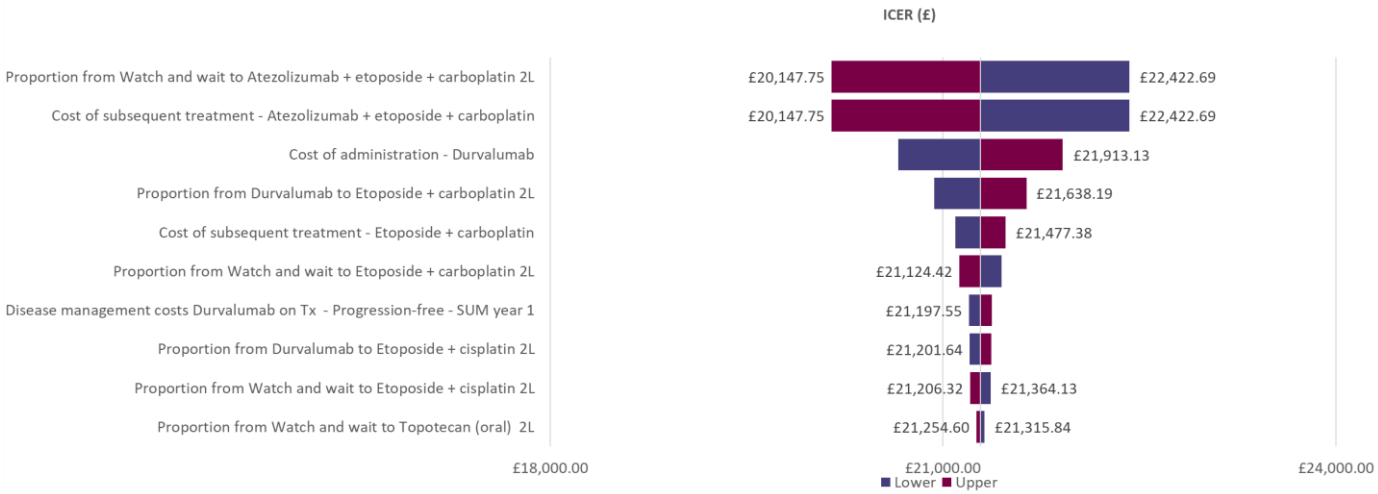
of each parameter on model outcomes. Parameters with no associated uncertainty, such as drug costs, are excluded from the analysis. Interdependent variables that cannot be varied individually, such as efficacy extrapolation parameters, were also excluded. The top 10 most influential parameters included in the one-way sensitivity analysis are presented in Table 80 and the results presented graphically in Figure 39.

Table 80. DSA results

Parameter	ICER with low value	ICER with high value	Difference
Proportion from Watch and wait to Atezolizumab + etoposide + carboplatin 2L	£22,422.69	£20,147.75	£2,274.94
Cost of subsequent treatment - Atezolizumab + etoposide + carboplatin	£22,422.69	£20,147.75	£2,274.94
Cost of administration - Durvalumab	£20,657.31	£21,913.13	£1,255.82
Proportion from Durvalumab to Etoposide + carboplatin 2L	£20,932.26	£21,638.19	£705.93
Cost of subsequent treatment - Etoposide + carboplatin	£21,093.06	£21,477.38	£384.32
Proportion from Watch and wait to Etoposide + carboplatin 2L	£21,446.03	£21,124.42	£321.61
Disease management costs Durvalumab on Tx - Progression-free - SUM year 1	£21,197.55	£21,372.89	£175.33
Proportion from Durvalumab to Etoposide + cisplatin 2L	£21,201.64	£21,368.81	£167.17
Proportion from Watch and wait to Etoposide + cisplatin 2L	£21,364.13	£21,206.32	£157.81
Proportion from Watch and wait to Topotecan (oral) 2L	£21,315.84	£21,254.60	£61.24

Abbreviations: 2L, second-line; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio.

Figure 39: Tornado diagram



Abbreviations: 2L, second-line; ICER, incremental cost-effectiveness ratio.

The results show that the most influential parameters related to the proportion of patients receiving subsequent treatments and the cost associated with these treatments. Specifically, the proportion of patients receiving atezolizumab + etoposide + carboplatin as a subsequent treatment in the “watch and wait” arm as well as the cost associated with atezolizumab + etoposide + carboplatin had the greatest impact on the ICER.

B.3.12.3 Scenario analysis

To further explore the challenges and uncertainty around the modelled results, a series of scenario analyses were performed where specific alternative model assumptions were varied.

The results are presented in Table 81. ICERs ranged between £17,228.04 (using a discount rate of 1.5% on costs and health outcomes) and £25,464.25 (using a time horizon of 20 years).

Table 81: Scenario analysis results

Parameter	Base case	Scenario	Rationale	ICER (£/QALY)	Change from base case (%)	Absolute change from base case
PFS – Durvalumab arm	1-knot spline normal	Generalised gamma	• The selection of OS and PFS curves was based on an assessment of PHA, statistical and visual fit to observed data, hazard function evaluation, and validation of the clinical plausibility of long-term projections, as described in Section 133B.3.4.1.2 • Generalised gamma was considered a plausible alternative to the 1-knot spline normal	£21,429.12	0.7%	+£143.90
PFS - "Watch and wait" arm	1-knot spline normal	Generalised gamma		£21,144.46	-0.7%	-£140.76
PFS - Both arms	1-knot spline normal	Generalised gamma		£21,288.28	0.0%	+£3.06
OS – Durvalumab arm	2-knot spline normal	2-knot spline odds	• The selection of OS and PFS curves was based on an assessment of PHA, statistical and visual fit to observed data, hazard function evaluation, and validation of the clinical plausibility of long-term projections, as described in Section B.3.4.1.3 • 2-knot spline odds was considered a plausible alternative to the 2-knot spline normal	£20,819.44	-2.2%	-£465.78
OS - "Watch and wait" arm	2-knot spline normal	2-knot spline odds		£22,584.30	6.1%	+£1,299.08
OS – Both arms	2-knot spline normal	2-knot spline odds		£22,060.50	3.6%	+£775.28
Cure timepoint (months) - Both arms	60 months (5 years)	36 months (3 years)	• The lower value considered plausible by clinical experts	£21,269.04	-0.1%	-£16.18
Cure fraction - Both arms	90%	80%	• To assess parameter uncertainty	£21,352.58	0.3%	+£67.36
Discount rates (costs and health outcomes)	3.5%	1.5%	• Aligns with NICE guidelines	£17,228.04	-19.1%	-£4,057.18

Parameter	Base case	Scenario	Rationale	ICER (£/QALY)	Change from base case (%)	Absolute change from base case
Health state utility values	PF: [redacted] PD: [redacted]	PF: [redacted] PD: [redacted]	• To address the concern that the utility values derived from the trial data may be relatively high compared to clinical practice	£21,265.82	-0.1%	-£19.41
		PF: [redacted] PD: [redacted]		£21,268.54	-0.1%	-£16.68
		PF: [redacted] PD: [redacted]		£21,279.52	0.0%	-£5.70
AE disutility	Included	Excluded	• To assess the impact disutilities associated with AE have on the ICER	£21,285.75	0.0%	+£0.53
Age-adjusted utility	Included	Excluded	• To assess the impact adjusting utility values for age has on the ICER	£21,279.97	0.0%	-£5.26
Time horizon (years)	39 years	20 years	• To assess the impact a shorter time horizon has on the ICER	£25,464.25	19.6%	+£4,179.03
Vial sharing	Included	Excluded	• Treatments using a weighted dosage are subject to wastage and/or vial sharing	£21,285.22	0.0%	+£0.00
Source of the subsequent treatment distribution	KOL input	ADRIATIC trial data	• To assess the impact the data directly from ADRIATIC trial has on the model outcomes	£24,618.51	15.7%	+£3,333.29

Abbreviations: AE, adverse event; KOL, key opinion leader; OS, overall survival; PFS, progression-free survival

B.3.13 Subgroup analysis

No relevant subgroup analyses have been carried out.

B.3.14 Benefits not captured in the QALY calculation

The model captures benefits related to patients' QoL over a lifetime, as well as decrements related to adverse events. Clinicians indicated that no benefits had been omitted from the QALY calculations. However, additional benefits of treatment with a new intervention may not be fully accounted for in the QALY calculation. For instance, health improvements may translate into societal benefits if patients are healthy enough to return to work. Furthermore, better patient health may reduce the need for informal caregiving. In addition, there it has been suggested that it is not always possible to capture all benefits with a single index. For example in Devlin et al it was discussed that generic measures (on which HRQoL measures are based) are not sensitive, and perhaps the estimated QALY gain does not accurately reflect the experience of a cancer patient.[84] While some of these aspects can be incorporated into the analysis,

B.3.15 Validation

B.3.15.1 Validation of cost-effectiveness analysis

The technical accuracy of calculations in the model was assessed by a senior health economist who was not involved in the development of the model. Validation consisted of the following:

- Systematically checking individual formulae on a sheet-by-sheet basis
- Testing the model using extreme input values to ensure results remain valid and directionally correct
- Cross checking input values against source references
- Ensuring transformation and derivation of model input values is as described and has been conducted correctly
- Testing functionality (including navigation and any other macros) for errors
- A check of the PSA and DSA including distributions used and rationales used for distribution choices.

The long-term disease progression and survival extrapolations used in the economic model were subject to external validation: the comparison to long-term data from published RCTs was part of the global model external validation process and has been described throughout B.3.4.

In addition, the model approach, assumptions and parameter inputs were thoroughly validated with clinical experts.[17]

B.3.16 Interpretation and conclusions of economic evidence

A *de novo* economic model was developed to assess the cost-effectiveness of durvalumab consolidation therapy compared to “watch and wait” in the UK for patients with LS-SCLC who have not progressed following CRT. “Watch and wait” was considered the only relevant comparator for durvalumab in this patient population in the absence of any other recommended consolidation therapy for patients who have not progressed following CRT.

The economic model was a PSM developed with a 39-year lifetime time horizon that estimated cost and outcomes from the perspective of the NHS and PSS in the UK. The efficacy and safety of durvalumab consolidation therapy and “watch and wait” (represented by the placebo arm in the ARDIATRIC trial) in the analysis were based upon the ADRIATIC trial, a global, multicentre, randomized, double-blind, placebo-controlled phase III trial of patients with limited-stage SCLC who have not progressed following CRT. Health-state utility estimates were also derived using EQ-5D-5L data from the ADRIATIC trial and were therefore directly applicable to the patient population of interest. Costs and resource use inputs, and the value set used to derive utility values from EQ-5D-5L data, were based on UK sources relevant to the base case perspective.

The results of the evaluation show that durvalumab is associated with an increase of [redacted] life years, and [redacted] QALYs compared with “watch and wait”. Durvalumab is associated with an increase in costs of [redacted] versus “watch and wait”, when applying the commercial access arrangement for durvalumab. This results in an ICER of £21,285 per QALY versus “watch and wait”. The higher total QALYs associated with durvalumab is reflective of the clinically meaningful and statistically significant improvements in PFS and OS versus placebo demonstrated in the

ADRIATIC trial, and also the higher utility associated with remaining progression-free status compared to disease progression. The higher total costs with durvalumab were primarily driven by the differences in treatment acquisition costs, with “watch-and-wait” being associated with zero treatment acquisition costs.

Sensitivity and scenario analyses were conducted to identify key drivers within the model, and to assess the extent to which uncertainty in model parameters might impact the cost-effectiveness results. The one-way sensitivity analysis showed that parameters related to the proportion of patients receiving subsequent treatments and the cost associated with these treatments had a large impact on the ICER.

The PSA showed that the probabilistic results are consistent with the deterministic results and that durvalumab is associated with 69.2% probability of being cost effective at a willingness to pay threshold of £30,000.

The scenario analyses demonstrated that varying the assumptions for subsequent treatment distributions in both arms was influential on the ICER. Varying factors such as the discount rate and time horizon also influenced the ICER. All the scenario analyses remained below the WTP threshold of £30,000 per QALY.

The main strengths of the evaluation are:

- The economic analysis was based on a simple, transparent, and well-accepted partitioned survival model structure which is widely used in advanced oncology.

- Where possible, UK-specific evidence has been used to inform the economic model, including clinical effectiveness and QoL (EQ-5D) data from ADRIATIC, and costs and resource use taken from well-established UK sources and previous NICE appraisals in comparable disease areas.

- The ADRIATIC data and model inputs, including survival extrapolations, HCRU and subsequent treatments, were reviewed by UK clinical experts via an advisory board and follow-up questionaries.

- Extensive sensitivity analyses have been conducted including PSA, DSA and scenario analyses, which showed that the results are robust to changes in parameter and structural assumptions.

- The model underwent a systemic technical validation process.

A limitation of the economic evaluation is the uncertainty surrounding the long-term extrapolation of efficacy data, which is often the case within partitioned survival models. However, the choice of extrapolation distributions was validated with UK clinical experts and the analysis has made use of the best available evidence identified by systematic means.

B.3.16.1 Conclusion

The results of this economic analysis indicate that durvalumab is a cost-effective treatment when assessed against the NICE WTP threshold of £30,000 per QALY. It can be considered a cost-effective option versus “watch and wait” for the treatment of patients with limited-stage SCLC who have not progressed following CRT from the perspective of the UK NHS and PSS. This conclusion was consistent across the PSA, deterministic analyses and all of the scenario analyses.

The observed clinically meaningful improvement in PFS with durvalumab versus “watch and wait” provides extended life and increased opportunity to achieve functional cure for patients at an early stage of the SCLC treatment pathway, addressing a significant unmet medical need. Through significantly improving outcomes in patients with a very poor prognosis, durvalumab would therefore establish a new SoC in this underserved LS-SCLC population, representing a paradigm shift in disease management.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality of life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Cost effectiveness analysis – additional information

Appendix N: ADRIATIC trial – additional information

Appendix O: References

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Summary of Information for Patients (SIP)

December 2024

File name	Version	Contains confidential information	Date
ID5073_Durvalumab in LS-SCLC_SIP_4Dec2024_ACIC	1.0	No	4 December 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

RESPONSE
Durvalumab (IMFINZI®).

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

RESPONSE
This treatment will be used by adults with a form of small-cell lung cancer called limited-stage small-cell lung cancer (LS-SCLC) whose disease has not progressed following treatment with platinum-based chemotherapy which has been given at the same time as radiotherapy (known as chemoradiation or chemoradiotherapy [CRT]).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

RESPONSE
A regulatory submission to the Medicines and Healthcare products Regulatory Agency (MHRA) for durvalumab in LS-SCLC is planned. For information regarding the anticipated indication for durvalumab, please refer to Section B.1.1 of the main submission.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

RESPONSE

AstraZeneca UK Limited actively engages with the following patient advocacy groups in lung cancer, with the aim of strengthening patient insights and responding to requests for information: Roy Castle Lung Cancer Foundation, Ruth Strauss Foundation, Asthma + Lung UK, Macmillan Cancer Support, and Cancer Research UK.

AstraZeneca UK is also a corporate supporter of the UK Lung Cancer Coalition (UKLCC), which includes patient advocacy groups.

Funding provided to UK patient groups is published annually on the AstraZeneca UK Limited website: https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

RESPONSE

Lung cancer is the most frequently diagnosed cancer worldwide, with an estimated 2.5 million new cases and 1.8 million deaths globally in 2022.[1] In the UK, there were approximately 49,000 new cases of lung cancer between 2017 and 2019, with approximately 35,000 deaths reported for the same period.[2] Lung cancer can be divided into two main groups: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).[3] Small-cell lung cancer is a highly aggressive neuroendocrine carcinoma with poor prognosis,[4, 5] comprising approximately 15% of all lung cancers.[5-7] In England, approximately 3,400 newly diagnosed cases of SCLC were registered in 2021.[8]

Small-cell lung cancer can be further divided into two stages: limited-stage (LS-SCLC) and extensive-stage (ES-SCLC). In LS-SCLC, the cancer is contained in a single area such as one lung and/or nearby lymph nodes and can be treated with radiotherapy.[9] In ES-SCLC, the disease has spread to other sites (metastasised) such as the other lung or more distant parts of the body and can be treated with radiotherapy.[9] The population of interest for this submission is patients with LS-SCLC who have received first-line therapy with platinum-based CRT and whose disease has not progressed.

Approximately 30% of patients with SCLC are diagnosed with LS-SCLC[6, 7, 10] which is associated with substantial patient burden. Symptoms of LS-SCLC include fatigue and shortness of breath, with patients also experiencing the long-term physical effects of treatment, and an emotional impact of an uncertain prognosis.[11] The disease also has a high personal and psychologic burden among caregivers, whose duties consume a substantial portion of their time, and where they experience similar symptoms and impact of SCLC as those reported by patients.[11]

As the disease advances, the most common metastatic sites (i.e. other sites in the body that the cancer has spread to) in patients with LS-SCLC include the contralateral lung,

brain, liver, bone, bone marrow, and adrenal glands.[5, 7] Brain metastases are particularly common in SCLC, occurring in ~10% of patients at presentation and developing subsequently in a further 40–50% of patients.[5]

Adverse events (AEs) (also referred to as side effects) of current treatments can also negatively impact patients. Chemotherapy is commonly associated with AEs such as nausea, loss of appetite, fatigue, hair loss, and diarrhoea/constipation, and even low-grade toxicity can influence patients' willingness to comply with treatment.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

RESPONSE

Following initial assessment of signs, symptoms, and medical history, including smoking history, SCLC is usually diagnosed via a chest X-ray and/or computed tomography (CT) scan to screen for the presence of tumours, followed by tests for the presence of cancerous cells in sputum, fluid around the lungs (pleural fluid), or tissue biopsies.

Further tests, such as magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans and additional biopsies, are used to assess whether the cancer has metastasised and to determine the stage of the disease (how far a cancer has spread and grown in the body).[12, 13]

Biomarker testing in SCLC is not routinely carried out or recommended in current guidelines, owing to the absence of validated biomarkers with prognostic or predictive relevance that can be used for disease classification or to inform treatment decisions.[13] For example, neither programmed cell death-ligand 1 (PD-L1) nor tumour mutational burden testing is recommended in routine clinical practice.[13]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

RESPONSE

There are currently no approved treatments specifically designed to enhance the effect or durability of first-line platinum-based CRT in LS-SCLC in the UK. Instead, following CRT, patients undergo active monitoring (known as watch and wait) for disease progression prior to initiating second-line treatments for disease progression/recurrence.

The NICE guideline on lung cancer (NG122) provides guidance on the management of LS-SCLC.[14] Standard of care involves CRT which is administered either as:[14]

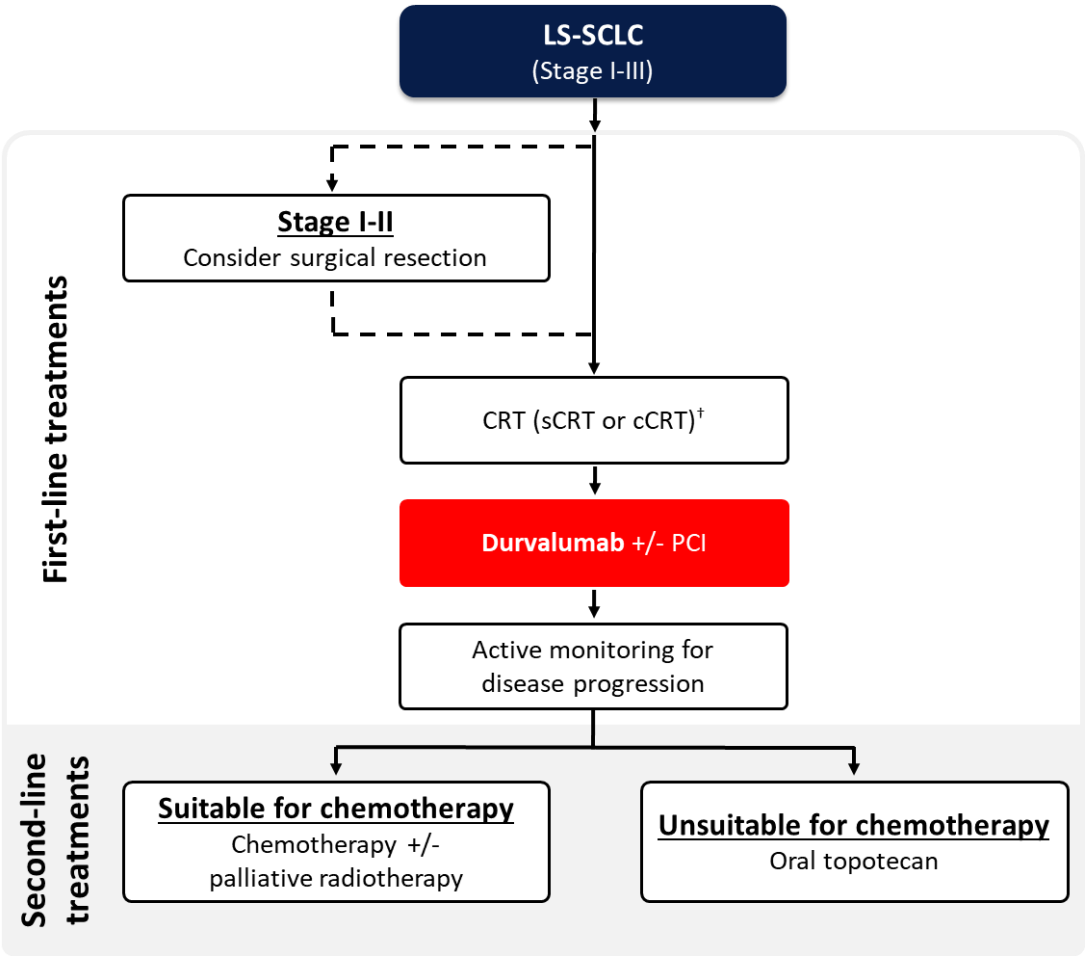
- **Concurrent CRT**: Where chemotherapy and radiotherapy are given at the same time, followed by prophylactic cranial irradiation (PCI) if patients can tolerate this regimen, or

- **Sequential CRT:** Where radiotherapy is administered before chemotherapy if patients are not considered well enough to tolerate concurrent CRT

For patients who relapse following first-line treatment, second-line chemotherapy may be offered alongside palliative radiotherapy.[14] If chemotherapy is not considered suitable, oral topotecan is the only recommended treatment option for these patients.[15] For LS-SCLC the European Society for Medical Oncology (ESMO) guidelines[13] provide similar recommendations to NICE guideline NG122.[14]

The current treatment pathway for LS-SCLC management in the UK, including the proposed positioning of durvalumab, is presented in Figure 1.

