NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer [ID6404]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer [ID6404]

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 submission** from:
   a. Roy Castle Lung Cancer Foundation
   b. British Thoracic Oncology Group

4. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group

5. **External Assessment Group response to factual accuracy check of EAR**

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: cost-comparison

Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer [ID6404]

Document B

Company evidence submission

August 2024

File name	Version	Contains confidential information	Date
ID6404_CASPIAN_DocumentB_CIC_13AUG24_redacted	1.0	No	14/08/24

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

B.1.1 *Decision problem*

This cost-comparison 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). Durvalumab (IMFINZI) with etoposide and carboplatin or cisplatin (EP) is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).[1]

The only comparator included in this submission is atezolizumab with carboplatin (hereinafter referred to as "EP"), which has been recommended by NICE for the same indication and offers similar health benefits to durvalumab with EP. AstraZeneca has been advised by UK clinical experts that the SoC for first-line treatment of patients with ES-SCLC in the National Health Service (NHS) is atezolizumab + EP.[2] Hence, other regimens have not been considered.

This submission presents data for the following outcomes: overall survival (OS), progression-free survival (PFS), response rates, adverse events (AEs), and health-related quality of life (HRQoL), which is consistent with the decision problem outlined by NICE. The economic analysis follows the NICE reference case and therefore ensures alignment with the NICE decision problem.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated extensive-stage small-cell lung cancer	As per scope	NA
Intervention	Durvalumab with platinum-based chemotherapy (etoposide with either carboplatin or cisplatin).	As per scope	NA
Comparator(s)	• Atezolizumab + EP	Atezolizumab + EP is recommended by NICE as a treatment option for untreated ES-SCLC. Atezolizumab is routinely commissioned by the NHS and represents established NHS practice in England for patients with ES-SCLC.[3] This is aligned with advice received from UK-practicing clinicians,[2] and with recommended treatment algorithms.[4,5]	Aligned with expected EU licence and with UK clinical practice.
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope	NA

Economic analysis	Durvalumab + EP has been selected to be appraised as a cost-comparison. Durvalumab + EP is likely to provide similar health benefits at a similar or lower cost than atezolizumab + EP for ES-SCLC (recommended in published NICE technology appraisal guidance (TA638)). 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.	A cost comparison analysis of durvalumab + EP versus atezolizumab + EP will be presented.	NA
Subgroups to be considered	–	Pre-specified subgroups were included in the pivotal trial (CASPIAN) and the relevant efficacy data is presented in this submission (Section B.2.6). These subgroups were based on demographics, geographical region, carboplatin or cisplatin use and disease characteristics No subgroup analyses	NA

		are presented for the economic evaluation.	

B.1.2 *Description of the technology being evaluated*

The mechanism of action, marketing authorisation, dose, method of administration, and price of durvalumab are described in Table 2. The summary of product characteristics and UK public assessment report are provided in Appendix C.

Table 2. 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 binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 receptors. In doing so, it releases the inhibition of immune responses in the tumour microenvironment, resulting in prolonged T-cell activation and anti-tumour activity.[6]
Marketing authorisation/CE mark status	Durvalumab in combination with etoposide and either carboplatin or cisplatin for the first -line treatment of adults with extensive-stage small cell lung cancer (ES -SCLC) was approved by the European Medicines Agency on 27 August 2020.[7]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Durvalumab is indicated for the following indications:[1]** • *Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy* • *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* • *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* • *Durvalumab in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC)* • *Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab 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.*
Method of administration and dosage	For ES-SCLC, durvalumab is administered as an intravenous infusion at a dose of 1500 mg[a] in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy. Durvalumab will be administered until the patient experiences disease progression or exhibits unacceptable toxicity.
Additional tests or investigations	No additional tests or investigations outside current practice are expected.

List price and average cost of a course of treatment	The list price for durvalumab is £592 for a 120mg vial and £2466 for a 500mg vial.
Patient access scheme/commercial arrangement (if applicable)	[redacted]

[a]Patients with a body weight of 30 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg. In combination with chemotherapy dose every 3 weeks (21 days), followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