Figure 1: Proposed positioning of durvalumab in the NHS clinical pathway of care for LS-SCLC



†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.
Abbreviations: 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.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

RESPONSE

Patients with SCLC are known to experience a high symptom burden and uncertainty around their future.[11, 16] This negatively impacts their health-related quality of life (HRQoL), with worse HRQoL reported for SCLC than NSCLC.[11, 16] For patients with SCLC, the most frequent symptoms associated with both LS-SCLC and ES-SCLC include coughing, wheezing, dyspnoea and chest pain, as well as fatigue, loss of appetite and weight.[5, 11] Additionally, patients with LS-SCLC are known to face the long-term physical effects of treatment, financial implications, and the emotional impact of an uncertain prognosis.[11] Furthermore, LS-SCLC has a high personal and psychologic burden among caregivers, whose duties consume a substantial portion of their time, and they experience similar symptoms and impact of SCLC as those reported by patients with the disease.[11]

A study of patients with SCLC and NSCLC found that the mean global health status (GHS) score for patients with SCLC (38.3) was substantially lower than the normative reference value (67.1).[17] Scores on physical, role, cognitive and social functioning domains were significantly lower for SCLC than NSCLC.[17] Similarly, another study demonstrated that HRQoL scores trended towards being lower for SCLC (n=44) than for NSCLC (n=301) across disease or treatment states.[18]

Measures of a patient's health status can be represented by a health state utility value (HSUV) which indicates a patient's preference for a particular health state. Real-world evidence has shown that patients with LS-SCLC have higher HSUVs compared with those with ES-SCLC (0.802 vs 0.718; p=0.005), demonstrating they have better HRQoL.[19] In addition, patients with stable LS-SCLC have reported statistically significantly higher HSUVs (i.e. better HRQoL) compared with those with progressive disease (0.775 vs 0.674; p=0.003).[19]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

RESPONSE

Durvalumab is a type of treatment called an immunotherapy.[20] Durvalumab is designed to specifically recognise and attach to a protein called 'programmed cell death ligand 1' (PD-L1), which is present on the surface of many cancer cells. In tumour cells, PD-L1 switches off the body's immune cells that would otherwise attack the cancer cells. By attaching to PD-L1, durvalumab blocks its effects, allowing the immune system to attack the cancer cells and slow down or stop the growth of the cancer.[21]

As there are currently no approved treatments specifically designed to enhance the effect or durability of first-line platinum-based chemoradiation (CRT) in LS-SCLC in the UK, durvalumab will be the first and only treatment available for these patients who would otherwise receive active monitoring (i.e. watch and wait) for their disease.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- ~~Yes~~ / **No**

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

RESPONSE

No. Durvalumab is intended to be used as monotherapy (i.e. used on its own) in patients with LS-SCLC whose disease has not progressed following platinum-based CRT.[22]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

RESPONSE

Durvalumab (1,500 mg) is given by intravenous infusion (i.e. via a drip) by a healthcare professional, such as a nurse. Treatment is given over a one hour period every 4 weeks.[22]

Treatment with durvalumab (1,500 mg) can continue, once every 4 weeks, until the cancer progresses or patients have received durvalumab for a maximum of 24 months.

The administration method of durvalumab (intravenous) has minimal impact on patients and caregivers.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

RESPONSE

There is only one relevant clinical trial that provides evidence for the use of durvalumab to treat adults with LS-SCLC whose disease has not progressed following platinum-based CRT. This clinical trial, called ADRIATIC, has compared the efficacy and safety of durvalumab versus placebo (a dummy treatment known as a control with no active substance).[23, 24] ADRIATIC is a large, international trial which included patients in the UK, and is still ongoing.

ADRIATIC included adults (aged ≥18 years) with LS-SCLC who had achieved complete response (CR), partial response (PR), or stable disease (SD) and whose disease had not progressed following treatment with platinum-based CRT. To be included in the trial, participants had to be in good general health and have adequate organ function.

In total, 264 participants were given durvalumab and 266 participants were given placebo.

The outcomes measured in the trial included survival (how long participants remained alive after starting treatment), how long patients remained alive without their cancer getting worse, and the time to the first occurrence of death or distant metastasis (where the cancer has spread to other organs in the body). Quality of life was also measured using several different questionnaires that were completed by participants at a range of points (from 0 to 104 weeks) over the trial. Adverse events of treatment were also measured.

Further details about the study design (including criteria for participant selection) are available from the following sources:

- Cheng et al (2024). Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. New England Journal of Medicine. 2024.[24]
- ClinicalTrials.gov (2024). 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).[25]

3e) Efficacy

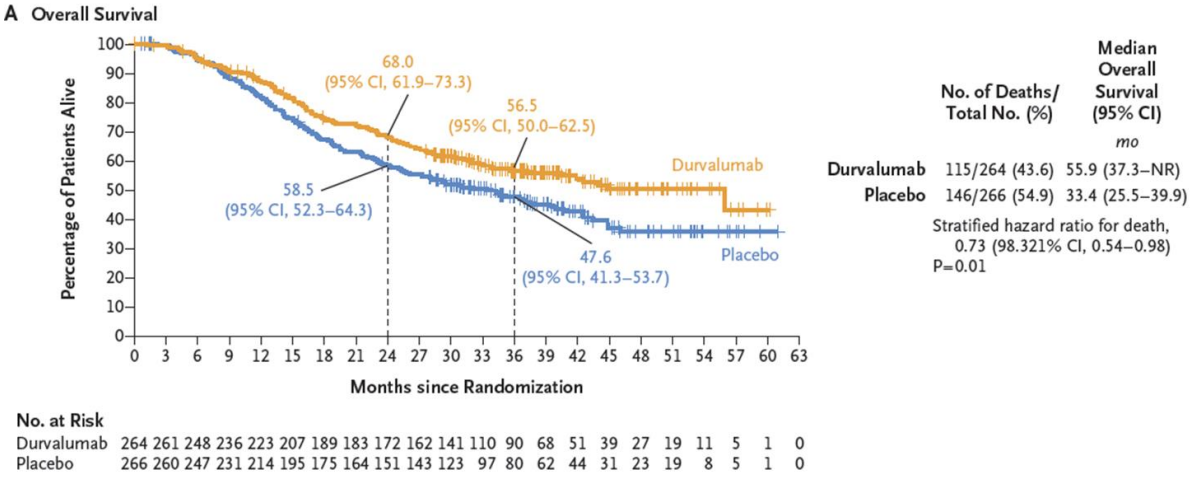
Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

RESPONSE

In the ADRIATIC trial, overall survival was clinically meaningful and statistically significantly greater (i.e. longer) in the group of participants who received durvalumab compared with the group of participants who received placebo. Participants who received durvalumab lived longer compared with those who received placebo (55.9 months vs 33.4 months) (Figure 2).

Figure 2: Kaplan-Meier plot of overall survival in ADRIATIC



Abbreviations: CI, confidence interval; NR, not reached. Source: ADRIATIC study publication Figure 1A.[24]

In addition, those who received durvalumab also lived longer on average without their disease getting worse (16.6 months) than participants who received placebo (9.2 months).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used, does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

RESPONSE

Quality of life was assessed in ADRIATIC using several different questionnaires that were completed by the participants until they stopped taking the study treatment. These included questionnaires on general health (EQ-5D), the impact of having cancer (EORTC-QLQ-C30), and on specific issues that are known to affect people with lung cancer (EORTC-QLQ-LC13).

The results of the questionnaires showed that durvalumab did not have a negative impact on participants' general health, physical and emotional wellbeing, or symptoms associated

with LS-SCLC, with stable or slight improvements while on treatment, and a trend towards a longer time to deterioration.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

RESPONSE

Like all medicines, durvalumab is associated with side effects; however, not everybody experiences them.

During the clinical trial (ADRIATIC), the most common side effects experienced by participants receiving durvalumab were those already known to occur with durvalumab when used in other types of cancer, such as cough, hyperthyroidism (overactive thyroid gland), and pruritis (itchiness). The most frequently reported side effects that occurred in >5% of patients who received durvalumab in ADRIATIC were radiation pneumonitis (60 patients; 22.9%), decreased appetite (44 patients; 16.8%), hyperthyroidism (42 patients; 16.0%), cough (40 patients; 15.3%), and pruritis (34 patients; 13.0%) were the most common in the durvalumab group.

A full list of side effects has been included in the patient information leaflet (PIL).[26]

Immunotherapies such as durvalumab can be associated with immune-mediated side effects, and inflammation in different organs of the body including the lungs, liver, intestines or glands.[26] Immune-mediated side effects are typically treated with corticosteroids; however, the treating doctor may decide to delay the next dose of durvalumab or stop durvalumab treatment altogether if these side effects occur.[26] In ADRIATIC, immune-mediated side effects with durvalumab treatment were manageable and consistent with the established safety profile of durvalumab, occurring in 84 patients (32.1%) mainly as a result of hypothyroid (13.7%) and pneumonitis side effects (11.8%).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

RESPONSE

Treatment with durvalumab slows down disease progression, leading to people with LS-SCLC living longer compared with those who received placebo. Durvalumab resulted in no detriment in quality of life compared with placebo and keeps patients in better health for a longer period, potentially reducing the time and effort required from a caregiver, and ultimately improving the caregiver's quality of life and productivity.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

RESPONSE

Durvalumab for the treatment of LS-SCLC has no known disadvantages compared with current standard of care used to treat the disease.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

RESPONSE

How the model reflects the condition

- The economic model was designed to simulate LS-SCLC by modelling different stages of the disease using categories called 'health states' (Figure 3). In the model, hypothetical patients occupy a health state and can move between states over time. The health states that this model uses are:
    - 'Progression-free' (the cancer is not getting worse)
    - 'Progressed disease' (the cancer is getting worse)
    - 'Death'
- In the model, patients start in the 'Progression-free' state, and then may either die, or experience worsening of the disease.

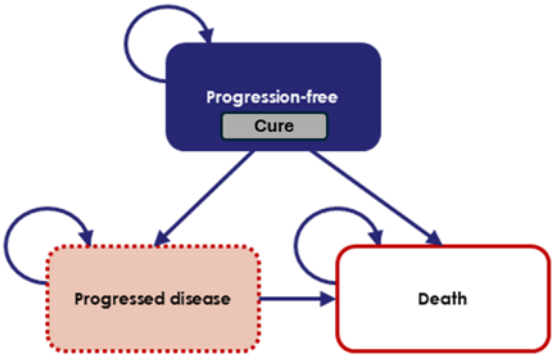
- In addition, it is assumed that a proportion of patients are cured (patients who are disease free for 3–5 years are considered to have achieved functional cure i.e. when a patient is in a prolonged remission, but there is still a small amount of the disease present)

- The model assessed the cost-effectiveness of durvalumab compared to a “watch and wait” strategy (placebo) in patients with LS-SCLC who have not progressed following CRT

- Patients experience different quality of life and accrue different costs depending on the health state they are in, with those in ‘Progression-free’ experiencing the best quality of life and lowest costs, and those in the ‘Progressed disease’ health state experiencing the worst quality of life and higher costs

- The model works by simulating how patients move between the health states when they are given different treatments; the more effective the treatment, the more time patients will spend in the ‘Progression-free’ health state

Figure 3. Model structure



Clinical trial outcomes used in the model

- The ADRIATIC clinical trial studied the efficacy (looking at the overall survival and the time until the disease progressed) as well as quality of life for those receiving durvalumab and the side effects associated with treatment. These data were all included in the model

- In the model, trial data were extrapolated to model efficacy outcomes over a total of 39 years based on a starting age of 61.5 years (the median age of patients in ADRIATIC). Statistical prediction models were used to estimate future outcomes based on the data available. The extrapolation distributions selected were based on how well the models could replicate the observed data, the statistical fit of each model, assessment of the proportional hazard assumptions and how realistic the predictions were from a clinical perspective, based on input from oncologists

Modelling how much a treatment extends life

- Treatment with durvalumab extends life by delaying cancer progression. In the ADRIATIC clinical trial, people lived longer without their disease progressing, with a higher proportion of trial participants remaining alive in the durvalumab group compared with the placebo group at 24 months (68.0% vs 58.5%) and 36 months (56.5% vs 47.6%)

Modelling how much a treatment improves quality of life

- The model considers quality of life to be mainly driven by the health state patients are in (whether their cancer is getting worse) rather than the treatment they are on

- The model also considers that patients may experience side effects that may negatively impact quality of life; data from the ADRIATIC clinical trial informed the types of side effects experienced by patients receiving durvalumab or placebo, and how many patients experienced each side effect

- Quality of life was captured via the use of questionnaires on general health (EQ-5D), the impact of having cancer (EORTC QLQ-C30), and on specific issues that are known to affect people with lung cancer (EORTC QLQ-LC13). NICE prefer the use of EQ-5D to estimate quality of life (QoL), so this was used in the model

Modelling how the costs of treatment differ with the use of durvalumab

- Costs that were considered in the model include treatment acquisition, treatment administration, resource use (costs for healthcare professionals and hospitals), costs of treating side effects, and costs of subsequent treatments

- Durvalumab displays better efficacy compared to 'watch and wait'. This translates into patients spending more time in the 'Progression-free' health state and a lower proportion of patients dying, with patients progressing to the death health state assumed to receive terminal care

Uncertainty

- As previously mentioned, the model is based on predictions of long-term outcomes informed by the data collected in the ADRIATIC study. This is common practice in economic evaluations of new drugs but is a source of uncertainty in the analysis. Clinicians were consulted in selecting the extrapolations used in the analysis and alternative models were also tested

- Uncertainty in the model inputs and structure was explored using sensitivity and scenario analyses; these analyses assessed the impact on the model outputs when inputs are varied by a defined amount

Health economic model results

- Durvalumab is associated with an improvement in survival, a gain in quality-adjusted life years (QALYs) and greater costs than the watch and wait strategy
- Durvalumab was found to have an incremental cost-effectiveness ratio of £21,285.22 compared with the watch and wait strategy
- The detailed results are considered commercially confidential and are presented in Section B.3.11 of the company submission (Document B)
  - All results presented in Sections **Error! Reference source not found.** of the company submission (Document B) use the price based on the commercial arrangement for durvalumab. List prices are used for all other treatments, such as subsequent treatments

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

RESPONSE

Current treatment for patients with LS-SCLC is limited to chemotherapy delivered either concurrently or sequentially with radiotherapy,[13, 14] and there have been no innovations in the management of first-line LS-SCLC for several decades.

Despite this, a proportion of patients with LS-SCLC do achieve cure with current standard of care. This was validated by UK clinicians who confirmed that the majority of patients who remain progression-free for 3 years or longer following CRT can be considered to have achieved functional cure (i.e. they are in a prolonged remission with a small amount of the disease still present).[27] This highlights the curative potential of durvalumab in patients with LS-SCLC.

Durvalumab therefore represents the first treatment in several decades to have shown an improvement in survival and disease progression for patients with LS-SCLC, compared with placebo, and would establish a new standard of care in this underserved LS-SCLC population, representing a paradigm shift in disease management.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

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

RESPONSE

Use of durvalumab in LS-SCLC is not expected to raise any equality issues.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

RESPONSE

Useful information on lung cancer and LS-SCLC:

- UK Lung Cancer Coalition: https://www.uklcc.org.uk/about-lung-cancer
- Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/lung-cancer
- Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/limited-extensive?_gl=1*rqyaba*_gcl_aw*R0NMLjE3MjYyMzAyMTkuQ2p3S0NBand4WS0zQmhBdUVpd0F1N1k2czJHQ2hIdkM3dUhadV9qZi16S0h3amN6cjhBSzhiUVVZLWVaR0Z5azh0YUJFMWN6eU8xTVN4b0NjckFRQXZEX0J3RQ..*_gcl_dc*R0NMLjE3MjYyMzAyMTkuQ2p3S0NBand4WS0zQmhBdUVpd0F1N1k2czJHQ2hIdkM3dUhadV9qZi16S0h3amN6cjhBSzhiUVVZLWVaR0Z5azh0YUJFMWN6eU8xTVN4b0NjckFRQXZEX0J3RQ..*_gcl_au*NjU3MTU3NDQyLjE3MjYyMzAyMTk.*_ga*MjM4MjY5NTcwLjE3MTQzODI2NDg.*_ga_58736Z2GNN*MTcyNzg1ODY4Ny4xMi4xLjE3Mjc4NTg3NjYuNDYuMC4w
- Macmillan Cancer Support: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer
- NHS: https://www.nhs.uk/conditions/lung-cancer/

Further information on NICE and the role of patients**:**

- Public Involvement at NICE: Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs: Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

RESPONSE

Adverse event (AE): An occurrence that has a negative impact on the health or well-being of a patient in a clinical trial during or within a certain length of time after the study

Biopsy: A medical procedure that involves removing a tissue sample from the body for examination by a doctor

Chemoradiation therapy (CRT): A cancer treatment that combines chemotherapy and radiotherapy. Chemotherapy uses anti-cancer drugs that circulate in the bloodstream to destroy cancer cells. Radiotherapy uses high-energy rays, similar to X-rays, to destroy cancer cells

Clinical trial: A research study that evaluates the safety and effectiveness of new medical treatments and procedures in human participants

Complete response (CR): When all signs of cancer have disappeared after treatment. This is also known as complete remission

Computed tomography (CT) scan: A diagnostic imaging procedure that uses X-rays and a computer to create detailed images of the inside of the body

Concurrent chemotherapy and radiotherapy (cCRT): Combined chemotherapy and radiotherapy (also known as chemoradiation or chemoradiotherapy) cancer treatment that involves administering chemotherapy and radiotherapy at the same time

Health state utility value (HSUV): A number on a scale that represents how much someone prefers a health state, with 1 representing full health, 0 representing death, and negative numbers representing states worse than death

Immunotherapy: A treatment that uses the body's immune system to fight cancer by helping the immune system recognise and attack cancer cells. Immunotherapy can be used to prevent, control, or eliminate cancer

Limited-stage small-cell lung cancer (LS-SCLC): A type of small-cell lung cancer (SCLC) that is contained in a single area and can be treated with radiotherapy

Metastatic disease: Where the cancer has spread to other organs or sites in the body

Magnetic resonance imaging (MRI): A non-invasive medical imaging technique that uses radio waves and strong magnetic fields to create detailed pictures of the inside of the body

Overall survival (OS): The average length of time a patient is alive after the start of treatment

Partial response (PR): When the size of a tumour or the amount of cancer in the body decreases, but the cancer does not go away completely. This is also known as partial remission

Positron emission tomography (PET) scan: A nuclear medicine imaging test that uses a radioactive substance to create detailed pictures of the inside of the body. PET scans are used to diagnose and evaluate a variety of conditions, including cancer

Programmed cell death-ligand 1 (PD-L1): A protein that regulates the body's immune system. PD-L1 is found on some normal cells, but is present in higher amounts on some types of cancer cells

Progression free survival (PFS): The average length of time after the start of treatment in which a person is alive, and their cancer does not grow or spread

Quality-adjusted life year (QALY): One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale).

Quality of life (QoL) measures: Tools that assess a person's well-being and satisfaction by measuring aspects of their life. They can help determine the impact of a treatment or disease on a patient's life from the patient's perspective

Standard of care (SoC): The treatment that is widely used by health professionals and accepted by medical experts as the proper treatment for a particular disease

Stable disease (SD): When the cancer is neither increasing nor decreasing in size or severity. This means that the tumours are either staying the same size or shrinking, and no new tumours are developing

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2024;74(3):229-63.
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13. Dingemans AC, Früh M, Ardizzoni A, Besse B, Faivre-Finn C, Hendriks LE, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. Annals of Oncology. 2021;32(7):839-53.
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18. Labbé C, Leung Y, Lemes JGS, Stewart E, Brown C, Cosio AP, et al. Real-world EQ5D health utility scores for patients with metastatic lung cancer by molecular alteration and response to therapy. Clinical Lung Cancer. 2017;18(4):388-95. e4.
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22. AstraZeneca. Data on file. Durvalumab (IMFINZI) draft Summary of Product Characteristics. 2024.
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24. Cheng Y, Spigel DR, Cho BC, Laktionov KK, Fang J, Chen Y, et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. New England Journal of Medicine. 2024.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Clarification questions

January 2025

File name	Version	Contains confidential information	Date
ID5073_EAG clarification company responses_V1.0_130225_Redacted	1.0	Yes	13th February 2025

Section A: Clarification on effectiveness data

Clinical pathway

A1. Company submission (CS) Figure 2 suggests that the company is positioning durvalumab in patients with stage I-III limited-stage small-cell lung cancer (LS-SCLC) after chemoradiotherapy (CRT), regardless of whether they previously received chemotherapy concurrent with radiotherapy (cCRT) or sequential CRT (sCRT). Is our interpretation correct?

Company response:

Yes, that is the correct interpretation.

In the UK, the current standard of care (SoC) in limited-stage small-cell lung cancer (LS-SCLC) is platinum-based chemotherapy delivered concurrently with twice-daily radiotherapy (1, 2). However, sequential CRT (delayed initiation of radiotherapy following chemotherapy [sCRT]) may be considered for patients unsuitable for concurrent CRT (cCRT) due to poor World Health Organisation/Eastern Cooperative Oncology Group Performance Status (WHO/ECOG PS) (≥2), comorbidities, and/or disease volume (1, 2).

Expert clinical opinion confirmed that patients who receive sCRT for LS-SCLC are expected to benefit from treatment with durvalumab (3), with precedent from the PACIFIC-6 study where durvalumab demonstrated encouraging efficacy in non-small-cell lung cancer (NSCLC) patients following sCRT (4). In PACIFIC-6, treatment with durvalumab resulted in a median progression-free survival (PFS) of 10.9 months (95% confidence interval [CI]: 7.3, 15.6), and 12-month overall survival (OS) and PFS rates of 84.1% and 49.6%, respectively (4). These survival rates are comparable with those observed for the durvalumab arm of PACIFIC (12-month PFS: 55.7%; 12-month OS: 83.1%) and higher than those observed for the placebo arm (12-month PFS: 34.5%; 12-month OS: 74.6%) (4, 5). This is further supported by an American Society of Clinical Oncology (ASCO) rapid recommendation update which recommends that patients with LS-SCLC and ECOG PS 3–4 who have received sCRT may be offered durvalumab for up to 2 years if there are no

contraindications to immunotherapy and there is improvement in performance status (6).

A2. CS Figure 2: Is it expected that durvalumab will be delivered at the same time as prophylactic cranial irradiation (PCI) or would one be delivered after the other?

Company response

Prophylactic cranial irradiation (PCI) is typically used only after careful consideration of potential adverse effects that may impact cognitive function. As per the ADRIATIC study protocol, PCI was conducted after completion of cCRT and protocol-mandated brain imaging to confirm the absence of cerebral metastases and completed within 1 to 42 days prior to randomisation and the first dose of durvalumab. It would therefore be expected that durvalumab be administered after completion of PCI in clinical practice.

Systematic literature review (SLR)

A3. Priority question: CS Appendix D.1.2: Please explain why studies of patients who are receiving or who have received sCRT were not considered for data extraction.

Company response

A key inclusion criterion of the ADRIATIC trial was patients who received four cycles of first-line cCRT consisting of platinum-based therapy plus etoposide. All cCRT studies included in the systematic literature review (SLR) were aligned with the patient eligibility criteria for ADRIATIC and the population included in the trial.

Studies with patients who are receiving or who have received sCRT were included in the SLR; however, data were not extracted from these studies consistent with the eligibility criteria of ADRIATIC. Studies that assessed sCRT were tagged independently of whether they reported durvalumab treatment. Of the 69 studies originally identified by the SLR that included sCRT, there was no mention of durvalumab identified in the study abstracts.

Data for sCRT from a further seven studies that were not originally included (according to the SLR protocol), and from two studies from which cCRT data was already extracted, have subsequently been extracted. Of these newly extracted studies, only two were published post-2012, neither of which mention durvalumab, and the remaining studies were published between 2002 and 2009, prior to the availability of durvalumab.

A4. Priority question: During the SLR, were any studies of durvalumab treatment following sCRT that included the population of interest in this appraisal identified at full text screening (and thus were 'tagged' and not data extracted)?

Company response

Studies that assessed sCRT were tagged in the SLR independently of whether they reported durvalumab treatment. Of the 69 studies originally identified by the SLR that included sCRT, there was no mention of durvalumab identified in the study abstracts.

Data for sCRT from a further seven studies that were not originally included (according to the SLR protocol), and from two studies from which cCRT data was already extracted, have subsequently been extracted. Of these newly-extracted studies, only two were published post-2012, neither of which mention durvalumab, and the remaining studies were published between 2002 and 2009, prior to the availability of durvalumab.

ADRIATIC trial

A5. How many patients were randomised into the trial from the United Kingdom (UK) study site (CS section B.2.3.1.2)?

Company response

There was one patient from the UK study site who was randomised into the durvalumab treatment arm of ADRIATIC.

The COVID-19 pandemic is expected to have negatively impacted recruitment into ADRIATIC from the UK, principally through late diagnosis. For chemoradiotherapy to be an option for patients with LS-SCLC, early diagnosis is key; however, during the COVID-19 pandemic this was often not possible as patients were not having standard surveillance scans for other conditions, nor did they have easy access to radiology services. Furthermore, patients with coughs were often kept away from healthcare environments as they were presumed to have COVID-19.

However, in post-COVID-19-pandemic UK, especially in areas where the targeted lung health check (TLHC) programme is undertaken, it is anticipated that there will be cancer stage migration towards the numbers observed in Europe.

As a substantial number of participants from the rest of Europe were included in ADRIATIC (n=206/530 [39%]), the low number of patients included from the UK is therefore not anticipated to be a treatment effect modifier.

A6. Priority question: CS section B.2.3.1.5 states that the final data cut of the ADRIATIC trial was anticipated in quarter 4 of 2024. Is this or a further interim analysis available? (The company's decision problem meeting form indicates that [redacted].) What results (outcome measures) have been or are expected to be updated?

Company response

The statement that the final data cut of the ADRIATIC trial was anticipated in quarter 4 of 2024 is incorrect.

A data cut-off (DCO) for the planned second OS interim analysis (OS-IA2) occurred on [redacted]. 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).

ADRIATIC trial outcomes

A7. CS Appendix Table 22: Please describe the reliability and validity of the Patient Global Impressions Severity (PGIS) measures in LS-SCLC, referring to appropriate references.

Company response

The Patient Global Impressions Severity (PGIS) questionnaire was used in ADRIATIC to assess patients' overall impression of the severity of their cancer symptoms. Previous studies have evaluated the use of patients' global impression (PGI) after symptom management in advanced cancer patients (7, 8). These studies concluded that the PGI is a validated global rating-of-change scale used to assess subjective patients' response based on the individual feeling of improvement or deterioration after receiving a treatment (7). Furthermore, it was concluded that PGI could be considered a cancer-specific QoL measure and is a good measure for patients and clinicians to use together to identify areas of concern that require attention and monitor changing needs (8).

A8. CS section B.2.3.1.14 states that a clinically meaningful improvement in scores on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module (EORTC QLQ-LC13) questionnaires is "a decrease from baseline score of ≥10 for the symptom scales/items". Please provide references to studies and other sources of evidence in support of this.

Company response

A high score on a functional or Global Health Score (GHS)/quality of life (QoL) scale (scale of 0 to 100) represents a high level of functioning or global health-related quality of life (HRQoL) (i.e. better health status/function), while a high score on a symptom scale/item represents a high level of symptom burden.

A minimum clinically meaningful change is defined as a change in the score from baseline of ≥10 for scales/items from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC Quality of Life Questionnaire Lung Cancer module (EORTC QLQ-LC13) (9). Furthermore, a 10-point EORTC-QLQ-C30 score change represents a change in supportive care needs, and scores changing ≥10 points should be highlighted for clinical attention (10).

ADRIATIC trial statistical analyses

A9. During the ADRIATIC trial, was there any cross-over (treatment switching) between the trial arms? If so, what proportion of patients switched treatments, were analyses of OS adjusted for this, and, if so, what adjustment method was used?

Company response

There was no cross-over (treatment switching) between the trial arms in ADRIATIC; however, subsequent treatments were permitted in the trial.

Patients who received subsequent therapy prior to disease progression or death were censored at their last evaluable assessment prior to taking the subsequent therapy. The most common therapy classes for first subsequent anti-cancer therapy (i.e., second-line) were cytotoxic chemotherapy (82 [31.1%] patients in the durvalumab group, 114 [42.9%] patients in the placebo group) and immunotherapy (17 [6.4%] patients in the durvalumab group, 31 [11.7%] patients in the placebo group) (Table 1).

Table 1: First subsequent anti-cancer treatments permitted in ADRIATIC (FAS)

Treatment	Durvalumab (n=264)	Placebo (n=266)
Number of subjects with first subsequent therapy, n (%)†		
	[redacted]	[redacted]
Chemotherapy regimen, n (%)		
Cytotoxic chemotherapy monotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy platinum doublet	[redacted]	[redacted]
Chemotherapy + immunotherapy‡	[redacted]	[redacted]
Chemotherapy + targeted therapy	[redacted]	[redacted]
Chemotherapy + immunotherapy + targeted therapy‡	[redacted]	[redacted]
Other chemotherapy combination	[redacted]	[redacted]
Immunotherapy regimen, n (%)		
Immunotherapy monotherapy‡	[redacted]	[redacted]
Immunotherapy + immunotherapy‡	[redacted]	[redacted]
Immunotherapy + targeted therapy‡	[redacted]	[redacted]
Targeted therapy monotherapy, n (%)		

Treatment	Durvalumab (n=264)	Placebo (n=266)
	[redacted]	[redacted]
Antibody-drug conjugate monotherapy		
	[redacted]	[redacted]
Line of treatment§		
Second-line	[redacted]	[redacted]
Third-line	[redacted]	[redacted]
Not applicable	[redacted]	[redacted]
Therapy class§		
Cytotoxic chemotherapy	[redacted]	[redacted]
Immunotherapy‡	[redacted]	[redacted]
Targeted therapy	[redacted]	[redacted]
Antibody-drug conjugate therapy	[redacted]	[redacted]
Other	[redacted]	[redacted]

†First therapies post-discontinuation of treatment. ‡Immunotherapy includes any therapy in which at least one mechanism of action involves modulation of the immune system. §Subjects with therapies in more than one category are counted once in each of those categories.
For all other categories, subjects are counted once in each category.
Radiotherapies are excluded from the subsequent anti-cancer therapies received.

The most common therapy classes for second subsequent anti-cancer therapy (i.e., third-line) were cytotoxic chemotherapy (45 [17.0%] patients in the durvalumab group, 48 [18.0%] patients in the placebo group) and immunotherapy (3 [11.1%] patients in the durvalumab group, 12 [4.5%] patients in the placebo group (Table 2).

Table 2: Second subsequent anti-cancer treatments permitted in ADRIATIC (FAS)

Treatment	Durvalumab (n=264)	Placebo (n=266)
Number of subjects with second subsequent therapy, n (%)†		
	[redacted]	[redacted]
Chemotherapy regimen, n (%)		
Cytotoxic chemotherapy monotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy platinum doublet	[redacted]	[redacted]
Chemotherapy + immunotherapy‡	[redacted]	[redacted]
Chemotherapy + targeted therapy	[redacted]	[redacted]
Chemotherapy + immunotherapy + targeted therapy‡	[redacted]	[redacted]
Other chemotherapy combination	[redacted]	[redacted]

Treatment	Durvalumab (n=264)	Placebo (n=266)
Immunotherapy regimen, n (%)		
Immunotherapy monotherapy‡	[redacted]	[redacted]
Immunotherapy + immunotherapy‡	[redacted]	[redacted]
Immunotherapy + targeted therapy‡	[redacted]	[redacted]
Targeted therapy monotherapy, n (%)		
	[redacted]	[redacted]
Line of treatment§		
Second-line	[redacted]	[redacted]
Third-line	[redacted]	[redacted]
>Third-line	[redacted]	[redacted]
Not applicable	[redacted]	[redacted]
Therapy class§		
Cytotoxic chemotherapy	[redacted]	[redacted]
Immunotherapy‡	[redacted]	[redacted]
Targeted therapy	[redacted]	[redacted]
Experimental therapy	[redacted]	[redacted]

†Second therapies post-discontinuation of treatment.
‡Immunotherapy includes any therapy in which at least one mechanism of action involves modulation of the immune system.
§Subjects with therapies in more than one category are counted once in each of those categories.
For all other categories, subjects are counted once in each category.
Radiotherapies are excluded from the subsequent anti-cancer therapies received.
Abbreviations: FAS, full analysis set.

ADRIATIC trial results

A10. Priority question: CS section B.2.4.3 states that OS analyses were stratified by both disease status and receipt of PCI. However, a footnote to CS Table 16 [overall survival (OS) results for the FAS population] states: "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."

i) Please explain this discrepancy (i.e. non-use of disease status in the stratified Cox model).

Company response

Per the Statistical Analysis Plan (Section 4.2.2, Progression-free Survival), "*in order to ensure there are at least 5 events within each strata; if there are too few events observed in the tumour, node, and metastasis [TNM] Stage I/II stratification level then TNM stage may be excluded from the stratified models leaving receipt of PCI as the sole stratification factor.*" Please note, the primary analysis of OS follows the same methodology as for PFS (please refer to Section 4.2.3, Overall Survival).

At the time of OS IA1, there were fewer than 5 deaths in the placebo group stratum of patients with Stage I/II and who received PCI (Table 3). Therefore, only receipt of PCI was included as a stratification factor in the stratified analysis of OS.

ii) Please provide the results when the analyses are also stratified by disease status in addition to receipt of PCI, if this is how this outcome was planned *a priori* to be analysed. Please provide the results in a table akin to CS Table 16 and in a Kaplan-Meier (KM) plot akin to CS Figure 4.

Company response

The stratified analysis of OS, adjusting for both receipt of PCI (yes vs no) and TNM Stage (Stage I/II vs III) is presented in Table 3. The results (HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]) are consistent with the primary analysis of OS that only adjusted for receipt of PCI (HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]). Had it been statistically tested, the analysis stratified by receipt of PCI and TNM stage would have met the prespecified O'Brien Fleming type boundary for declaring statistical significance (2-sided p-value <0.01679).

Table 3: Overall survival, durvalumab vs placebo, stratified by TNM stage and receipt of PCI (FAS)

	Durva (n=264)	Placebo (n=266)
Number of deaths, n (%)	[redacted]	[redacted]
Stage I/II; no PCI	[redacted]	[redacted]
Stage I/II; PCI	[redacted]	[redacted]
Stage III; no PCI	[redacted]	[redacted]
Stage III; PCI	[redacted]	[redacted]
Censored subjects, n (%)	[redacted]	[redacted]
Still in survival follow-up†	[redacted]	[redacted]
Terminated prior to death‡	[redacted]	[redacted]
Median OS follow-up§	[redacted]	[redacted]
95% CI§	[redacted]	[redacted]
Survival rate at 24 months (OS24)§	[redacted]	[redacted]
95% CI§	[redacted]	[redacted]
Survival rate at 36 months (OS36)§	[redacted]	[redacted]
95% CI§	[redacted]	[redacted]
HR, durvalumab versus placebo¶, §§	[redacted]	
98.321% CI for HR¶, ††	[redacted]	
95% CI for HR¶	[redacted]	
2-sided p-value‡‡	[redacted]	

†Includes subjects known to be alive at data cut-off.
‡Includes subjects with unknown survival status or subjects who were lost to follow-up.
§Calculated using the Kaplan-Meier technique. CI for median overall survival is derived based on Brookmeyer-Crowley method with log-log transformation. CI for OS24 and OS36 are derived based on a log(-log(.)) transformation.
¶The hazard ratio and CI were calculated using a stratified Cox proportional hazards model, adjusting for TNM stage (Stage I/II versus III) and receipt of PCI (yes versus no), with treatment as only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach.
††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 analysis was performed using the stratified log-rank test, adjusting for TNM stage (Stage I/II versus III) and receipt of PCI (yes versus no).
§§A hazard ratio <1 favours durvalumab to be associated with a longer survival than placebo.
One month is calculated as 30.4375 days.
Stratification factor is based on the values entered into the IVRS.
Abbreviations: CI confidence interval; FAS, full analysis set; HR, hazard ratio; IVRS, Interactive Voice Response System; NR Not reached; OS, overall survival; OS24, proportion of patients alive at 24 months from randomisation; OS36, proportion of patients alive at 36 months from randomisation; PCI, prophylactic cranial irradiation; TNM, tumour, node, and metastasis.
Source table: IEMT000657_029.

A11. Priority question: CS section B.2.4.3 states that "Sensitivity analyses [of OS] were performed to assess treatment bias". The only sensitivity analysis of OS mentioned in the CS relates to the censoring indicator of OS being reversed (CS section B.2.6.1.1.1). Was this the only sensitivity analysis undertaken? If not, please describe the other analyses and present the results narratively and graphically in the same style as used to present the results of the sensitivity analyses of progression-free survival (PFS) in CS section B.2.6.1.2.1.

Company response

We confirm that only one sensitivity analysis was planned in the ADRIATIC statistical analysis plan (SAP) to assess attrition bias, using a Kaplan-Meier (KM) plot of time-to-censoring where the censoring indicator of the primary OS analysis is reversed. This is presented in Section B.2.6.1.1.1 and Appendix N.3.1.1 of the Company Submission.

A12. Priority question: Pages 12 and 97 of the ADRIATIC trial interim clinical study report (CSR) provided with the CS outlines the subsequent anti-cancer treatments trial participants received after discontinuation of the study treatment, stating that participants received [redacted] or [redacted]):
i) If available, please provide details of the specific therapies participants received (i.e. drug generic/brand name), along with the number and percentage of participants receiving each one, and ii) please comment on the extent to which the treatments received reflect those used in clinical practice in England.

Company response

Details of the specific therapies received by patients are unavailable.

With regard classes of treatments received by patients, the most common post-discontinuation disease-related anti-cancer therapies were cytotoxic chemotherapy and immunotherapy. Cytotoxic chemotherapy (either as monotherapy or in combination) was received by 88 (33.3%) patients in the durvalumab group and 121 (45.5%) patients in the placebo group. Of these patients, 54 (20.5%) in the durvalumab group and 56 (21.1%) in the placebo group received cytotoxic chemotherapy platinum doublet, and 47 (17.8%) in the durvalumab group and 57 (21.4%) in the placebo group received cytotoxic chemotherapy monotherapy. Immunotherapy, either as monotherapy or in combination was received by 23 (8.7%) patients in the durvalumab group and 39 (14.7%) patients in the placebo group.

A second line of post-discontinuation disease-related anti-cancer therapy was received by 92 (34.8%) patients in the durvalumab group and 124 (46.6%) patients in the placebo group. A total of 47 (17.8%) patients in the durvalumab group and 56 (21.1%) patients in the placebo group received a third line. An equal number of patients in both treatment groups (22 patients [8.3%]) received more than 3 lines of post-discontinuation disease-related anti-cancer therapy.

As described in Section B.3.6.4.1 of the CS, the types and proportions of subsequent therapies were derived from data in ADRIATIC and then validated and adjusted through clinical expert opinions to ensure alignment with real-world clinical practice.

Following an advisory board, the proportion of patients receiving subsequent therapy after progression was presented to clinical experts. These proportions were calculated based on the number of patients receiving any subsequent anti-cancer therapy (n=[redacted] for the durvalumab arm and n=[redacted] for the placebo arm) and the total number of progressed patients in each arm (n=126 for the durvalumab arm and n=158 for the placebo arm). As a result, [redacted]% and [redacted]% of patients in the intervention and placebo arms, respectively, were assumed to require subsequent treatment.

Subsequent therapies included those received by ≥5% of patients in either arm of the ADRIATIC study. These treatments were single-agent chemotherapy (n=[redacted] for the durvalumab arm and n=[redacted] for the placebo arm), platinum-doublet chemotherapy (n=[redacted] for the durvalumab arm and n=[redacted] for the placebo arm), and immune-oncology (IO) therapies combined with chemotherapy (n=[redacted] for the durvalumab arm and n=[redacted] for the placebo arm).

A13. Please report the rates of missing data (or compliance) for the durvalumab monotherapy and placebo arms for the PRO-CTCAE and PGIS endpoints.

Company response

Missing data or compliance rates for the PRO-CTCAE and PGIS endpoints were not reported in the ADRIATIC clinical study report (CSR). Instead, the proportion of subjects with a completed PGIS assessment for each visit is presented. At baseline, the proportion of subjects with a completed PGIS assessment was similar between treatment groups ([redacted] with durvalumab versus [redacted] with placebo) and remained [redacted] through Week 16, and [redacted] through Week 32 for both treatment groups (CSR Appendix, Table 14.2.14).

Please note, for the PRO-CTCAE outcome, only the frequency of symptoms (by time point) was presented in the CSR (CSR Appendix, Table 14.2.15). Missing data or compliance rates for PRO-CTCAE were not collected in ADRIATIC and are therefore not available.

A14. Were missing data imputed in the analyses of the EORTC QLQ-C30, QLQ-LC13, PRO-CTCAE, PGIS and EQ-5D-5L endpoints (that is, the analyses that produced the results presented in CS sections B.2.6.4)? If so, please describe the method(s) used.

Company response

Missing data were not imputed for the EORTC QLQ-C30, QLQ-LC13, PRO-CTCAE, PGIS, and EQ-5D-5L endpoints. For these endpoints, the number of evaluated forms at each time point included questionnaires that had a completion date and at least one subscale that was non-missing.

Changes in patient-reported outcome (PRO) score compared with baseline were evaluated in ADRIATIC. For each subscale, when <50% of the subscale items were missing, the subscale score was divided by the number of non-missing items and multiplied by the total number of items on the subscales (11). Where at least 50% of the items were missing, that subscale was treated as missing, and missing single items were treated as missing. Where there was evidence that the missing data were systematic, missing values were handled to ensure that any possible bias was minimised.

A15. CS section B.2.6.4.2.3: Please provide the reasons for missing data on the EQ-5D-5L outcome and the number and proportion of participants with missing data for each reason, broken down by trial arm (i.e. durvalumab monotherapy and placebo) at baseline, Week 8 (to correspond with the results presented in CS section B.2.6.4.2.3) and at the longest follow-up timepoint.

Company response

The specific reasons for missing data for the EQ-5D-5L outcome were not collected in ADRIATIC and are therefore not available.

Rates of missing data (i.e. non-compliance) at baseline were similar between treatment groups ([redacted]% with durvalumab versus [redacted]% with placebo), comparable at Week 8 ([redacted]% with durvalumab versus [redacted]% with placebo) and were the same ([redacted]%) at the longest follow-up timepoint (Week 272) in both treatment groups (CSR Appendix, Table 14.2.13.1).

A16. Priority question: CS section B.2.6.4.2.3: Please provide the mean and standard deviation for the EQ-5D-5L index score and VAS score at baseline and at each measurement timepoint for the durvalumab monotherapy and placebo arms, for the FAS population, using the table below. Please include the number of participants in each arm providing data at each timepoint.

Company response

The mean and standard deviation for the EQ-5D-5L index score and VAS score at baseline and at each measurement timepoint for the durvalumab monotherapy and placebo arms, for the FAS population, are presented in Table 4 and Table 5, respectively.

Table 4: EQ-5D-5L index score at baseline and at each measurement timepoint for durvalumab monotherapy and placebo (FAS)

Timepoint	Durvalumab (N=264)			Placebo (N=266)		
	n	Mean	SD	n	Mean	SD
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 128	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 144	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 152	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 160	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	Durvalumab (N=264)			Placebo (N=266)		
	n	Mean	SD	n	Mean	SD
Week 168	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 176	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5L, EuroQoL-five dimensions-five levels; FAS, full analysis set; N/n, number of patients; SD, standard deviation.
Source: CSR Appendix, Table 14.2.13.2.

Table 5: EQ-5D-5L VAS score at baseline and at each measurement timepoint for durvalumab monotherapy and placebo (FAS)

Timepoint	Durvalumab (N=264)			Placebo (N=266)		
	n	Mean	SD	n	Mean	SD
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 128	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 144	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 152	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 160	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 168	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 176	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5L, EuroQoL-five dimensions-five levels; FAS, full analysis set; N/n, number of patients; SD, standard deviation; VAS, visual analogue score.
Source: CSR Appendix, Table 14.2.13.2.

A17. The ADRIATIC trial only included people with LS-SCLC whose disease had not progressed after cCRT. Is it expected that the clinical efficacy of durvalumab in people whose disease has not progressed after sCRT will be the same or different to that in people whose disease has not progressed after cCRT? Please provide the rationale for your answer.

Company response

The 2025 National Comprehensive Cancer Network (NCCN) Guidelines recommend patients with good PS (0–2) receive cCRT, and those with poor PS (3–4) receive either cCRT or sCRT (12). Treatment with cCRT is associated with improved survival and better disease control compared with sCRT, and is recognised as the preferred treatment strategy for stage III, unresectable NSCLC (4). Despite this, many patients receive sCRT in real-world clinical practice, with rates of sCRT use being higher across Europe than other regions (4). Among patients with LS-SCLC who receive CRT with curative-intent, there is a high risk of disease relapse, with the majority of patients (75%) with locally advanced disease experiencing disease recurrence within two years of treatment (13). As patients with LS-SCLC have a poor prognosis, with median OS of 2–3 years, estimated 5-year OS rate of 29–34%, and median PFS of 13.5–15.5 months with current treatment, there is a substantial unmet need for new therapies that extend OS and prolong disease progression.