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

- Small-cell lung cancer (SCLC) is an aggressive form of lung cancer, associated with a poor prognosis and a 5-year OS of approximately 5% to 6%[8,9],[10,11].
- Prior to the introduction of IO, patient survival in ES-SCLC was associated with a median OS of approximately 10 months when treated with EP alone.[12] The addition of atezolizumab + EP significantly improved outcomes, extending median OS to 12.3 months.[13] While this represents a meaningful step forward, survival rates remain very low, and the OS benefit and tolerability of atezolizumab + EP remains unclear beyond 2 years
- In England, there are an estimated 3,452 cases of SCLC diagnosed annually, nearly all of whom are at an advanced stage by the time of diagnosis[8,9]
- Given the rapidly progressive nature of the disease, patients present with varying performance statuses, co-morbidities, clinical symptoms[2]
- ES-SCLC is associated with a considerable symptom burden, due to cough, chest pain, dyspnoea, arm/shoulder pain, fatigue, and appetite loss
- ES-SCLC has a considerable impact on patients' quality of life
    - Studies have reported mean 5-dimension EuroQol questionnaire (EQ-5D) scores of 0.52[14] and 0.74,[15] compared with a UK population norm of 0.78 for 65–74 year olds[16]
- The latest NCCN and ESMO guidelines recommend IO agents such as durvalumab or atezolizumab (+ EP) as primary or preferred first-line options for ES-SCLC
- Atezolizumab is the only IO treatment to be approved by NICE for first-line use in ES-SCLC[3]
- Therefore, there is a substantial unmet need for more effective and less toxic treatment options to improve the outlook and burden for patients with ES-SCLC

B.1.3.1 Disease overview

Small-cell lung cancer represents an aggressive form of lung cancer, accounting for approximately 10% of all lung cancers in England.[8,9] It differs significantly from the more prevalent non-small-cell lung cancer (NSCLC) in terms of its characteristic morphology,

course of disease and life expectancy (Table 3). Unlike NSCLC, smoking contributes to the aetiology of SCLC. Similar to NSCLC, SCLC shows sensitivity to cytotoxic and targeted therapies, including IO agents. Consistent with SCLC being a distinct lung cancer subtype, recommendations for the management of SCLC differ significantly from those for NSCLC and new therapies in development for lung cancer are generally investigated for NSCLC and SCLC in separate trials. SCLC has a particularly poor prognosis, having a 5-year OS of approximately 5% to 6%.[10,11]

Table 3. Comparison of SCLC and NSCLC

T	SCLC	NSCLC
Relative prevalence	Approximately 10% of lung cancer[8]	90% of lung cancer[8]
Cell types/tumour composition[17]	Small-cell lung cancer	Adenocarcinoma Squamous cell carcinoma Large cell carcinoma
Relationship to smoking[18]	Nearly universal	Variable
Stages[19]	LS or ES	0–IV
Annual incidence (per 100,000 patients)	7.65†	68.85‡
Mean 5-year survival	5-6%[10,11]	24.6%[10]

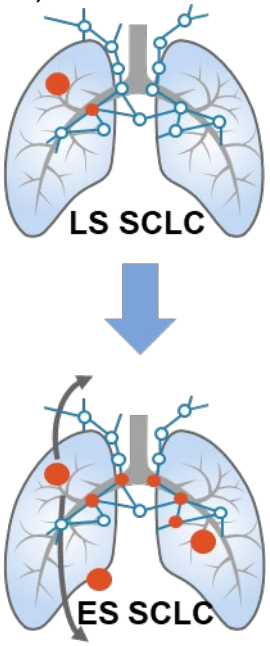
Abbreviations: ES, extensive-stage; LS, limited-stage; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

†Based on a calculation, assuming an annual incidence of all types of lung cancer in England and Wales of 34,516,[8] a proportion of SCLC of 10%[8] and a population of England of 45.119 million people.[20]
‡Based on a calculation, assuming an annual incidence of all types of lung cancer in England of 34,516,[8] a proportion of NSCLC of 90%,[8] and a population of England of 45.119 million people.[20]

B.1.3.1.1 Staging of small-cell lung cancer

Two different staging systems are used to define the spread of SCLC, namely the American Joint Committee on Cancer Tumor size, Lymph Nodes affected, Metastases (AJCC TNM) staging system (**Table 5**) and the older Veterans' Administration (VA) scheme (Table 4). According to the latter two-stage system, SCLC is classed as limited-stage (LS) or extensive-stage (ES) (Figure 1). LS-SCLC is defined as tumour confined to the hemithorax of origin, the mediastinum, and supraclavicular lymph nodes, which can be encompassed within a tolerable radiation therapy port. Patients not considered to have LS-SCLC have ES-SCLC.[21] ES-SCLC corresponds to AJCC stage IV disease, the criterion for which is the presence of tumours of any size present in both lungs or in the lungs and another organ (T any, N any, M1a/b), or stage T3–4 disease. T3 disease is a tumour >5 but ≤7 cm in diameter, directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumours), phrenic nerve, parietal pericardium, or separate tumour nodule(s) in the same lobe as the primary. T4 disease is defined as a tumour of >7 cm diameter, or tumour of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a ipsilateral lobe different from that of the primary.[22]