ADRIATIC has demonstrated that consolidation durvalumab significantly improved both OS and PFS in patients with LS-SCLC who have not progressed following cCRT. These results support the addition of consolidation durvalumab as the first systemic therapeutic option to be added to the treatment paradigm for patients with LS-SCLC in nearly four decades. Results from ADRIATIC have led to the inclusion of consolidation durvalumab after completion of cCRT in both the NCCN and ASCO Guidelines (6, 12). Furthermore, the ASCO Guidelines add that patients with LS-SCLC and ECOG PS 3–4 due to SCLC who have been treated with sCRT may also be offered consolidation durvalumab for up to 2 years if there are no other contraindications to immunotherapy and there is an improvement in their PS following initial sCRT (6).

Furthermore, following landmark positive findings from the PACIFIC study, which evaluated consolidation durvalumab following cCRT in patients with unresectable Stage III NSCLC, results from PACIFIC-6 and PACIFIC-R, provide further data to support the benefits of consolidation durvalumab in patients with unresectable NSCLC who received sCRT. Expert clinical opinion confirmed that patients who receive sCRT for LS-SCLC are expected to benefit from treatment with durvalumab (3), with precedent from the PACIFIC-6 study where durvalumab demonstrated encouraging efficacy in NSCLC patients following sCRT (4). In PACIFIC-6, treatment with durvalumab resulted in a median PFS of 10.9 months (95% CI: 7.3, 15.6), and 12-month OS and PFS rates of 84.1% and 49.6%, respectively (4). These survival rates are comparable with those observed for the durvalumab arm of PACIFIC (12-mo PFS: 55.7%; 12-mo OS: 83.1%) and higher than those observed for the placebo arm (12-mo PFS: 34.5%; 12-mo OS: 74.6%) (4, 5). In an analysis of PACIFIC-R that included 163 (14.1%) patients who had received prior sCRT, median PFS (mPFS) in the FAS was 24.1 months (95% CI: 20.2, 27.8), with similar mPFS reported in patients who received prior cCRT and sCRT (cCRT mPFS: 25.6 months; 95%CI: 20.7, 31.1 vs sCRT mPFS: 23.2 months; 95%CI: 16.9-28.8). In the FAS, median OS was not reached (95% CI: 46.3, NR), 3-year OS (OS36) was 63.2% (95% CI: 60.3, 65.9), and the 3-year OS rate in the subgroups of patients with prior cCRT and sCRT was comparable (cCRT OS36: 64.8%; 95% CI: 61.5, 67.9 vs sCRT OS36: 57.9%; 95% CI: 49.8, 65.2) (14).

As both ADRIATIC and PACIFIC evaluate consolidation durvalumab in post-cCRT settings, promising efficacy results from both PACIFIC-6 and PACIFIC-R may potentially be extrapolated to support the use of consolidation durvalumab in patients with LS-SCLC following sCRT.

A18. Section B.2.5 of the CS states that a “a summary of the quality assessment results for ADRIATIC is provided in Table 15” and that “a complete quality assessment of ADRIATIC is provided in Appendix D”. However, Appendix D.3 says “A full quality assessment of the ADRIATIC trial is provided in Section B.2.5 of Document B”.

a. Please specify which of these two locations is meant to contain the complete assessment.

Company response

The complete quality assessment results for ADRIATIC are provided in Section B.2.5, Table 15, of the CS, with additional supporting information provided in Appendix D.3.

We also note that Appendix D.3 states that the Cochrane risk-of-bias (ROB) 2 was used. However, critical appraisal results from ROB 2 are not provided in Appendix D or CS Document B.

b. Please can you provide this.

Company response

Quality assessment was only performed on full text publications using the Cochrane risk-of-bias (ROB) 2 tool. At the time of the SLR searches, the only publication identified for the ADRIATIC trial was an abstract for data presented at the ASCO Annual Meeting, 2024 (15), with data extractions for ADRIATIC limited to the information provided in the congress abstract, as per the SLR protocol. Further information on the ADRIATIC trial was subsequently published in a full journal article (Cheng, 2024), included in the CS (16); however, as this was published after the time of the SLR electronic searches it was not subject to quality assessment via the Cochrane ROB 2 tool.

Quality assessment for full text publications identified by the SLR using the ROB 2 tool is presented in Table 6.

Table 6: Quality assessment of full text publications – Cochrane risk-of-bias (ROB) 2 checklist

Item	Faivre-Finn et al. 2017	Bogart et al. 2023	Wang et al. 2023	Spiro et al. 2006	Han et al. 2008	Sculier et al. 2008	Sundstrom et al. 2002	Sekine et al. 2017	Schild et al. 2004	Kubota et al. 2014	Hu et al. 2020	Zhao et al. 2020
Domain 1. Randomisation process												
1.1 Was the allocation sequence random?	[redacted]											
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	[redacted]											
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	[redacted]											
Domain 2. Deviations from intended interventions												
2.1 Did baseline differences between intervention groups suggest a problem with the randomisation process?	[redacted]											
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	[redacted]											

Item	Faivre-Finn et al. 2017	Bogart et al. 2023	Wang et al. 2023	Spiro et al. 2006	Han et al. 2008	Sculier et al. 2008	Sundstrom et al. 2002	Sekine et al. 2017	Schild et al. 2004	Kubota et al. 2014	Hu et al. 2020	Zhao et al. 2020
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Domain 3. Missing outcome data												

Item	Faivre-Finn et al. 2017	Bogart et al. 2023	Wang et al. 2023	Spiro et al. 2006	Han et al. 2008	Sculier et al. 2008	Sundstrom et al. 2002	Sekine et al. 2017	Schild et al. 2004	Kubota et al. 2014	Hu et al. 2020	Zhao et al. 2020
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Domain 4. Measurement of the outcome												
4.1 Was the method of measuring the outcome inappropriate?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Item	Faivre-Finn et al. 2017	Bogart et al. 2023	Wang et al. 2023	Spiro et al. 2006	Han et al. 2008	Sculier et al. 2008	Sundstrom et al. 2002	Sekine et al. 2017	Schild et al. 2004	Kubota et al. 2014	Hu et al. 2020	Zhao et al. 2020
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Domain 5. Selection of the reported result												

Item	Faivre-Finn et al. 2017	Bogart et al. 2023	Wang et al. 2023	Spiro et al. 2006	Han et al. 2008	Sculier et al. 2008	Sundstrom et al. 2002	Sekine et al. 2017	Schild et al. 2004	Kubota et al. 2014	Hu et al. 2020	Zhao et al. 2020
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis? Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.2... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.3... multiple eligible analyses of the data?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Domain 6. Overall bias												
Overall assessment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please note responses to each domain question are provided for both reviewers (reviewer 1 / reviewer 2).
Abbreviations: N, no; NA, not applicable/available; NI, no information; NR, not reported; PN, probably no; PY, probably yes; ROB, risk of bias; SC, come concerns; Y, yes.

Table 6 continued

Item	Gronberg et al. 2021	Peters et al. 2022	Qiu et al. 2021	Wang et al. 2023	McClay et al. 2005	Skarlos et al. 2001	Takada et al. 2002	Gronberg et al. 2016	Sun et al. 2013	Colaco et al. 2012	Blackstock et al. 2005
Domain 1. Randomisation process											
1.1 Was the allocation sequence random?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Domain 2. Deviations from intended interventions											
2.1 Did baseline differences between intervention groups suggest a problem with the randomisation process?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Item	Gronberg et al. 2021	Peters et al. 2022	Qiu et al. 2021	Wang et al. 2023	McClay et al. 2005	Skarlos et al. 2001	Takada et al. 2002	Gronberg et al. 2016	Sun et al. 2013	Colaco et al. 2012	Blackstock et al. 2005
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Domain 3. Missing outcome data											
3.1 Were data for this outcome available for all,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Item	Gronberg et al. 2021	Peters et al. 2022	Qiu et al. 2021	Wang et al. 2023	McClay et al. 2005	Skarlos et al. 2001	Takada et al. 2002	Gronberg et al. 2016	Sun et al. 2013	Colaco et al. 2012	Blackstock et al. 2005
or nearly all, participants randomised?											
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Domain 4. Measurement of the outcome											
4.1 Was the method of measuring the outcome inappropriate?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Item	Gronberg et al. 2021	Peters et al. 2022	Qiu et al. 2021	Wang et al. 2023	McClay et al. 2005	Skarlos et al. 2001	Takada et al. 2002	Gronberg et al. 2016	Sun et al. 2013	Colaco et al. 2012	Blackstock et al. 2005
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Domain 5. Selection of the reported result											
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis? Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Item	Gronberg et al. 2021	Peters et al. 2022	Qiu et al. 2021	Wang et al. 2023	McClay et al. 2005	Skarlos et al. 2001	Takada et al. 2002	Gronberg et al. 2016	Sun et al. 2013	Colaco et al. 2012	Blackstock et al. 2005
5.2... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.3... multiple eligible analyses of the data?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Domain 6. Overall bias											
Overall assessment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please note responses to each domain question are provided for both reviewers (reviewer 1 response/reviewer 2 response).
Abbreviations: N, no; NA, not applicable/available; NI, no information; NR, not reported; PN, probably no; PY, probably yes; ROB, risk of bias; SC, come concerns; Y, yes.

Section B: Clarification on cost-effectiveness data

Please note that after considering the EAG's clarification questions, specifically B3 and B4, some of the model inputs have been updated which impact the base case results. We would like to thank the EAG for bringing this to our attention and the full details of the changes made are provided in our responses.

The base case deterministic incremental cost-effectiveness ratio (ICER) has increased from £21,285 to £21,326 (Table 7).

Table 7: Updated base case

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Durvalumab	[redacted]	[redacted]	[redacted]	-	-	-	-	-
"Watch and wait"	£22,230.72	4.796	3.892	[redacted]	[redacted]	[redacted]	£21,326.45	£21,326.45

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Efficacy

B1. Priority question: The EAG are unable to verify the match between the splines (extrapolation curves) in the company submission graphs and those reported in Sheet!PSM Extrapolations within the Excel model (as shown in Tables 8-11 and Figures 1-4 below). We observe that, in the economic model, the splines present a steeper decline. Please explain these differences and update the model if required.

Table 8: Inconsistencies in the Estimated 10- and 15-year PFS for durvalumab spline models in the CS and the company model

Trial	CS Table 43		Company model	
	10-year PFS rate, %	15-year PFS rate, %	10-year PFS rate, %	15-year PFS rate, %
1-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]

Table 9: Inconsistencies in the Estimated 10- and 15-year PFS for placebo ("wait and watch") spline models in the CS and the company model

Trial	CS Table 47		Company model	
	10-year PFS rate, %	15-year PFS rate, %	10-year PFS rate, %	15-year PFS rate, %
1-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]

Table *10*: Inconsistencies in the Estimated 10- and 15-year OS for durvalumab spline models in the CS and the company model

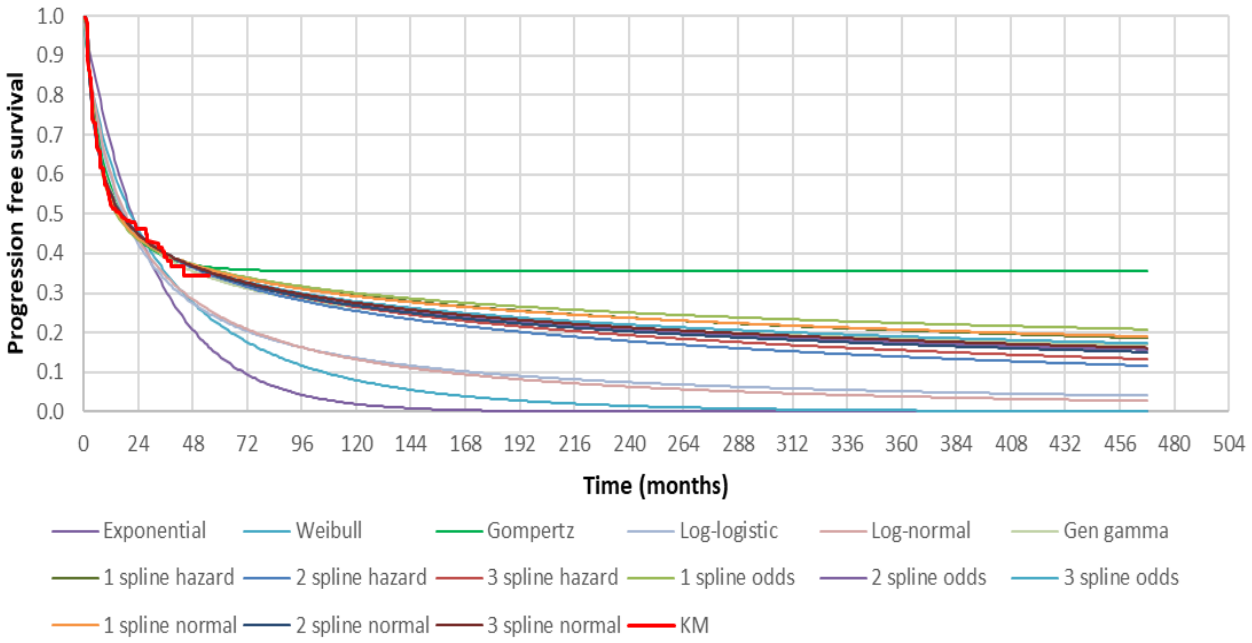
Trial	CS Table 51		Company model	
	10-year PFS rate, %	15-year PFS rate, %	10-year PFS rate, %	15-year PFS rate, %
1-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Inconsistencies in the Estimated 10- and 15-year OS for placebo ("Wait & watch") spline models in the CS and the company model

Trial	CS Table 55		Company model	
	10-year PFS rate, %	15-year PFS rate, %	10-year PFS rate, %	15-year PFS rate, %
1-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot spline normal	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1: Inconsistencies in the PFS for Durvalumab between CS and the economic model

CS Figure 21



Model figure from Sheet!PSM Extrapolations

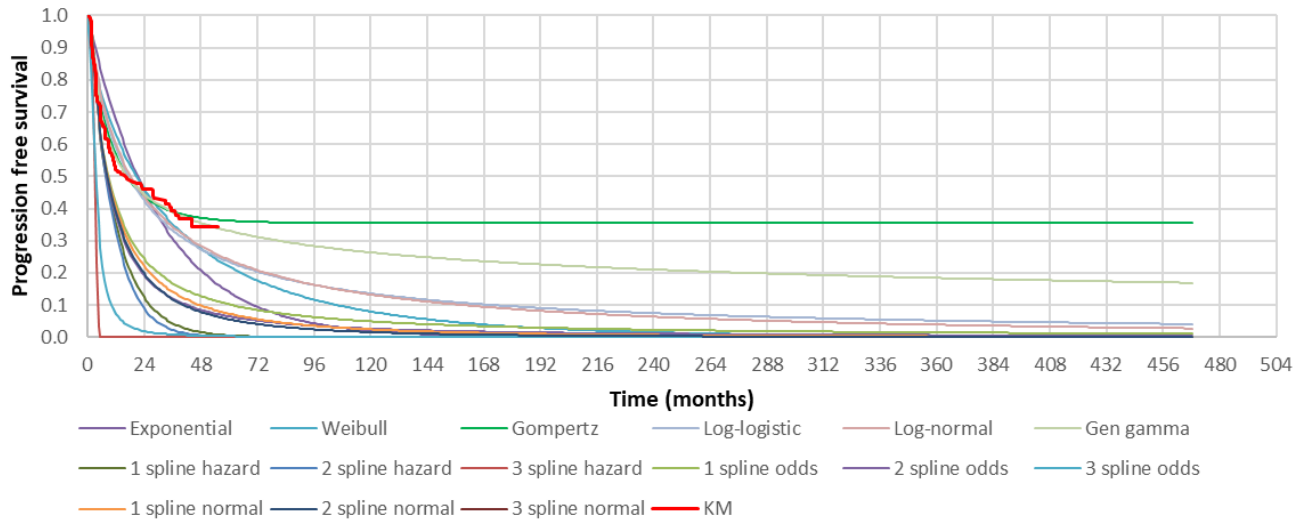
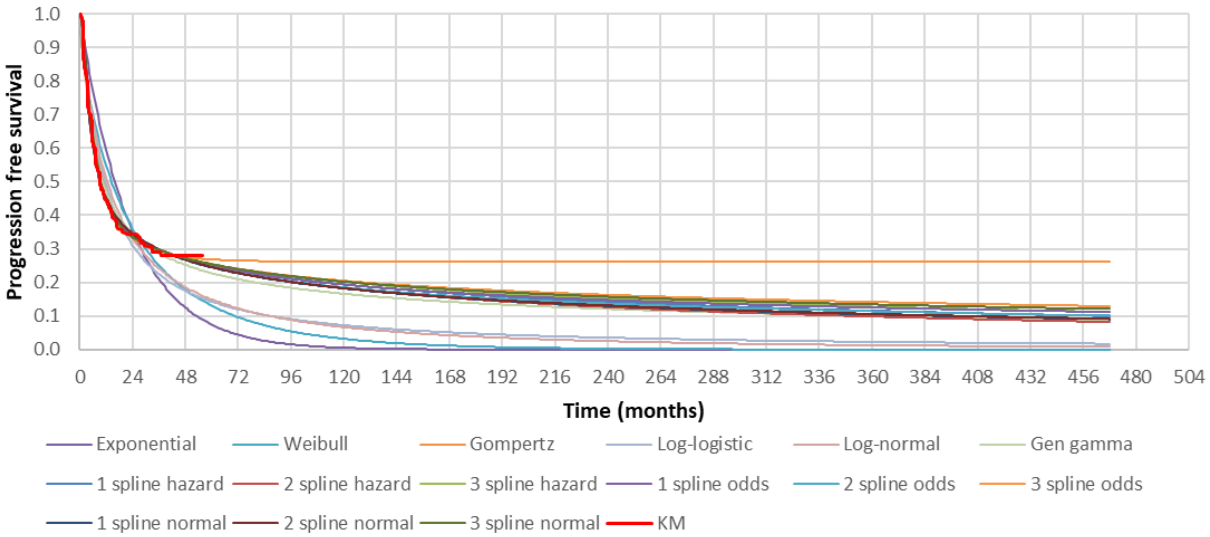


Figure 2: Inconsistencies in the PFS for "Wait & Watch" between CS and the economic model

CS Figure 26



Model figure from Sheet!PSM Extrapolations

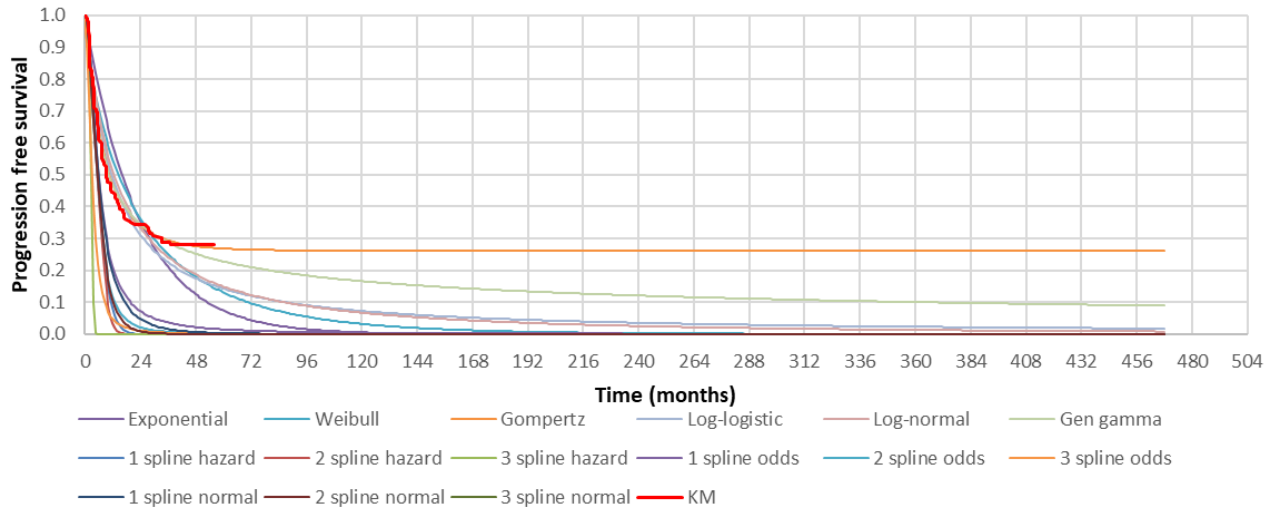
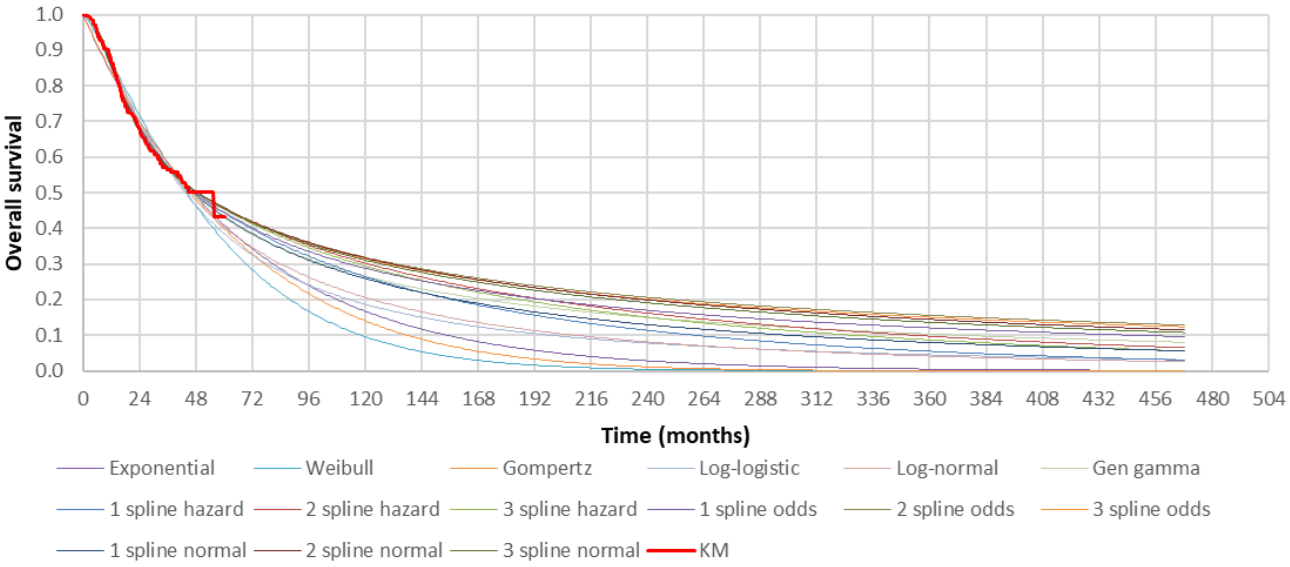


Figure 3: Inconsistencies in the OS for Durvalumab between CS and the economic model

CS Figure 29



Model figure from Sheet!PSM Extrapolations

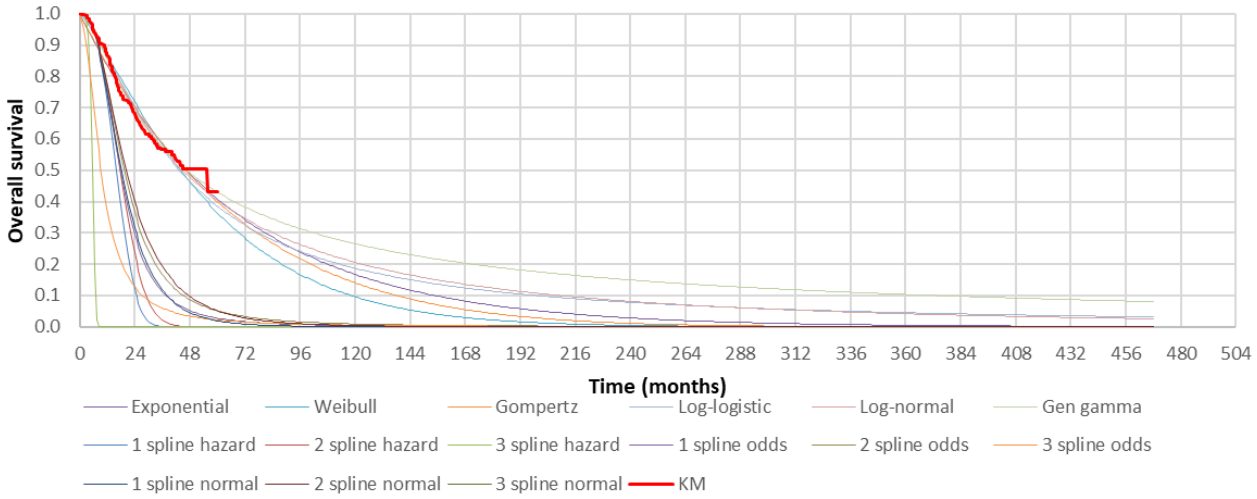
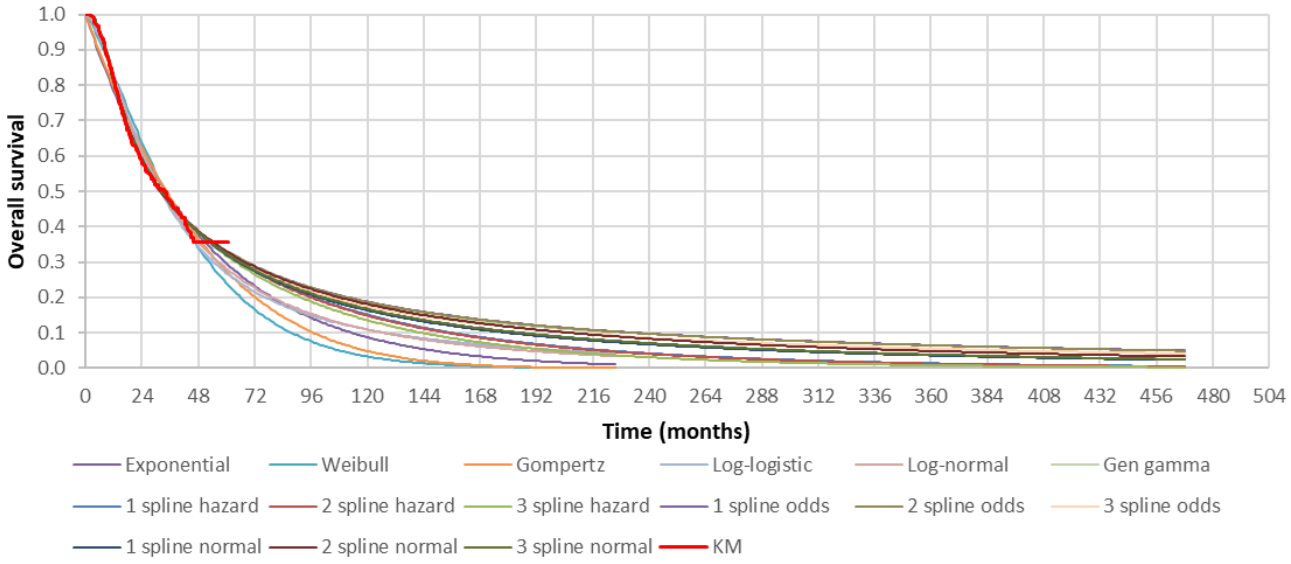
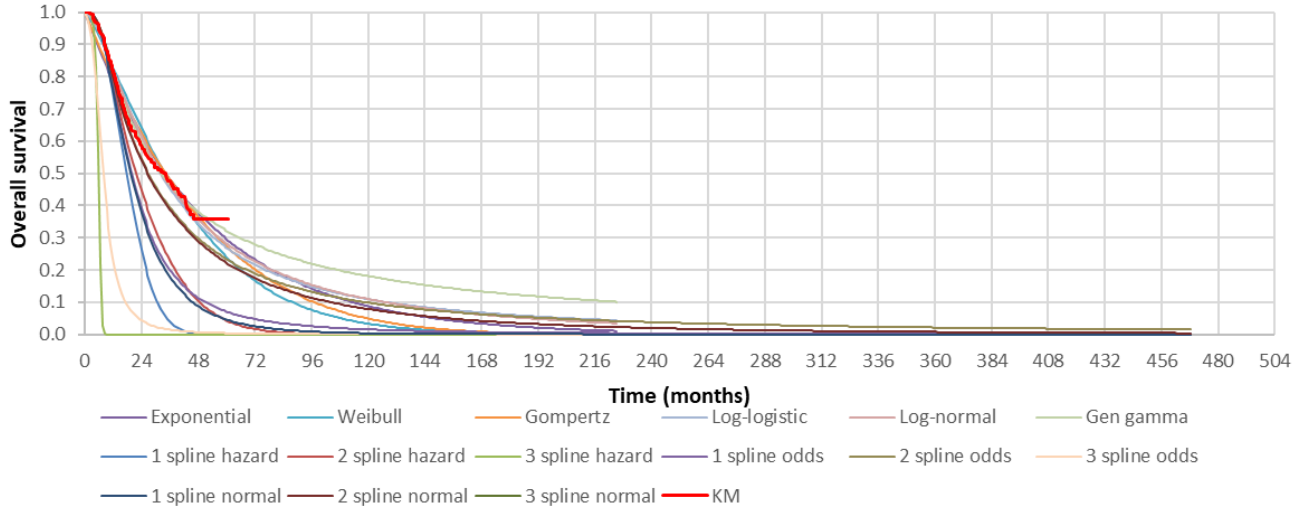


Figure 4: Inconsistencies in the OS for "Wait & Watch" between CS and the economic model

CS Figure 34



Model figure from Sheet!PSM Extrapolations



Company response

Thank you for bringing this to our attention. This issue arises because the graphs on the ‘PSM Extrapolations’ sheet are based on calculations from the ‘Extrapolations Data’ sheet. The formula used to calculate the extrapolations of the spline models on this sheet were incorrect. As a result, we have corrected the formulas in columns BQ:BY, CH:CP, DT:EB, and EK:ES.

Please note that these corrections do not impact the ICER, as the data on the ‘Extrapolations Data’ sheet were intended solely for graphical purposes. The model itself is informed by the extrapolations on the ‘Surv_calcs (PSM + TTD)’ sheet. The ‘Extrapolations Data’ has now been updated to align with the data on the ‘Surv_calcs (PSM + TTD)’ sheet.

B2. Priority question: Please provide the files mentioned in Chapter 14 ("Summary Tables and Figures, Listings and Narratives") of the "ADRIATIC Interim CSR" document, page 191. These files are the source of several parameters mentioned in the company submission (see clarification question B4) and the EAG would like to access the document to verify these parameters.

Company response

We confirm that CSR Appendix Chapter 14 has been included as part of the updated reference pack.

Costs

B3. Please clarify the choice of the carboplatin 150 mg/15ml price. The EAG have noticed that this drug's price varies from £56.92 (Teva UK Ltd) to £70.70 (Fresenius Kabi Ltd) in the BNF 2024. Additionally, the eMIT 2024 lists a price of £12.18 for carboplatin 150 mg/15 mL.

Company response

The price of £60.59 was selected as a conservative estimate, based on the average BNF price for carboplatin 150 mg/15ml, which ranges from £56.92 (Teva UK Ltd) to £70.70 (Fresenius Kabi Ltd), resulting in an average price of £63.81. Since none of the listed prices matched £63.81, the closest options were £60.59 and £65.83, with £60.59 chosen as a more conservative figure.

However, the eMIT price of £12.18 is the most appropriate for use in this context, as it reflects actual NHS procurement costs, which are more relevant for economic modelling in NICE HTA submissions. The model and ICER have been updated to reflect this price, resulting in an approximate change of £20/QALY in the ICER.

Model Inputs

B4. The EAG are unable to check the sources of several model input parameters reported in the CS and used in the company's model because the sources have not been provided with the CS or it is unclear where the parameters are in the original sources (please see Table 12 below). Please provide the sources and/or clarify how the values for the parameters were derived from the corresponding sources, by stating where they can be found in the source and, if applicable, the calculations needed to derive the model input value. Where required, please update the economic model.

Table 12: EAG queries on sources of model input parameters

Parameters	Location in company submission	Source	EAG Comment
Baseline characteristics – height and weight	CS Table 38	ADRIATIC CSR, Table 14.1.4 and 14.1.5 (Data on file) *Source not provided to EAG with CS*	Please provide the source
Cure fraction	CS 3.4.2	ADRIATIC Advisory Board meeting report *Complete source not provided to EAG with CS (please see clarification question C1)*	Please provide the source
Time to discontinuation	CS Figure 35	ADRIATIC CSR *CSR chapter 14 was not provided to the EAG with the CS (please see clarification question B2)*	Please provide the source and location
Estimated PFS for "watch and wait"	CS Table 46	Parametric extrapolation curves – specifically Gompertz curve	Please clarify how this extrapolation was derived
Health utility values	CS Tables 60 and 63	ADRIATIC CSR *CSR chapter 14 was not provided to the EAG with the CS (please see clarification question B2)*	Please provide the source
"Outpatient oncology visits" cost	CS Tables 67 and 68	NHS Reference costs 2022/23, service code 370	Please clarify how this cost was derived
ECG cost	CS Table 68	NHS Reference costs 2022/23, service code EY50Z	Please clarify how this cost was derived
Distribution of patients across	CS Table 70	ADRIATIC CSR, sections 10.6 and 14.1.23	Please provide the source and how

Parameters	Location in company submission	Source	EAG Comment
subsequent treatments		*CSR chapter 14 was not provided to the EAG with the CS (please see clarification question B2)*	this distribution was derived
Distribution of patients across subsequent treatments – clinical expert opinion	CS Table 71	ADRIATIC Advisory Board meeting report *Complete source not provided to EAG with CS (please see clarification question C1)*	Please provide the source

Abbreviations: CS, Comnpany Submission; CSR, clinical study report; EAG, External Assessment Group; ECG, electrocardiogram; NHS, National Health Service;

Company response

Please see the company's responses in Table 13.

Table 13: Compony response to EAG queries on model input parameter sources

Parameters	Company comments	Source
Baseline characteristics – height and weight	The baseline characteristics reported in Table 38 are provided in Table 14.1.4 and 14.1.5 of the **'D933QC00001 PFS_IA_OS_IA1 Tables and Figures'** document. This document has been added to the reference pack	'**D933QC00001 PFS_IA_OS_IA1 Tables and Figures'**
Cure fraction	The cure fraction is sourced from **ADRIATIC Advisory Board Meeting Report - Data on File.** The cure fraction is based the following statement which can be found under the 'Long-term remission' section: *"All advisors agreed that 100% is not clinically plausible with most suggesting 90–95%"*	**ADRIATIC Advisory Board Meeting Report - Data on File**
Time to discontinuation	Figure 35 in the CS is taken directly from the CEM and is based on the data in column B and C on the KM_data (PSM + TTD) sheet. Time to discontinuation is defined as the time from randomisation to the earlier of the date of permanent study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment was	N/A

Parameters	Company comments	Source
	censored based on the last recorded date on which the patient was known to be alive.	
Estimated PFS for "watch and wait"	The values for the 10- and 15-year PFS in the placebo arm were incorrectly entered in Table 46. The correct values for the Gompertz distribution are 24.71% and 21.74%, for the 10- and 15-year time points, respectively. These figures assume no cure point and that PFS is not constrained by OS.	N/A
Health utility values	The health state utility values presented in Tables 60 and 63 of the CS are derived from the mixed model point estimates provided in Table 59 of the CS. The equations used to calculate these utility values are detailed in Section B3.5.1 of the CS. The mixed model point estimates for repeated measures and the corresponding health state utility values are not included in the CSR. All relevant information concerning the health state utility values is comprehensively provided within the CS.	N/A
"Outpatient oncology visits" cost	Upon review, the outpatient oncology visits cost presented in Tables 67 and 68 of the CS are incorrect. The correct value is £199.08. This value is obtained using outpatient care costs from NHS reference costs 2022/23. It is calculated as the weighted average of WF01A-B under the service code 307 (medical oncology). This value has been corrected in the model (cells E66:E68 on the Country_data sheet). This amend changes the ICER by approximately £60/QALY.	NHS Reference costs 2022/23, 370 - medical oncology. Weighted average WF01A-B
ECG cost	Upon review, the ECG cost presented in Table 68 of the CS is incorrect. The correct value is £370.94 and reflects the total unit cost associated with EY50Z - Complex Echocardiogram. This value has been corrected in the model (cell E76 on the Country_data	NHS Reference costs 2022/23, service code EY50Z

Parameters	Company comments	Source
	sheet). This change has no impact on the ICER.	
Distribution of patients across subsequent treatments	Please see response below the table. Details on the distribution of patients across subsequent treatments is provided within the '**D933QC00001 PFS_IA_OS_IA1 Tables and Figures**' document, specifically **Table 14.1.20.**	**D933QC00001 PFS_IA_OS_IA1 Tables and Figures', specifically, Table 14.1.20**
Distribution of patients across subsequent treatments – clinical expert opinion	Clinical expert opinion on the distribution of patients across subsequent treatments within the **ADRIATIC Advisory Board Meeting Report - Data on File** document. Further rationale is provided within Document B of the CS.	**ADRIATIC Advisory Board Meeting Report - Data on File**

Abbreviations: CEM, cost-effectiveness model; CS, company submission; CSR, clinical study report; ECG, electrocardiogram; IA, interim analysis; KM, Kaplan-Meier; KOL, key opinion leader; N/A, not applicable/available; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; QALY, quality-adjusted life year; TTD, time to discontinuation.

Distribution of patients across subsequent treatments:

In the ADRIATIC trial, 126 patients in the durvalumab arm and 158 patients in the "watch and wait" arm experienced disease progression. [redacted] patients in the durvalumab arm and [redacted] in the "watch and wait" arm received a subsequent therapy. Therefore, the proportion of progressed patients that required subsequent therapy was [redacted]% ([redacted]/126) and [redacted]% ([redacted]/158) in the durvalumab and "watch and wait" arms, respectively. Subsequent therapies included in the model were those received by ≥5% of patients in either arm of ADRIATIC (Table 14).

Table 14: Subsequent chemotherapy received by ≥5% in either arm

Types of subsequent chemotherapy received by ≥5% in either arm	Durvalumab, n (%)	"Watch and wait", n (%)
Single agent chemotherapy	[redacted]	[redacted]
Platinum-doublet chemotherapy	[redacted]	[redacted]
IO + chemotherapy	[redacted]	[redacted]
Total	[redacted]	[redacted]

Abbreviations: IO, immune-oncology.

The proportion of patients that progressed and received a subsequent therapy were weighted by the distribution of patients across the therapies that were received by

≥5% of patients in either arm of ADRIATIC. Patients that progressed but did not receive a subsequent therapy were assumed to receive BSC (Table 15).

Table 15: Weighted distribution of patients across subsequent therapies

Subsequent treatment	Durvalumab	"Watch and wait"
BSC	[redacted]	[redacted]
Single agent chemotherapy	[redacted]	[redacted]
Platinum-doublet chemotherapy	[redacted]	[redacted]
IO + chemotherapy	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; IO, immune oncology.

The IO + chemotherapy regimens included in the model were: etoposide + cisplatin, etoposide + carboplatin, durvalumab + etoposide + cisplatin, durvalumab + etoposide + carboplatin, and atezolizumab + etoposide + carboplatin. All patients were assumed to receive etoposide, with either cisplatin or carboplatin, with or without durvalumab or atezolizumab.

The proportion of patients receiving cisplatin was based on the CASPIAN trial results as reported by Paz-Ares et al. (2019) (17), where 25% of patients in both arms received cisplatin. It was assumed that the remaining 75% would receive carboplatin.

The proportion of patients receiving durvalumab as part of their IO + chemotherapy regimen was based on the proportion receiving it as subsequent therapy in the ADRIATIC trial ([redacted] = [redacted]%). The remaining patients were assumed to receive atezolizumab (100% - [redacted]% = [redacted]).

The resulting distribution of patients across subsequent treatments based on the ADRIATIC trial is presented in Table 16.

Table 16: Distribution of patients across subsequent treatments

Treatment	Durvalumab	"Watch and wait"
BSC ("watch and wait")	[redacted]	[redacted]
Topotecan (oral)	[redacted]	[redacted]
Etoposide + cisplatin	[redacted]	[redacted]
Etoposide + carboplatin	[redacted]	[redacted]
Durvalumab + etoposide + cisplatin	[redacted]	[redacted]
Durvalumab + etoposide + carboplatin	[redacted]	[redacted]
Atezolizumab + etoposide + carboplatin	[redacted]	[redacted]

Abbreviations: BSC, best supportive care.

B5. Different input values are reported in the company submission and in the company's model for several input parameters (Table 17 below). Please clarify which of the values should be considered in the company's base case. Where required, please update the economic model.

Table 17: EAG queries on discrepancies between reported model input parameters

Parameters	Location in company submission	Location in company model	Source	Which value (company submission or model) should be considered in the company's base case?
Topotecan price	CS Appendix Table 20 (list Price = £7.50 per capsule)	Country_data!P133 (list price: £75.00)	BNF 2024 (list price, £75.00)	
Drug administration cost	CS Table 66, (refer to SB12Z – Outpatient (£217.22)	Costs_Tx!G32 (only refer to SB12Z (£411.99)	NHS National Reference Cost 2022/23, Total HRGs!C2368 (refer to SB12Z, Total Cost)	Is it the outpatient cost or the total cost?
CT scans Years 1, 2, 3-5	CS Table 67 (value = 2)	Cost_DM!F19:F21 (value = 6)	NICE TA578 CS Table 45 (page 169) (value = 6)	

Abbreviations: BNF, British National Formulary; CS, Company Submission; CT, computed tomography; EAG, External Assessment Group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

Company response

The topotecan price in Table 20 of the CS Appendix is incorrect, showing the unit price (£7.50 per capsule) instead of the correct list price of £75.00. Therefore, the value that should be considered in the base case is £75.00. The price is correct in the model.

The drug administration cost of £411.99 reflects the total cost. While the reference in Table 66 of the CS is incorrect, the value presented in the table and used in the model is accurate.

For CT scans, the correct number for Years 1, 2, and 3–5 is 6. The value of ‘2’ shown in Table 67 is incorrect; however, the values in the model are correct.

Economic Model

B6. The EAG observed a minor error in the AIC/BIC tables in the economic model. The formulas are shifted to the following cells: “Survival (PSM)!F24:I32, U24:X32, F76:I84, and U76:X84”. Please, update the model considering the correct references.

Company response

Thank you for identifying this, it has been corrected in the model and the model rankings reflect to those reported in Tables 41, 44, 49, and 52 the CS. This change has no impact on the ICER.

Treatment effect waning

B7. Priority Question: Treatment effect waning is not applied in the company's model. Please provide the following scenario analyses:

i) No treatment effect waning but treatment benefit capped at 5 years after diagnosis

ii) Treatment effect waning at 2, 5, 10 years

Company response

The company maintains that treatment effect waning should not be incorporated into the model. This position is substantiated by the points outlined below.

Firstly, there is no established or definitive guidance on how to best model treatment effect waning, and all proposed methods rely on strong, often speculative assumptions that lack robust support from clinical evidence. The EAG's proposal to cap treatment benefit at 5 years and apply treatment waning at 2, 5, and 10 years is arbitrary and lacks clinical validation. Such assumptions not only lack evidence but also fail to account for the unique characteristics of this patient population and treatment context.

Moreover, previous NICE appraisals demonstrate that treatment effect waning has not been considered in similar contexts. Specifically, in the appraisals for small-cell lung cancer (TA638 and TA184), treatment effect waning was not considered in the models. Additionally, in TA798, which evaluates durvalumab for the maintenance treatment of unresectable non-small-cell lung cancer (NSCLC), treatment effect waning was deemed implausible. This was explicitly supported by nine clinical experts who stated durvalumab's treatment effect would not diminish over a patient's lifetime. Their reasoning was that durvalumab is used in a setting where patients are already treated with curative intent. In this context, those who remain disease-free for 5 years are unlikely to experience disease progression, rendering any assumption of waning effect after this timepoint both unnecessary and clinically unsound. During the clinician advisory board for durvalumab for the treatment of LS-SCLC, held on 11th October 2024, clinicians confirmed that patients with LS-

SCLC who remain disease-free for 3–5 years after CRT treatment are typically considered functionally cured. Therefore, introducing treatment waning after this timepoint is not only inconsistent with methodology applied in previous NICE appraisals but is also regarded as clinically implausible.

Clinicians also validated the extrapolated survival outcomes from the ADRIATIC trial presented in the base case analysis. Based on the 5-year OS and PFS Kaplan-Meier data in the intervention arm (50.32%), clinicians indicated that they would expect between 27% and 33% of patients to be alive at 10 years and 19% to 27% to be alive at 15 years. Introducing a treatment benefit cap or applying a treatment waning assumption at any point would distort these survival projections, leading to a misalignment between the model outcomes and clinically expected survival trajectories.

In summary, incorporating treatment effect waning into the model is not supported by clinical evidence or expert consensus and would lead to a misrepresentation of the treatment’s long-term efficacy and patient outcomes.

Section C: Textual clarification and additional points

C1. Priority question: A Word document entitled ‘ADRIATIC Advisory Board Meeting Report – Data on File (1)’ was supplied with the CS, but this document is blank. Please provide the complete version.

Please also supply a copy of CS reference 17 [‘AstraZeneca. Data on file. AstraZeneca UK MC: KEE input (advisory board) on limited-stage small cell lung cancer (durvalumab). ID: REF – 254603. November 2024’], if this is not the same reference as ‘ADRIATIC Advisory Board Meeting Report – Data on File (1)’.

Company response

We confirm that these are the same reference, and we have provided a new complete version.

References

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15. Spigel DR, Cheng Y, Cho BC, Laktionov KK, Fang J, Chen Y, 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.