Figure 1. Representation of tumour size, volume and location in LS and ES-SCLC



Abbreviations: ES, extensive-stage; LS, limited-stage; SCLC, small-cell lung cancer

Table 4. Veterans Administration Lung Study Group staging system

Stage	Characteristics
Limited small-cell lung cancer (LS-SCLC)	Tumour confined to the hemithorax of origin and the regional lymph nodes, the mediastinum, or the supraclavicular nodes Primary tumour and associated regional nodes can be encompassed within a radiation treatment port
Extensive small-cell lung cancer (ES-SCLC)	Disease has spread beyond the supraclavicular areas Distant metastases Patients not included in definition of limited disease

Abbreviations: ES-SCLC, extensive-stage small-cell lung cancer; LS-SCLC, limited-stage small-cell lung cancer.
Source: Zelen, 1973[23]

Table 5. Tumour/node/metastasis staging system for SCLC

Stage	Definition	ES-SCLC classifications	
T: Primary tumour		Stage IV	T3–T4
Tx	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy	Any	
T0	No evidence of primary tumour		
Tis	Carcinoma in situ Squamous cell carcinoma in situ (SCIS) Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension		
T1	Tumour ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)		
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension		
T1a	Tumour ≤1 cm in greatest dimension. A superficial, spreading tumour of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumours are uncommon		
T1b	Tumour >1 cm but ≤2 cm in greatest dimension		
T1c	Tumour >2 cm but ≤3 cm in greatest dimension		
T2	Tumour >3 cm but ≤5 cm or having any of the following features: (1) Involves the main bronchus, regardless of distance to the carina, but without involvement of the carina; (2) Invades visceral pleura (PL1 or PL2); (3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung		
T2a	Tumour >3 cm but ≤4 cm in greatest dimension		
T2b	Tumour >4 cm but ≤5 cm in greatest dimension		
T3	Tumour >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumours), phrenic nerve, parietal pericardium; or separate tumour nodule(s) in the same lobe as the primary		T3–T4

T4	Tumour >7 cm or tumour of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in an ipsilateral lobe different from that of the primary		
N: Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed	Any	Any
N0	No regional lymph node metastasis		
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension		
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)		
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)		
M: Distant metastasis			
Mx	Distant metastasis cannot be assessed		Any
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodules or malignant pleural or pericardial effusion†	M1a/b	
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single non-regional node)		
M1c	Multiple extrathoracic metastases in a single organ or in multiple organs		

Abbreviations: M, metastasis; N, lymph node; SCLC, small-cell lung cancer; T, tumour.

†Most pleural (pericardial) effusions with lung cancer are a result of the tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor.
Source: Amin et al, 2017[19]

B.1.3.1.2 Epidemiology

The 2024 National Lung Cancer Audit reports approximately 10% of patients with lung cancer have SCLC,[8] which is nearly always advanced by the time of diagnosis due to the aggressive nature of the disease.[24,25] With an annual incidence of around 34,516 cases of all types of lung cancer in England[8,20], it is estimated that there are approximately 3,452 cases of ES-SCLC in England each year. Approximately 55%[26] (1,898) of these patients have ES-SCLC. Further, 70%[9] (1,329) of ES-SCLC patients are drug-treated and would therefore be eligible for treatment with durvalumab + EP each year.

B.1.3.2 Burden of ES-SCLC

B.1.3.2.1 Symptom burden

Two of the most widely used tools to assess the symptom burden in patients with ES-SCLC are the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and the disease-specific European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module (EORTC QLQ-LC13).