16. Cheng Y, Spigel DR, Cho BC, Laktionov KK, Fang J, Chen Y, et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. New England Journal of Medicine. 2024.
17. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, 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.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Patient Organisation Submission

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of small cell lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	**RCLCF has received the following funding :** - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1820 Advisory board Honoraria) - Roche (1 year funding of GLCC project; £10,000 for Lung cancer Awareness Month initiative) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Novocure (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project) - Astra Zeneca (£30,000 for 1 year funding of GLCC project; £500 for Meeting Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium)

If so, please state the name of the company, amount, and purpose of funding.	- Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker honorarium) - Regeneron (£30,000 for 1 year funding of GLCC project) - Gilead (£30,000 for 1 year funding of GLCC project; £460 speaker honorarium) - Merck (£30,000 for 1 year funding of GLCC project) - J &J (£20,000 for Lung Cancer Awareness Month initiative)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	SCLC is widely accepted to be around 10 to 15% of lung cancer cases. A diagnosis of SCLC is devastating. Small cell is a particularly aggressive type of cancer, patients often being symptomatic at presentation. This is a rapidly progressive disease and as such, patients should be assessed quickly and systemic anticancer treatment started quickly. At diagnosis, SCLC is generally categorised in to limited or extensive disease. The overall 5 year survival for SCLC (limited and extensive stage disease) is only about 5%. For patient with limited stage SCLC, the 5 year survival is thought to range from about 15-30%. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There have been relative few developments in the treatment of small cell lung cancer in decades. As such, there is a huge need for therapies with better outcomes than currently available. Patients with limited stage SCLC at diagnosis, are treated with a combination of chemotherapy and radiotherapy (chemoradiation).
8. Is there an unmet need for patients with this condition?	yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We do not have any data, additional to that which is publicly available. In the phase 3 ADRIATIC study of patients with limited stage small cell lung cancer, who do not have disease progression after platinum based chemoradiation, durvalumab or placebo, was given every 4 weeks for up to 24 months. Results show that Durvalumab led to significantly longer overall survival than placebo [median 55.9 months, versus 33.4 months], as well as to significantly longer progressional free survival [median of 16.6 months, versus 9.2 months].

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with the side effects, associated with Durvalumab therapy.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• SCLC treatment has seen few advances. • The outcome from current standard treatment, for this patient group, is poor. There is massive unmet need. • Durvalumab in this indication, is shown to result in significantly longer overall survival and progression free survival, in patients with limited stage SCLC.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Professional organisation submission

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

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

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

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	Association of Respiratory Nurses
3. Job title or position	Lung Cancer Specialist Nurse
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of Respiratory Nurses (ARNS) was established in 1997 as a nursing forum to champion the specialty respiratory nursing community, promote excellence in practice, and influence respiratory health policy. ARNS also works to influence the direction of respiratory nursing care.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	no
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Stop further progression of disease, improve functional status, improve quality of life, improve symptoms
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction of disease burden, no further progression of disease following commencement of treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, lung cancer remains difficult to treat. All avenues of second line treatments should be explored to improve patient survival. Little in the way of maintenance therapy available for small cell lung cancer currently.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Immunotherapy in combination with chemotherapy for advanced disease, there is no maintenance treatment following chemo irradiation currently.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NG122, Atezolizumab with carboplatin and etopside 638

9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes currently well defined pathway for first line treatment with chemoradiation. Some variation in treatment for second line depending on previous experience of oncologist.
9c. What impact would the technology have on the current pathway of care?	Would improve the pathway and give patients more treatment options and a better chance of long term survival.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will progress the treatment options but will be given in the same way Durvalumab is currently administered for NSCLC
10a. How does healthcare resource use differ between the technology and current care?	Further doses of treatment would be given.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics only.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of oncology nurses to administer the drug. Education to oncologists and pharmacists to understand the regime and protocol. Resource in pharmacy to produce the correct drug mix for patients.
11. Do you expect the technology to provide clinically meaningful	Yes

benefits compared with current care?	
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	May depend on performance status and comorbidities.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use	Should be comparable to administering current medications, will involve additional trips to hospital and additional appts in chemo clinics.

or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	PDL1 expression of 1% or more and those patients whose disease has not progressed following platium-based chemoradiation therapy.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Progression free survival may also bring increased quality of life.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	yes
16a. Is the technology a 'step-change' in the management of the condition?	yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, patients with limited stage SCLC currently have no maintenance option following radical treatment.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Immunotherapy can cause inflammatory side effects which can lead to hospital admission and need treatment with steroids.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Life expectancy, progression free survival. Quality of life. Yes
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not currently used so unable to answer

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. How do data on real-world experience compare with the trial data?	n/a

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
21b. Consider whether these issues are different from issues with current care and why.	no

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a need for maintenance treatment options for patients with SCLC who have had radical treatment. • Durvalumab is successfully used in maintenance of NSCLC after chemoradiation, should be trialled in SCLC. • • •

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Professional organisation submission

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	**British Thoracic Oncology Group**
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	**An employee or representative of a healthcare professional organisation that represents clinicians? Yes** **A specialist in the treatment of people with this condition? Yes** **A specialist in the clinical evidence base for this condition or technology? No** **Other (please specify):**
5a. Brief description of the organisation (including who funds it).	**The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK. Funded by sponsorship from the annual conference and sponsorship**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	**Yes** **Platinum sponsorship BTOG 2024, £30,000 + VAT**
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	**Increase the chances of cure by reducing chances of disease recurrence.** **Increase survival by reducing the chances of, or delaying, disease recurrence.**
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	**Reduction in tumour size by 30% or more as determined by cross-sectional imaging.** **Or** **Reduction in metabolic activity (SUVmax) of an FDG-avid malignant lesion on PET scan by 30% or more.** **Or** **Statistically significant improvement in symptoms as documented on a recognised lung cancer specific, or general oncology, Quality of Life scale**
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**Yes: the prognosis of limited stage (LS) small cell lung cancer (SCLC) remains very poor, with a 5-year overall survival of just 30%.** **There has been little improvement in this from novel therapies for decades.**

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	**Standard of care is platinum-based chemotherapy (most likely etoposide and carboplatin, but also etoposide and cisplatin) with concurrent thoracic radiotherapy (twice daily, 45Gy in 30 fractions, over 15 days). Once daily thoracic radiotherapy is also used in some centres.**

	Prophylactic cranial irradiation (PCI) would be undertaken in those without contra-indications.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	**UK: NICE guidelines (NG122)** **Europe: ESMO Guidelines on SCLC (2021)** **USA: NCCN Guidelines for SCLC (2024)**
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	**Yes** **Only differences would be choice of platinum (cisplatin vs carboplatin) and radiotherapy regimen (OD vs. BD).**
9c. What impact would the technology have on the current pathway of care?	**Initial diagnosis pathway and treatment (chemoradiotherapy) will not change**
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	**No, see above**
10a. How does healthcare resource use differ between the technology and current care?	**It will add a 2 year course of immunotherapy to the end of the treatment pathway, with a treatment every 4 weeks throughout this period.** **Each treatment will involve outpatient oncology appointment, blood tests, and day-case immunotherapy. These will all be in addition to current care.**
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	**Specialist oncology outpatient clinics.**

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	**None. All facilities and equipment already in place.**
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	**Yes** **In the phase 3 ADRIATIC trial, adjuvant Durvalumab when compared to placebo increased median overall survival (mOS) from 33.4m to 55.9m, and increased median progression free survival (mPFS) from 9.2m to 16.6m.** **These results are both clinically and statistically significant. This is the first increase in OS as a result of change in systemic cancer therapy for many years.**
11a. Do you expect the technology to increase length of life more than current care?	**Yes, as evidenced by OS data above (Q11)**
11b. Do you expect the technology to increase health-related quality of life more than current care?	**No: there is no evidence for an improvement in quality of life (QoL). However Patient Reported Outcomes (PROs) for ADRIATIC (presented at World Conference on Lung Cancer 2024) showed no clinically meaningful worsening in QoL with Durvalumab compared to placebo.**
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**Only for patients with LS-SCLC, who have completed chemoradiotherapy, and in whom there is no disease progression, and in whom good performance status is maintained.**

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals	**Adjuvant Durvalumab will be more difficult for both patients and healthcare professionals, compared to current care, because current cause is no treatment after chemoradiotherapy.**

than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	**We know from other Durvalumab adjuvant protocols (PACIFIC) that treatment is usually straightforward. Grade 3-4 pneumonitis rates are low (3.1%) and only slightly higher than placebo (2.6%). Treatment discontinuation rates are 16.4% indicating, however, that side effects do occur and treatment will be more difficult than having no adjuvant immunotherapy.** **No regular concomitant therapies or additional tests are needed.**
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	**Treatment would only commence once a patient with confirmed LS-SCLC had completed chemoradiotherapy, progression had been excluded, and reasonable performance status maintained.** **Treatment would continue so long as there is clinical benefit (as assessed by radiological response), or until unacceptable toxicity develops.**
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	**No**
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	**Yes. This is the first adjuvant immunotherapy in LS-SCLC that has been shown to improve survival. This is the first increase in OS in LS-SCLC for many years. It is truly innovative.**

16a. Is the technology a 'step-change' in the management of the condition?	**Yes, see Q16**
16b. Does the use of the technology address any particular unmet need of the patient population?	**Yes: the poor outcomes of patient treated for LS-SCLC.**
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	**See Q11b: PROs demonstrate no meaningful impact on QoL with adjuvant Durvalumab.**

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	**Yes. Beyond the usual caveats of how well any clinical trial represents the Real World clinical experience, the trial data reflects current UK practice**
18a. If not, how could the results be extrapolated to the UK setting?	**N/A**
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	**Overall Survival (yes)** **Progression Free Survival (yes)** **Safety (yes)** **Quality of life (yes)**

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	**The use of median Progression Free Survival has long been used as a surrogate for Overall Survival. The use here is in keeping with that approach, and is affected by the same advantages and limitations as other studies.** **Note that Overall Survival improvement is also shown here, though.**
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	**No**
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	**No**
20. How do data on real-world experience compare with the trial data?	**There is no significant real-world data experience yet published to compare with trial data.**

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	**No**
21b. Consider whether these issues are different from issues with current care and why.	**N/A**

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• LS-SCLC has a poor prognosis: treatment and prognosis has advanced little for years. • Adjuvant Durvalumab improves mOS and mPFS with a highly clinically and statistically significant improvement. • Adjuvant Durvalumab will result increased healthcare resource use, being a 2 year course • Adjuvant Durvalumab is well tolerated, with known and manageable side effects • Adjuvant Durvalumab does not impact on QoL, as assessed by PROs

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Single Technology Appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Clinical expert statement

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

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **7 April 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Part 1: Treating limited-stage small-cell lung cancer after chemoradiation and current treatment options

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

1. Your name	Farah Louise Lim
2. Name of organisation	St Bartholomew's NHS trust
3. Job title or position	Consultant in medical oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with this condition? ☐ A specialist in the clinical evidence base for this condition or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE
8. What is the main aim of treatment for the condition? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve progression free survival, overall survival whilst maintaining quality of life.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement of clinical symptoms e.g. pain, shortness of breath A delay in tumour progression for a number of months.
10. In your view, is there an unmet need for new treatments for the condition?	The majority of patients with limited small cell lung cancer progress within 2 years and die within 5 years of having treatment, there have been no advances in the group of patients for over 20 years. We now have a chance to improve this.
11. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients in this group are treated with concurrent thoracic chemoradiotherapy with the use of platinum-etoposide and early thoracic radiotherapy, followed by prophylactic cranial irradiation when indicated. There are numerous guidelines – The National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO). The current pathway as it stands is well defined and in view of the fact that there have been limited advances in this field makes it pretty standard across professionals who treat this condition. Certainly, with the data from ADRIATIC showing a significantly improved overall survival and progression free survival. Hazard ratio for overall survival - 0.73. There is going to be shift of diagnosing patients with limited small cell cancer earlier, and incorporating immunotherapy earlier in their treatment paradigm, (starting 4-8 weeks after CRT) and potentially reducing the need for prophylactic cranial irradiation with surveillance MRI brain scanning whilst on immunotherapy instead.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Durvalumab is currently NICE approved in locally advanced unresectable NSCLC whose disease has not progressed after concurrent platinum based chemoradiation, and so this would be a similar indication for limited stage small cell lung cancer for which there have been no advances.

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Additional healthcare resources will be needed to fund the addition of maintenance durvalumab in the current treatment care, however in my opinion because these patients will take longer to progress and indeed live longer off treatment, this will have a knock-on effect on the palliative treatments (chemotherapy /radiotherapy) and bed cost that is required to treat these patients on relapse and to improve their quality of life. In this way we are ensuring we keep our patients well for as long as possible and in the fittest state possible. Because we already give immunotherapy to treat lung cancer, and we already give maintenance durvalumab for locally advanced NSCLC, I do not this additional step in the treatment of limited SCLC requires more training or equipment.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, I do Currently the majority of limited stage small cell lung cancer patients progress with 2 years of starting treatment, and once they develop extensive stage small cell lung cancer, their treatment options are also limited and they progress quite rapidly. In my opinion, if we can halt the progression of the disease early and maintain the fitness of these patients which is what the data from Adriatic is showing, we will not only help these patients live longer, but we will also be improving their quality of life by reducing their disease burden for a longer period of time.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I think as with everything, there are always exceptions, and whilst I would hope that the majority of patients who undergo chemo- Rt, would be fit enough (seeing as they were fit enough to undergo CRT), there might be a few who are not fit enough or certainly have extensive autoimmune conditions that would negate the giving of durvalumab, although I would expect this number of patients to be small.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	I think the main difficulty would be for the patients as they would need to come to hospital every 4 weeks for treatment and be seen and have bloods each time. However, I think that as long as you had an open discussion with the patient about why you were offering the new treatment and the data that showed the improvement in PFS and OS. I suspect most patients would be willing to have treatment, but I think having the discussion is important.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I think the main rules would be based on clinical assessment to ensure fitness before and during maintenance durvalumab, but also the patients would need a scan on completion of chemo/RT to ensure there was no progression, although this would be standard of care anyway and subsequent follow up scans with or without maintenance durvalumab would also be standard of care. Toxicity assessment with durvalumab would be per our hospital guidelines as with our other immunotherapy agents.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No. Yes, I think all the instruments used currently capture the benefits
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, I do in terms of improving the overall progression free survival and overall survival for patients with limited stage small cell lung cancer. This is a group of patients who have had no advances in their cancer care for over 20 years, it is the first step in changing the way we treat small cell lung cancer in the future, and addresses a huge unmet need in the group of patients.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The majority of patients who receive durvalumab in the current approved treatment settings have few side effects, most are grade 1 toxicities and certainly we are adept at knowing how to manage the more severe side effects with early recognition being key to managing the adverse effects.

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, apart from the use of topotecan on progression in the study, which would normally be the practice in the UK as well, but we currently have a shortage of the drug, hence would give alternative forms of treatment, which substantiates the point of having a strong treatment in the front line setting to prevent early progression. Overall survival, progression free survival, adverse events – yes NO
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO
22. How do data on real-world experience compare with the trial data?	Difficult to know sometimes, the patients who take part in clinical trials on balance are fitter and more motivated and so you have to take into account, although from my experience of having run the initial clinicals with immunotherapy and takin it into standard care, there wasn't ultimately that much difference in the patient population.
23. This appraisal covers both concurrent chemoradiotherapy (cCRT) and sequential chemoradiotherapy (sCRT) populations. However, the key trial of durvalumab for this condition (ADRIATIC) only includes people who have had cCRT. • What proportions of people with limited-stage small cell lung cancer having chemoradiotherapy would have cCRT and sCRT? • Would data from ADRIATIC be generalisable to the sCRT population? • Are you aware of any relevant data in the sCRT population?	In my institution, the majority of patients receive concurrent RT (80-90%). This may differ in other institutions. I do believe that the data would be generalisable to the sCRT population. No, I'm not

24. What proportion of people with the condition would be expected to survive long-term on current care? Is there a time point at which people could be considered to be cured?	Around 50% of patients with limited stage small cell lung caner are alive at 2 years, and only 20- 25% of patients survive till 5 years after current care. We normally say that if patients survive for more than 5 years after their initial treatment, it is rare for the cancer to come back, although in my experience I have seen a proportion of patients whose cancer comes back after 5 years.
25. How long would the treatment effect of durvalumab be expected to continue for after stopping treatment?	This differs for patients, but certainly in the patients with limited NSCLC, we are seeing the effect persist for years and that may well be the case for this patient group as well.
26. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	NO

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

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

This technology addresses an unmet need in limited stage small cell lung cancer.

This technology improves progression free survival and overall survival.

The adverse safety profile of this technology is well tolerated and well known to clinicians.

This technology will benefit all patient sub- groups.

This technology establishes a new standard of care of limited small cell lung cancer.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

Clinical expert statement

Information on completing this form

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

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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

Part 1: Treating limited-stage small-cell lung cancer after chemoradiation and current treatment options

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

1. Your name	Dr Tom Newsom-Davis
2. Name of organisation	British Thoracic Oncology Group / Chelsea and Westminster Hospital
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with this condition? ☒ A specialist in the clinical evidence base for this condition or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for the condition? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Answers as per Nominating Organisation (BTOG) submission, with no changes

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Answers as per Nominating Organisation (BTOG) submission, with no changes
10. In your view, is there an unmet need for new treatments for the condition?	Answers as per Nominating Organisation (BTOG) submission, with no changes
11. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Answers as per Nominating Organisation (BTOG) submission, with no changes
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Answers as per Nominating Organisation (BTOG) submission, with no changes
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care?	In addition to the answers included in the Nominating Organisation (BTOG) submission, I would like to add the following:

• Do you expect the technology to increase health-related quality of life more than current care? Answers as per Nominating Organisation (BTOG) submission, with no changes	An update of the ADRIATIC data presented at the European Lung Cancer Congress (Paris, March 2025) showed that median time to both intra-thoracic and extra-thoracic relapse were longer in the Durvalumab arm (60.0m, 70.9m respectively) than the placebo arm (52.3m, 56.5m respectively). Furthermore, median time to brain/CNS progression was longer (84.0 vs. 72.9m, HR 0.64).
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Answers as per Nominating Organisation (BTOG) submission, with no changes
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Answers as per Nominating Organisation (BTOG) submission, with no changes
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Answers as per Nominating Organisation (BTOG) submission, with no changes
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Answers as per Nominating Organisation (BTOG) submission, with no changes

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Answers as per Nominating Organisation (BTOG) submission, with no changes
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Answers as per Nominating Organisation (BTOG) submission, with no changes
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Answers as per Nominating Organisation (BTOG) submission, with no changes
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Answers as per Nominating Organisation (BTOG) submission, with no changes
22. How do data on real-world experience compare with the trial data?	Answers as per Nominating Organisation (BTOG) submission, with no changes
23. This appraisal covers both concurrent chemoradiotherapy (cCRT) and sequential chemoradiotherapy (sCRT) populations. However, the	The majority of patients receiving chemoradiotherapy for LS-SCLC in the UK received cCRT as opposed to sSCRT. This has not been reported in National Lung Cancer Audits (NLCA) to date. Studies looking at real-world treatment

key trial of durvalumab for this condition (ADRIATIC) only includes people who have had cCRT. • What proportions of people with limited-stage small cell lung cancer having chemoradiotherapy would have cCRT and sCRT? • Would data from ADRIATIC be generalisable to the sCRT population? • Are you aware of any relevant data in the sCRT population?	patterns across European countries, including UK, found similar rates of cCRT vs. sCRT. In the absence of data suggesting otherwise, the results of ADRIATIC are generalizable to the sCRT population. Looking at Durvalumab following cCRT vs. sSRT in NSCLC (as opposed to SCLC), we still have no 2-arm randomised data to determine whether there is a difference in efficacy of immunotherapy. I am not aware of any data of adjuvant Durvalumab following sCRT.
24. What proportion of people with the condition would be expected to survive long-term on current care? Is there a time point at which people could be considered to be cured?	Long term survival (>5yrs) in the real-world setting is 20-30%. I would consider a patient cured from LS-SCLC if they had reached 5 years without relapse. It might also be possible to conclude that, if a patient has reach 4 years without relapse, they are probably cured.
25. How long would the treatment effect of durvalumab be expected to continue for after stopping treatment?	I am not able to give an accurate estimate of this. It is likely measured in weeks, perhaps up to 2-3 months, but there is no data to reliably inform on a more precise answer.
26. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Answers as per Nominating Organisation (BTOG) submission, with no changes

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

Part 2: Key messages

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

LS-SCLC has a poor prognosis: treatment and prognosis has advanced little for years

Adjuvant Durvalumab improves mOS and mPFS with a highly clinically and statistically significant improvement

Adjuvant Durvalumab will result increased healthcare resource use, being a 2 year course

Adjuvant Durvalumab is well tolerated, with known and manageable, modest, side effects

Adjuvant Durvalumab does not impact on QoL, as assessed by PROs

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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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Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Declared competing interests of the authors and advisors

The authors, Dr Dorey and Dr Bhosle report none. Dr Dorey reports using durvalumab within the company's early access programme for limited stage small-cell lung cancer after chemoradiation, but reports receiving no financial or personal gain from this.

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).

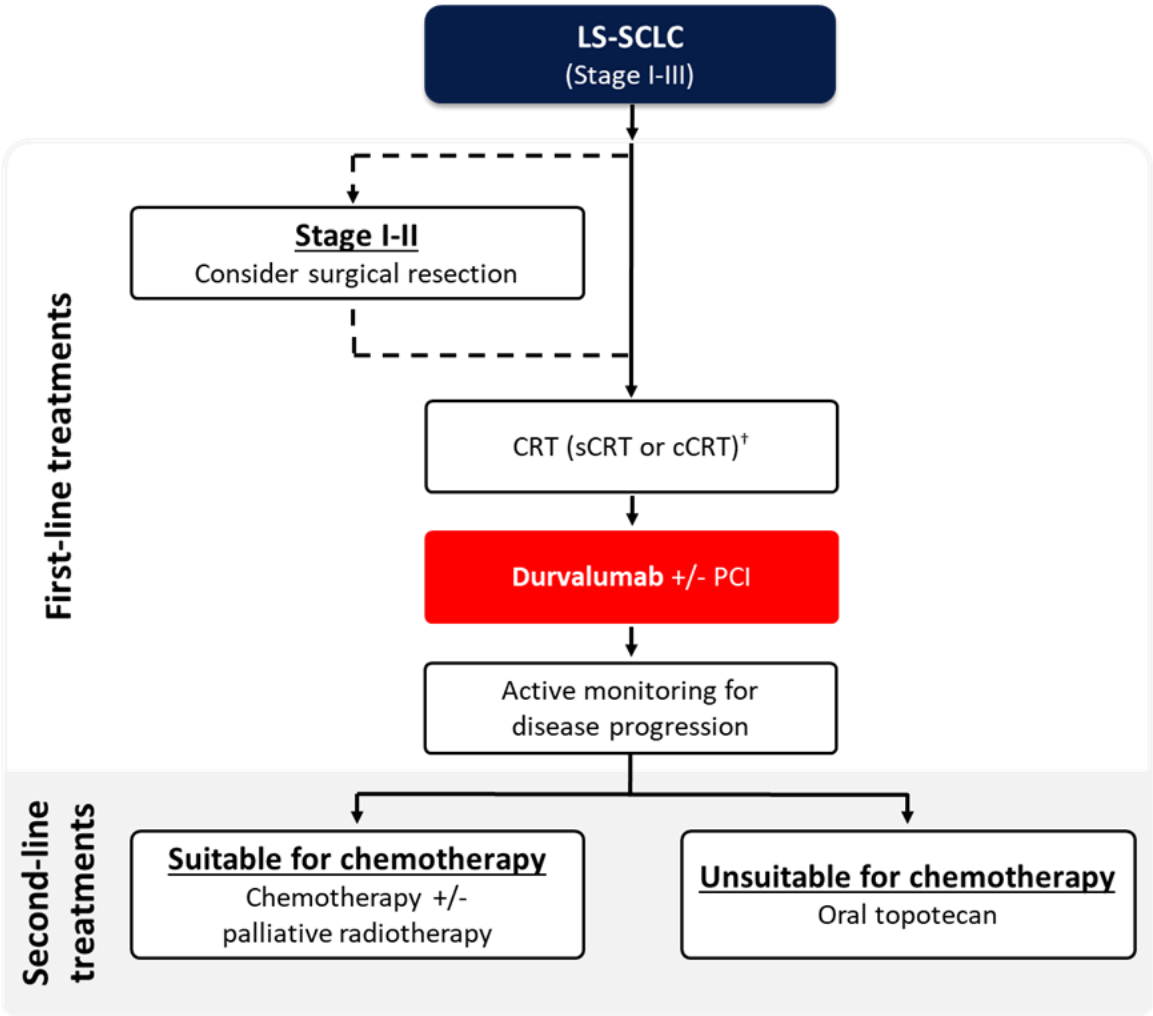

Figure 1 Company's proposed positioning of durvalumab in the LS-SCLC clinical pathway

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).

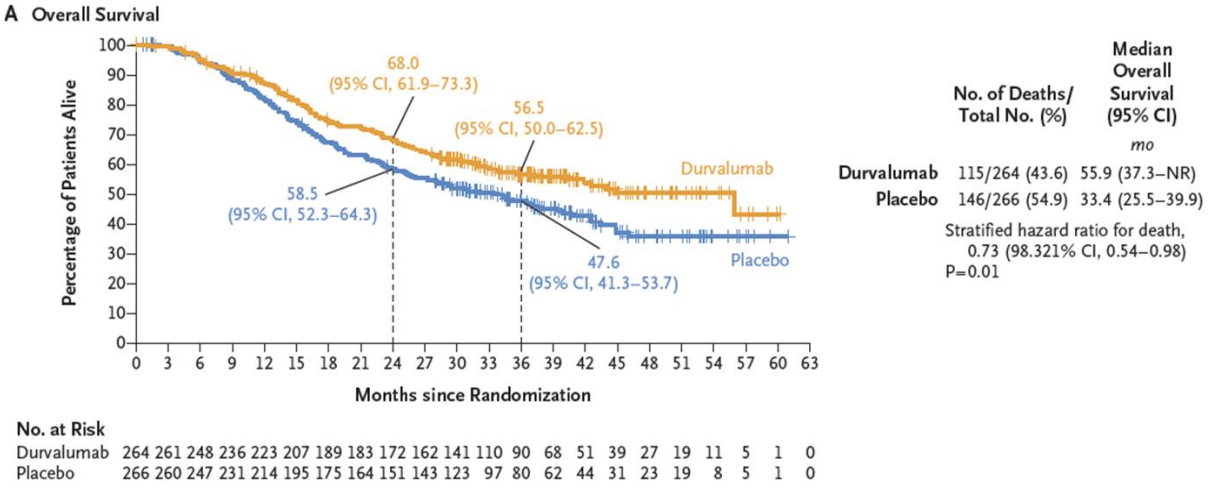

Figure 2 KM plot of OS results from ADRIATIC (FAS population, first interim analysis)

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).

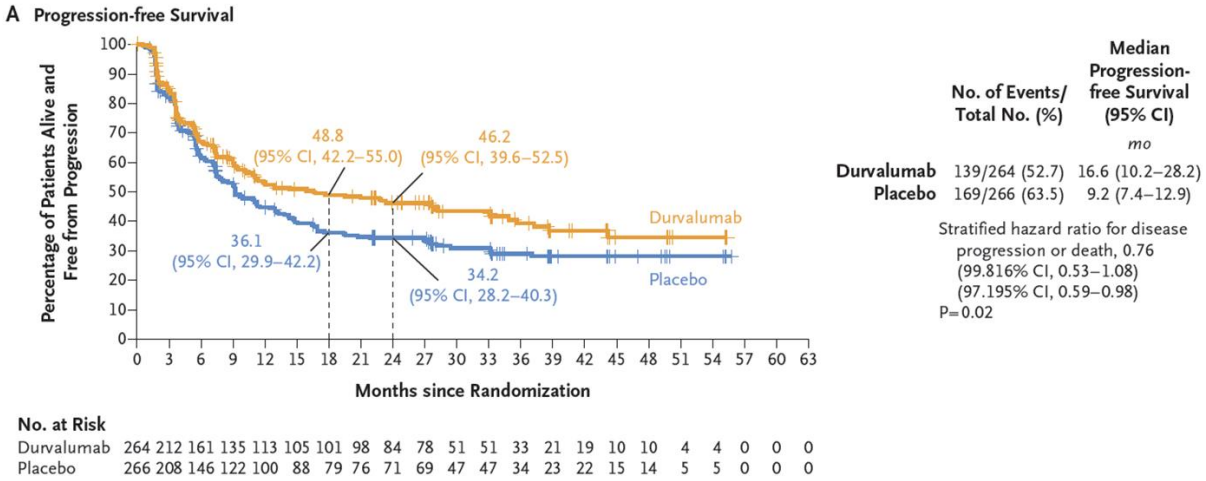

Figure 3 KM plot of PFS as assessed by BICR (FAS population, first interim analysis)

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).

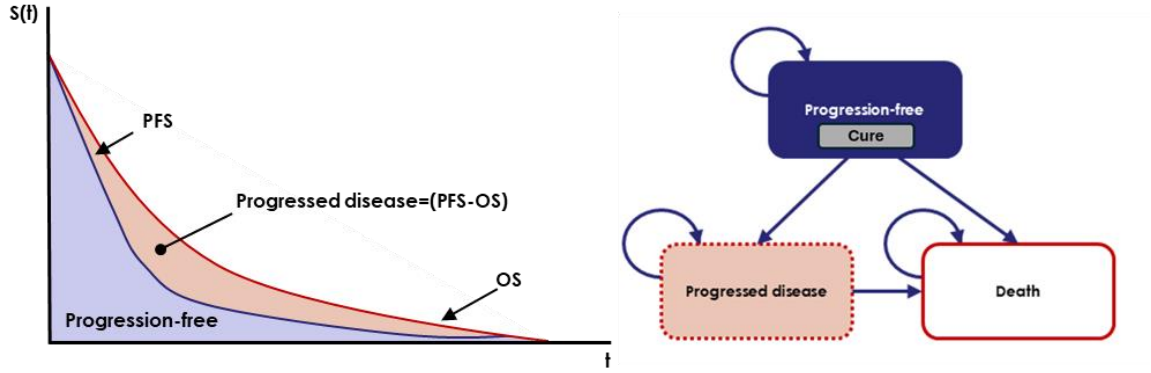

Figure 4 Company's economic model structure

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

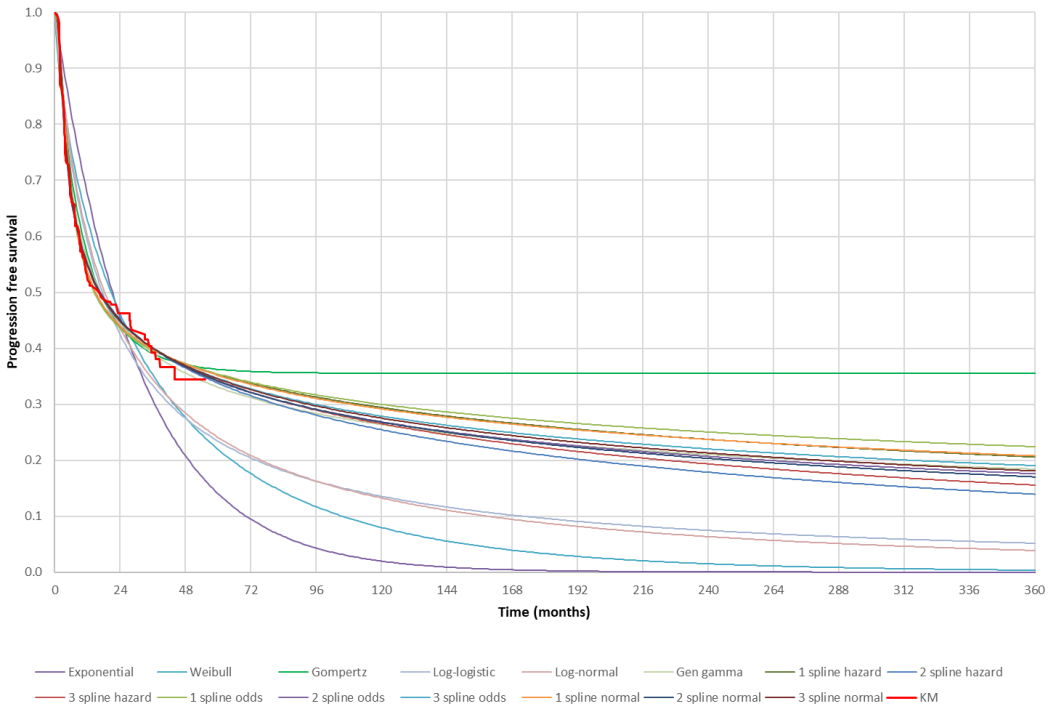

Figure 5: PFS KM curve and extrapolations from the company's revised base case for durvalumab (curves are not bounded by OS)

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

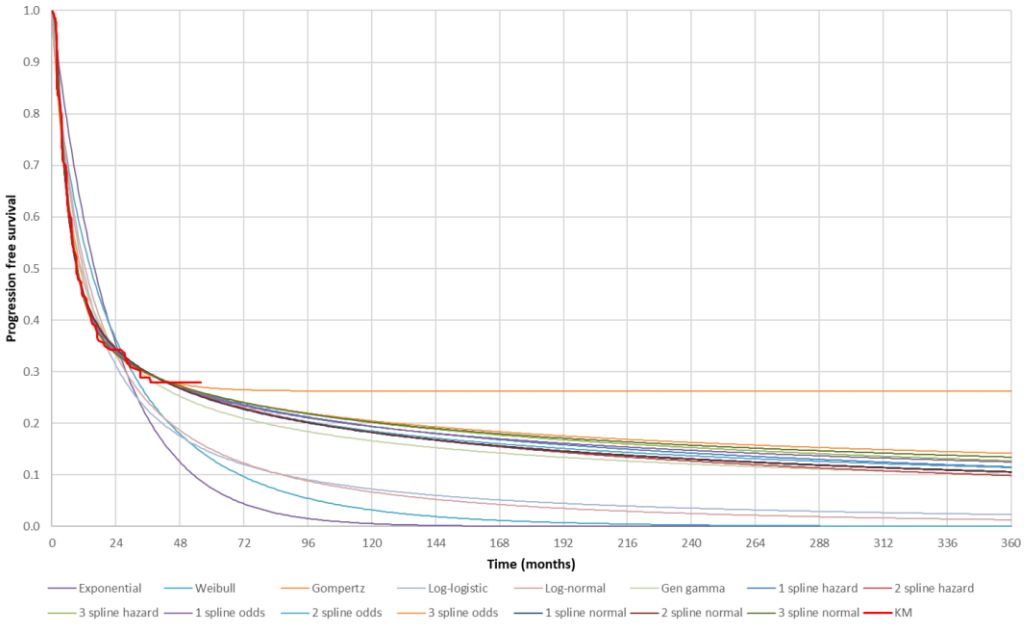

Figure 6: PFS KM curve and extrapolations from the company's revised base case for 'watch and wait' (curves are not bounded by OS)

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

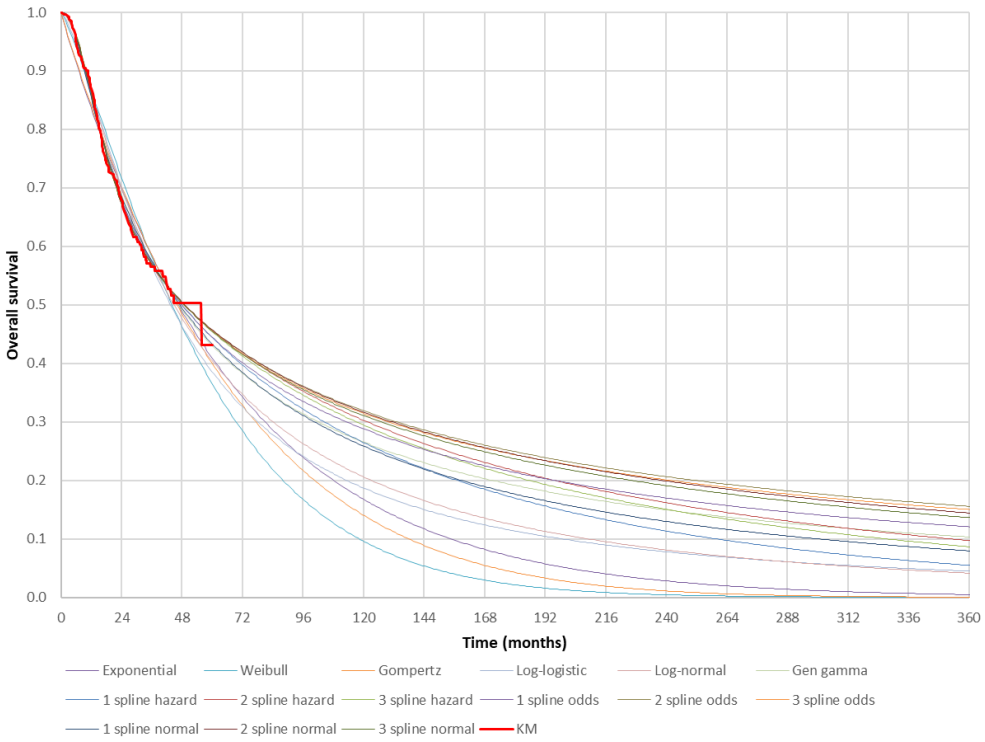

Figure 7: OS KM curve and extrapolations from the company's revised base case for durvalumab

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

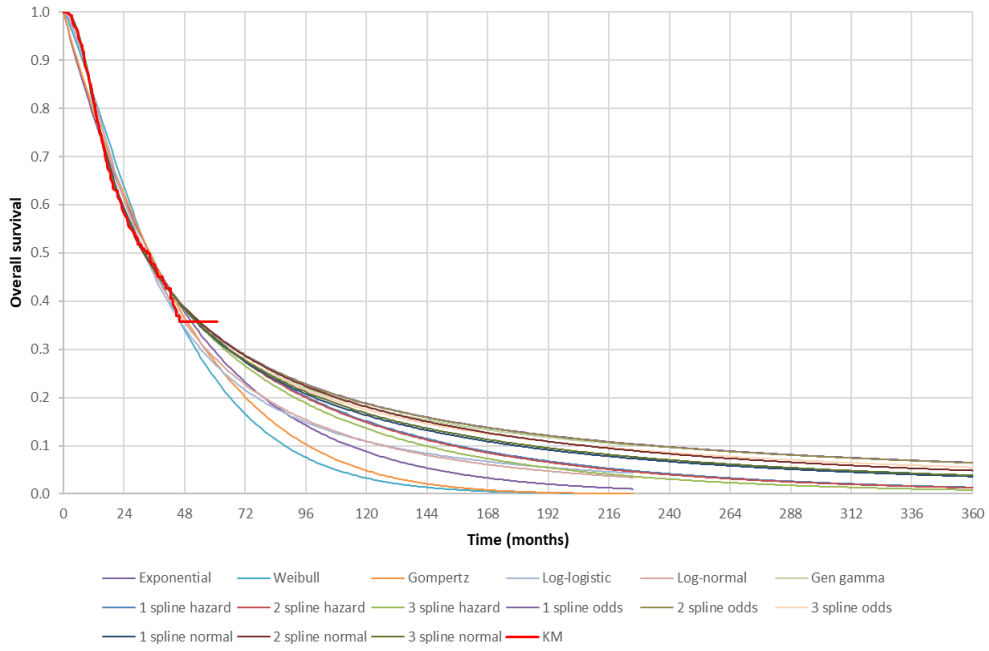

Figure 8: OS KM curve and extrapolations from the company's revised base case for durvalumab

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.

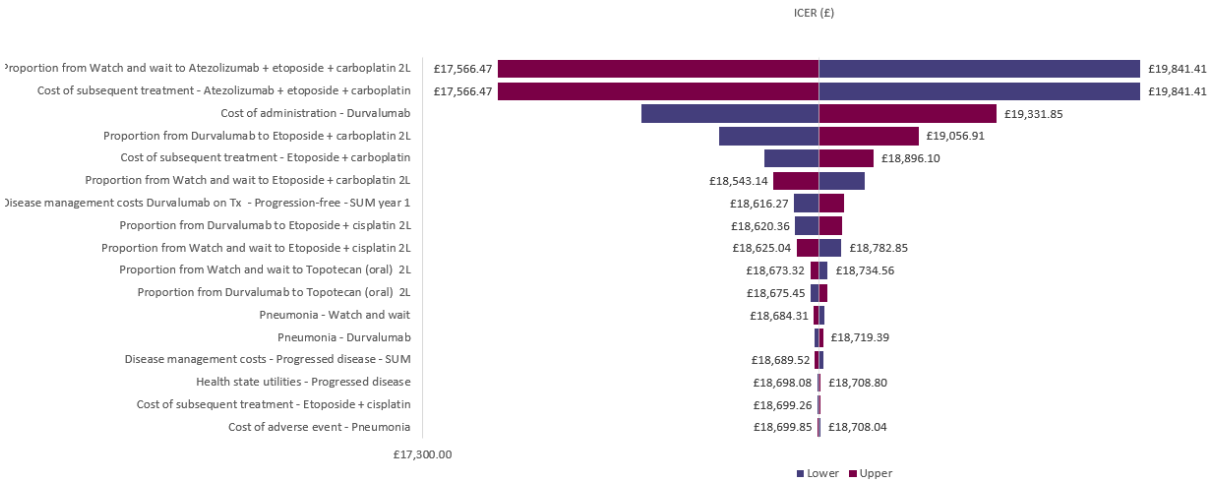

Figure 10 Tornado diagram for the company's base case using updated commercial arrangement for durvalumab

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.

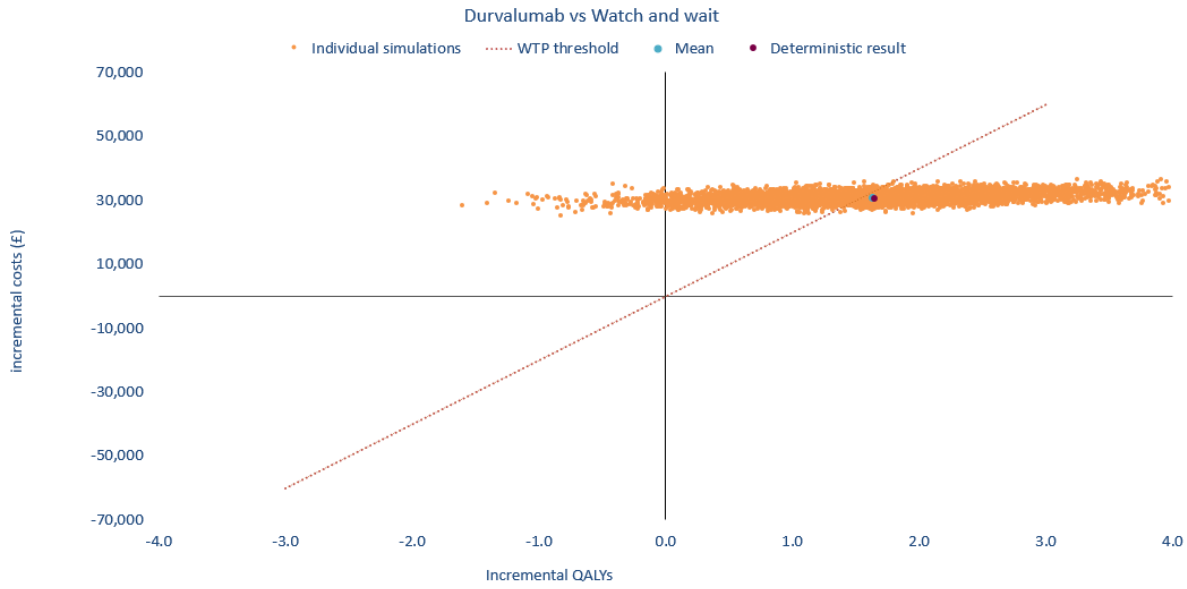

Figure 11 Scatterplot graph for durvalumab vs watch and wait using the company's base case and updated commercial arrangement

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

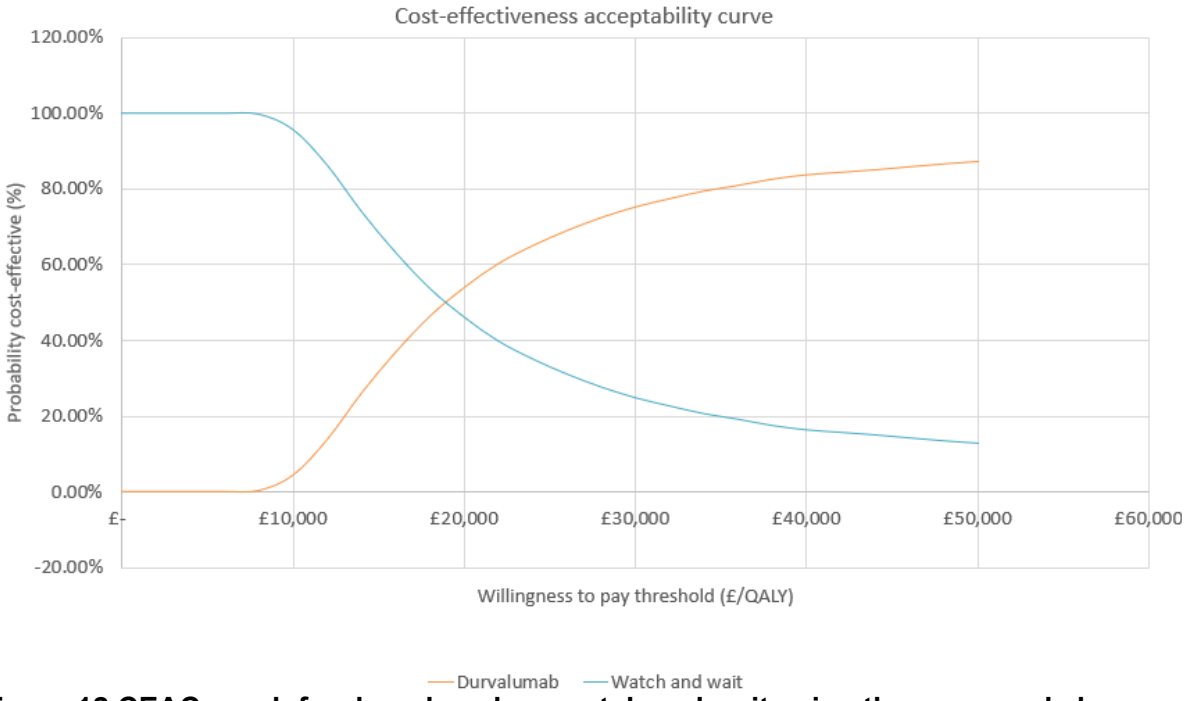

Figure 12 CEAC graph for durvalumab vs watch and wait using the company's base case and updated commercial arrangement

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).

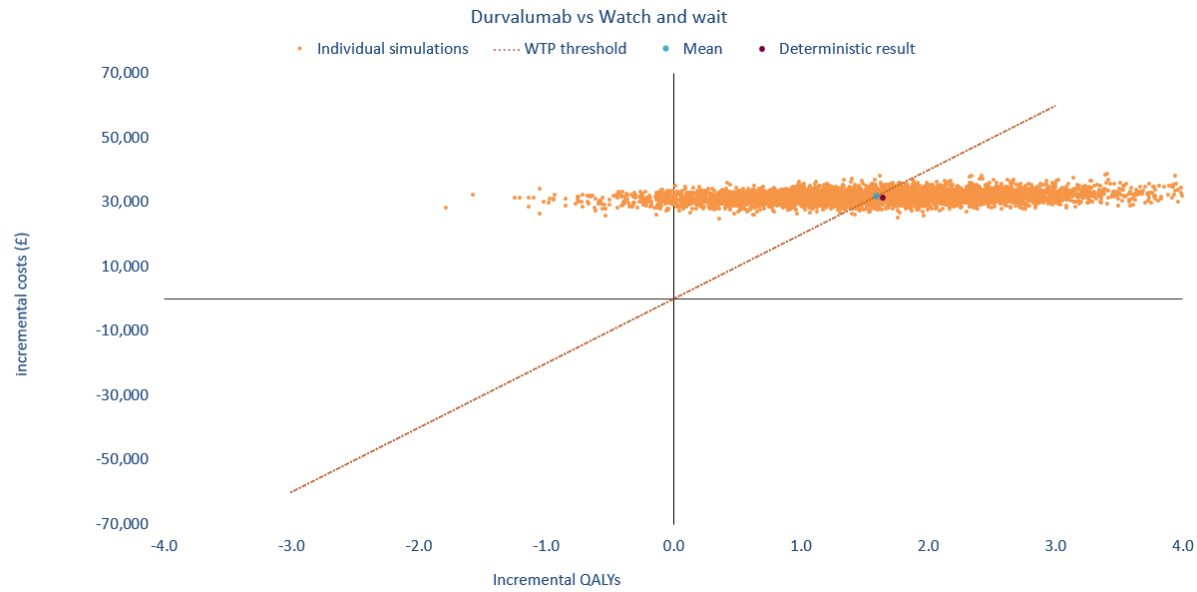

Figure 13 Scatterplot graph for durvalumab vs watch and wait using the corrected company's base case and updated commercial arrangement

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.

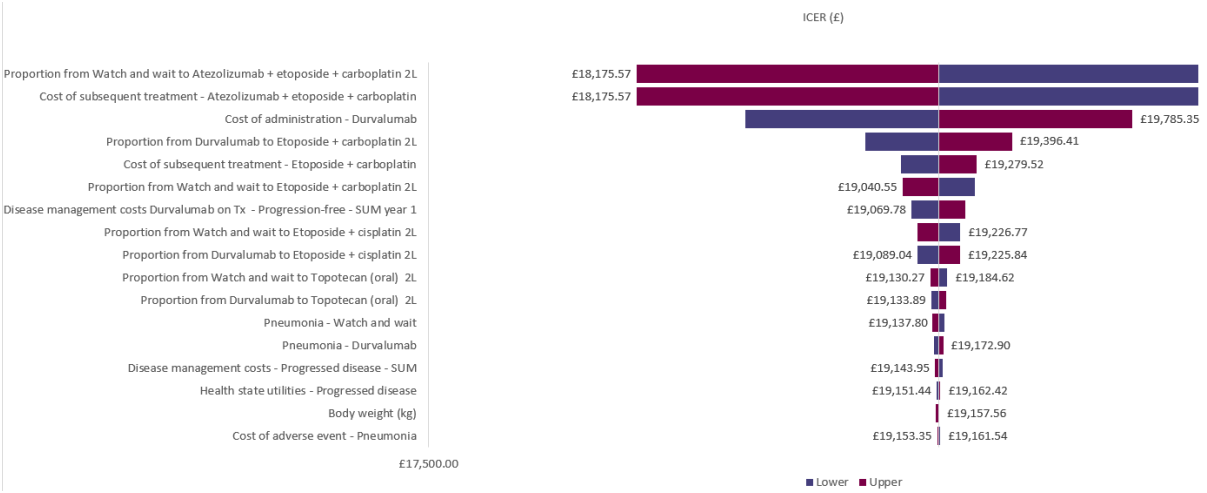

Figure 14 Tornado diagram for the corrected company's base case using updated commercial arrangement for durvalumab

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.

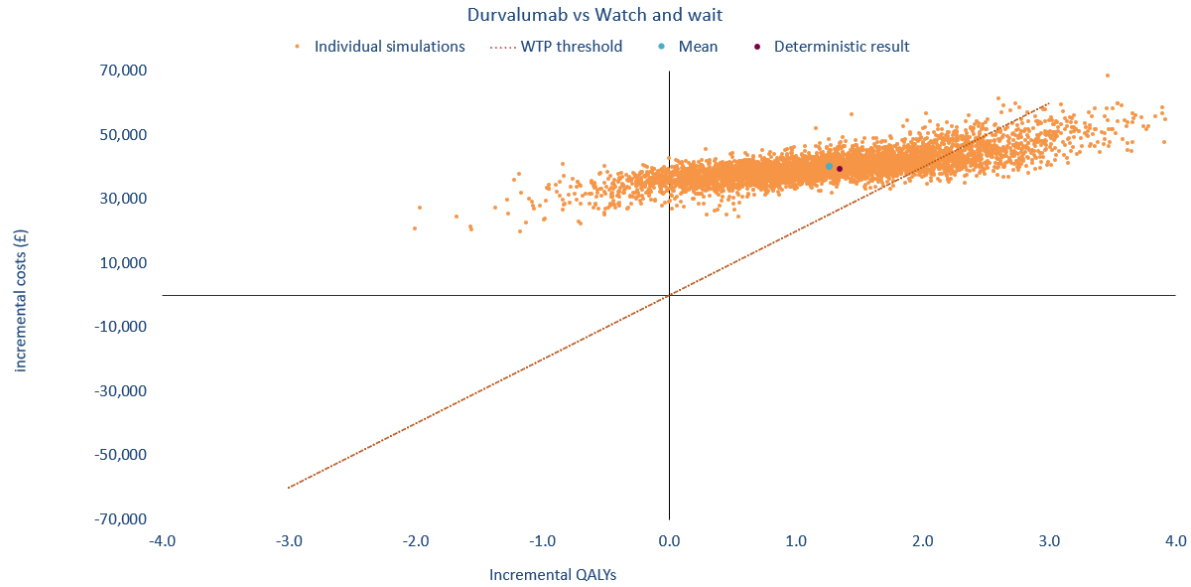

Figure 15 PSA scatterplot graph for durvalumab vs watch and wait using EAG preferred assumptions

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).

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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.

CONFIDENTIAL

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 [ID5073]

Results of updated treatment effect waning scenarios

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Date completed	**06/06/2025**

EAG comment: Table 1 and Table 2 show the cost-effectiveness results for two treatment effect waning scenarios applied to the company's and EAG's base cases: equalisation of PFS and OS hazards at 5 years, and tapering of the hazards between year 3 and 5.

Table 1 Company base case + treatment effect waning (equalization of hazard)

Scenario	Technology	Total cost	Total QALY	Incr. Cost (£)	Incr. QALY	ICER (£/QALY)
Treatment effect waning at 5 years	Watch and wait	[redacted]	[redacted]	[redacted]	[redacted]	£33,411
	Durvalumab					
Treatment effect waning between 3 and 5 years	Watch and wait	[redacted]	[redacted]	[redacted]	[redacted]	£39,524
	Durvalumab					

Table 2 EAG base case + treatment effect waning (equalization of hazard)

Scenario	Technology	Total cost	Total QALY	Incr. Cost (£)	Incr. QALY	ICER (£/QALY)
Treatment effect waning at 5 years	Watch and wait	[redacted]	[redacted]	[redacted]	[redacted]	£50,301
	Durvalumab					
Treatment effect waning between 3 and 5 years	Watch and wait	[redacted]	[redacted]	[redacted]	[redacted]	£57,500
	Durvalumab					

Single Technology Appraisal

Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation [ID5073]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

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

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 21 March 2025** using the below comments table.

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

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted] in pink.

Note: proposed amendments to the text are shown in **bold and underlined**.

Issue 1 Background information on durvalumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2 background information on durvalumab, page 10. The EAG description of the dose does not reflect the company submission.	Please can the text be amended as follows: 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).	The current text does not reflect what the draft SmPC states and so is inaccurate.	Amended as suggested, to align with the text in CS Table 2.

Issue 2 Study characteristics

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1.1, study characteristics, page 20. The EAG description of where the OS, PFS and adverse events results are found in the company submission are missing key sections.	Please can the text be amended as follows: 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**,	The sections of the CS where the OS and PFS results are presented are missing from the list.	Amended as suggested.

	B.2.6.1.2, B.2.10, B.2.12.1.1 and B.3.4.1).		
Section 3.2.1.1, study characteristics, page 21. The EAG's description of the latest second interim analysis does not state that the data is still undergoing analysis.	Please can the text be amended as follows: The company confirmed in clarification response A6 that a second, event-driven interim analysis of OS took place on 20th January 2025. No updated results were provided as analysis is ongoing.	To accurately explain why data from the second interim analysis has not been provided to the EAG.	The company's clarification response A6 does not explain that the analysis of the data from the [redacted] data-cut is ongoing. However, to make it clear to the reader that the analysis is ongoing, we have amended the text in section 3.2.1.1 of our report as follows: "The company confirmed in clarification response A6 that a second, event-driven interim analysis of OS took place on [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.**"

Issue 3 Progression-free survival goodness of fit

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.4.1, progression-free survival, page 55. The EAG description of the contents in Table 41 and Table 44 does not fully reflect the CS.	Please can the text be amended as follows: 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.	To accurately report what is shown in Tables 41 and 44 of the CS.	We have amended the wording as suggested by the company.

Issue 4 Overall survival goodness of fit

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.4.2, overall survival, page 58. The EAG description of the contents in Table 49 and Table 52 does not fully reflect the CS.	Please can the text be amended as follows: Goodness of the curve fit was provided by AIC **and BIC** statistics, presented in CS Tables 49 and 52.	To accurately report what is shown in Tables 49 and 52 of the CS.	We have amended the wording as suggested by the company.

Issue 5 Progression-free health state resource use

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7.3, resource use, page 69-70. The description of resource use provided by the EAG's experts has not been applied correctly in Table 23 of the EAG report.	Outlined below are components of the statements provided by the EAG's clinical experts that do not align with the values in Table 23 of the EAG's report under the 'EAG clinical experts' section: **1) Oncologist Visits:** The EAG clinical experts state that patients would see an oncologist or nurse practitioner at least 12 times per year when receiving durvalumab for Years 1 and 2. In Years 3 to 5, this decreases to 6-monthly visits, equivalent to 2 per year. However, in row 3 of Table 23 in the EAG report, this value is set to 0 in the durvalumab on-treatment arm. For patients off-treatment, experts stated 4–6 oncologist visits per year are required. Firstly, row 3 in the durvalumab off-treatment column of Table 23 in the EAG report is set to 4 rather than the range provided by clinical experts. Secondly, patients in the 'watch and wait' arm are considered off-treatment, and therefore the same number of outpatient oncologist visits should be applied to patients off-treatment in the durvalumab arm and patients in the 'watch and wait' arm (row 1 – 3 in Table 23 of the EAG report). Finally, the text reads	The values reported in Table 23 of the EAG report, which are then used in the EAG's model, did not accurately reflect the feedback provided by the EAG's clinical experts. The experts' feedback was only applied to the durvalumab arm, despite many of their statements being equally applicable to the 'watch and wait' arm. These amendments are	Thank you for highlighting this. We have now corrected Table 23 of the EAG report for oncologist visits, CT scans and chest X-ray. A summary of the corrections is provided below **<u>Oncologist visits</u>** In Year 3-5, patients in durvalumab off-treatment are assumed to have 2 oncologist visits, same as that in the "watch and wait" arm. **<u>CT scans</u>** In Year 3-5, patients in durvalumab (on-treatment and off-treatment) and

	"less frequently (six-monthly) in Year 3 to 5, ranging between four and six oncologist visits during off-treatment." This could be misinterpreted as 4–6 oncologist visits per year in Years 3 to 5 only. Therefore, please amend the text to "less frequently (six-monthly) in Year 3 to 5**. <u>Oncologist visits range between 4 and 6 oncologist visits during the off-treatment period per year (Years 1 to 5).</u>** **2) CT Scans:** The EAG's experts stated that patients would have, on average, four CT scans per year in Years 1 to 2 and at least one CT scan per year in Years 3 to 5. These values have been applied to patients on and off treatment in the durvalumab arm but have not been applied to patients in the 'watch and wait' arm (rows 7 to 9 in Table 23 of the EAG report). Since the statement provided by the clinical experts is not specific to patients receiving durvalumab, these values should be applied to all treatment arms. **3) Chest X-rays:** It was stated that most centres use CT scans for surveillance, not X-rays; therefore, the number of chest X-rays required has been set to 0 for patients on and off treatment in the durvalumab arm. However, chest X-rays have still been	necessary because the EAG uses these values to inform their preferred base case.	'watch and wait' arms are assumed to have 1 CT-scan. **<u>Chest X-rays</u>** We assume no chest X-ray across both the arms. **<u>Blood tests</u>** Not a factual inaccuracy. For clarity, we have reworded the text in Section 4.2.7.3 of the EAR.

	included for patients in the ‘watch and wait’ arm, which contradicts the statement provided by the experts (rows 4 to 7 in Table 23 of the EAG report). **4) Blood Tests:** The experts suggested that patients would also have one blood test per oncologist visit. This statement has been used to inform the number of blood tests for patients on and off treatment in the durvalumab arm. The EAG then notes that the experts agree with the company that there would be no blood tests for the ‘watch and wait’ arm. Since the ‘watch and wait’ arm represents an off-treatment arm, this should also be applied to patients off-treatment in the durvalumab arm. Therefore, the EAG have incorrectly applied the expert’s statement about patients requiring one blood test per oncologist visit when receiving durvalumab to patients off durvalumab. Based on the above, the three columns on the right side of Table 23 in the EAG report under the heading ‘EAG clinical experts’ should be amended as shown below, and the corresponding values should be updated in the model: **EAG clinical experts**		

Item	Durvalumab on treat.	Durvalumab off-treat.	'Watch and wait'
Outpatient oncologist visit: Year 1	12	4-6	**4-6**
Outpatient oncologist visit: Year 2	12	4-6	**4-6**
Outpatient oncologist visit: Year 3–5	**2**	**4-6**	**4-6**
Chest X-ray: Year 1	0	0	**0**
Chest X-ray: Year 2	0	0	**0**
Chest X-ray: Year 3–5	0	0	**0**
CT scan (chest): Year 1	4	4	**4**

	CT scan (chest): Year 2	4	4	**4**		
	CT scan (chest): Year 3–5	1	1	**1**		
	Blood test	12	**0**	0		

Issue 6 Resource use values applied in the EAG economic model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7.3, resource use, page 69-71. The EAG has not used a consistent approach when determining which value to use in the economic model when the consulted clinical experts provided a range. This issue is related to issue 5.	The EAG consulted clinical experts to determine the resource use in the progression-free and progressed disease health states. Some of the resource use values were provided as ranges and these ranges were reported in Tables 23 and 24 of the EAG report. However, in the economic model on the Costs_DM sheet, there are inconsistencies in how these range values are applied. For example, for outpatient oncologist visits in the progression-free health state (Costs_DM!L13:L15), the lower value of	To prevent the introduction of biases into the model and to ensure a consistent approach, this alignment is necessary This is important as the EAG uses these values to inform their preferred base case.	Thank you for highlighting this. For consistency, we have amended the EAG base case which includes the lower range of resource use based on our experts' opinions for progression-free and progressed states. Furthermore, we have conducted two additional

	the range provided by the experts is used. Conversely, for outpatient oncologist visits in the progressed disease health state (Costs_DM!G41), the upper value of the range provided by the experts is used. Please ensure a consistent approach is applied when utilising the ranges provided by clinical experts to avoid introducing biases into the model.		scenarios on the EAR base case using: • Mid range of resource use based on our experts' opinions for progression-free and progressed states • Higher range of resource use based on our experts' opinions for progression-free and progressed states For both the scenarios, there was no significant impact in the ICER. Please see EAR Table 36.

Issue 7 Cost of cyclophosphamide

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Section 4.2.7.4 subsequent treatment costs,	The cost per package for cyclophosphamide should be updated to £13.11 in table 26.	To align with the values used in the	Thank you for highlighting this error. We have

<table>
<tr>
<td>page 74. Incorrect cost of cyclophosphamide in Table 26 of the EAG report.</td>
<td>
<table>
<tr><th></th><th>Dose per admin</th><th>Formulation per vial (mg)</th><th>Vials per package</th><th>Cost per package (£)</th><th>Cost per treatment [a] (£)</th></tr>
<tr><td>Cyclophophamide</td><td>1.4 mg/m^2</td><td>1000</td><td>1</td><td><u>£13.11</u></td><td>£78.64</td></tr>
<tr><td>Doxorubicin</td><td>750 mg/m^2</td><td>200</td><td>1</td><td>£17.67</td><td>£742.11</td></tr>
<tr><td>Vincristine</td><td>50 mg/m^2</td><td>1</td><td>5</td><td>£38.42</td><td>£2,305.40</td></tr>
<tr><td colspan="5">Total cost of CAV treatment</td><td>£3,126.15</td></tr>
</table>
</td>
<td>EAG’s model.</td>
<td>amended the cyclophosphamide price in EAR Table 26.</td>
</tr>
</table>

Issue 8 Reference to the subsequent treatment assumptions from TA798

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7.4 subsequent treatment assumptions, page 73 paragraph 6 and page 74, paragraph 1. The EAG refers to TA798 and the committee’s preference align the subsequent treatment assumptions with the trial data.	The EAG references TA798 as justification for aligning subsequent treatment assumptions with the trial data. It is inaccurate to say the relationship between subsequent treatment assumptions and the trial data in TA798 are the same as in this appraisal.	Unlike the PACIFIC study, the subsequent treatments in the ADRIATIC study exhibit several discrepancies with UK clinical practice, rendering the approach outlined in TA798 irrelevant for this evaluation. These	Not a factual inaccuracy. We thank the company for the further clarification. However, as stated earlier, we acknowledge that there is uncertainty with respect to the subsequent treatment assumptions (highlighted as Key issue 3 in Page 5 of the EAR) and therefore, this warrants further

		discrepancies are detailed below, and are in addition to the point regarding Blueteq restrictions on immunotherapy retreatment: • Firstly, the immunotherapy treatment rate in the "wait and watch" arm of the PACIFIC study (31.2%) was already considered representative of UK clinical practice for the indicated population, and therefore no adjustment was deemed necessary. Based on clinical expert feedback from an advisory board, a similar rate is	discussion. We also would like to highlight that the EAG conducted several scenarios (besides our base case assumption in Section 6.2 of the EAR) in EAR Section 6 where we explored the impact on the overall cost-effectiveness results from changing the estimates for subsequent treatments. These include: • Using EAG clinical expert estimates on the EAG corrected company's revised model (Table 33 of the EAR) • Using the estimates from the company's advisory board report (i.e., values used in the company's base case) in the EAG preferred base case model (Table 36 of the EAR) • Using EAG clinical experts estimates based on Table 27 of the EAR (Table 36 of the EAR)

		anticipated in the ADRIATIC study to better reflect UK practice in LS-SCLC. Consequently, we have adjusted this figure to align more closely with clinicians' estimations. • Secondly, no subsequent treatments in the PACIFIC study were identified as being affected by supply shortages. Conversely, in the ADRIATIC study, topotecan was the most frequently administered subsequent treatment in both study arms.	

		Given the lack of available timelines for the restoration of topotecan supply, it is crucial to ensure that the subsequent treatment figures accurately reflect current UK clinical practice. • Thirdly, as per the EAG's clinical expert insights, additional amendments are advised to further align with UK clinical practice in this indication, specifically reducing the proportion assigned to cisplatin and incorporating	

		CAV within the list of subsequent therapies Finally, durvalumab re-treatment is not permitted in UK practice due to the risk of resistance. The efficacy of the durvalumab arm of the trial will not be affected by subsequent durvalumab treatment due to resistance. The presence of durvalumab retreatment in the trial will therefore not affect outcomes. It is therefore not suitable for decision making to consider the costs associated with re-treatment. It is evident that the proportions of subsequent treatments used in the ADRIATIC study currently do not align with UK clinical	

		practice for several reasons, and therefore a different approach to that outlined in TA798 should be adopted in this evaluation.	

Issue 9 Cost per treatment for CAV treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7.4 subsequent treatment costs, page 74. Table 26 of the EAG report.	Please amend the footnote below Table 26 in the EAG report to explain the cost per treatment assume wastage: Assuming RDI of 100%**,** six cycles of treatment**, <u>and assumes wastage.</u>**	Since the cost per treatment in the CS do not assume wastage, this footnote will add greater transparency and will avoid direct comparisons between the subsequent treatment costs reported in the CS.	Not a factual inaccuracy. For clarity, we have amended the wording in the footnote as suggested by the company.