Baseline data from the CASPIAN[27] (Section B.3.3.2) and IMpower133 trials in newly-diagnosed patients with ES-SCLC[13,28] provide an indication of the most debilitating symptoms in patients initiating therapy. Scores for cough, dyspnoea, and fatigue according to the QLQ-C30 or QLQ-LC13 were >30 (on a scale from 0–100 where higher scores indicate worse symptoms) while scores for chest pain and appetite loss were between 20 and 30 (Table 6).[27,28] The corresponding scores for the general population are 30 for fatigue, 23 for pain, 16 for dyspnoea and 10 for appetite loss.[29]

Table 6. Baseline symptom scores for patients with ES-SCLC enrolled in the CASPIAN and IMpower133 trials

Mean score (SD)	CASPIAN		IMpower 133	
	Durvalumab + EP (n=261)	EP (n=260)	Atezolizumab + CP/ET (n=201)	Placebo + CP/ET (n=202)
Cough	41.5 (25.9)	40.5 (26.4)	42.2 (27.7)	42.9 (29.2)
Chest pain	22.8 (25.5)	21.1 (25.2)	22.9 (26.6)	22.2 (25.7)
Dyspnoea	36.5 (28.7)	38.5 (30.6)	34.3 (25.9)	29.6 (25.9)
Arm/shoulder pain	16.9 (24.8)	13.2 (24.8)	22.2 (30.6)	19.4 (27.4)
Fatigue	35.3 (24.6)	37.1 (27.2)	42.0 (26.4)	38.7 (26.9)
Appetite loss	24.2 (30.2)	25.6 (32.5)	28.9 (32.3)	27.4 (31.9)

Abbreviations: CP/ET, carboplatin plus etoposide; EP, etoposide plus platinum; ES, extensive-stage; SCLC, small-cell lung cancer; SD, standard deviation.
Sources: Califano et al, 2019;[30] Paz-Ares et al, 2019;[31] Paz-Ares et al,2019;[27] Reck et al, 2019[13]

Baseline data from the CASPIAN and IMpower133 trials are consistent with findings from research to develop a patient-centred conceptual model to reflect the experience of patients with SCLC in terms of signs and symptoms, impact on their lives and treatment-related AEs.[32] Patients with ES-SCLC reported that shortness of breath and pain are their primary concerns, and they have also highlighted the impact of their disease on their reduced

function. Interviews with ES-SCLC patients (n=17) revealed that symptoms of SCLC (such as a burning sensation, fatigue, cough, discomfort, shortness of breath) and treatment-related side-effects (such as constipation, diarrhoea, fatigue, hair loss, vomiting) had an impact on many aspects of their life, including daily activities, emotional functioning, physical functioning and social functioning/relationships, as well as having cognitive, financial and school/work-related effects. The most frequently reported symptoms were shortness of breath and pain (35.3% and 29.4% of patients, respectively) and these symptoms were also ranked as the most important to improve (17.6% and 11.8% of patients, respectively).[32] The most frequently reported treatment-related AE was fatigue/tiredness (n=10, 58.8%), followed by nausea (n=8, 47.1%) and hair loss (n=7, 41.2%), whereas headache, loss of appetite and vomiting were less frequent (all n=4, 23.5%). The most frequently reported impact of ES-SCLC was reduced exertion capacity (n=11, 64.7%).[32]

B.1.3.2.2 Impact on quality of life

The symptoms associated with ES-SCLC and treatment adversely affect patients' HRQoL.

Various studies have compared HRQoL for patients with lung cancer, including patients with SCLC, with that of the general population. One study has reported a mean EORTC QLQ-C30 global health status (GHS) score of 38.3[33] for patients with ES-SCLC, which was substantially lower than the normative value used as reference (67.1).[29] Indeed, patients included in the CASPIAN[1] and IMpower 133[2] trials had a baseline GHS score of 54–56[31] and 52–54,[30] respectively. Two further studies have reported mean EQ-5D scores of 0.52[14] and 0.74,[15] compared with a UK population norm of 0.78 for 65–74 year olds.[16]

Several studies have shown that SCLC is associated with a lower HRQoL than NSCLC, consistent with the more aggressive course of disease. A Polish study compared EORTC QLQ-C30 scores from 72 patients with SCLC (LS or ES) and 185 patients with NSCLC, and found that scores on physical, role, cognitive and social functioning domains were significantly lower in SCLC.[33] Similarly, a Canadian study found that EQ-5D scores showed a trend for being lower for SCLC (n=44) than for NSCLC (n=301) across disease or treatment states.[14] However, other studies have not shown a difference in HRQoL[34] or symptom scores[14,35] between SCLC and NSCLC.

Within SCLC, there is evidence that patients with ES disease have lower HRQoL than those with LS disease.[36] A systematic review that identified 27 studies reporting on HRQoL in patients with SCLC found that the impact on HRQoL across SCLC stages appeared greatest in patients with ES-SCLC who were treatment naïve, and lower in those who responded to treatment (either LS or ES).[36] Effects were greatest on physical functioning and activities of daily living.

[1] The key trial to support this submission.

[2] Another IO trial in patients with SCLC.

B.1.3.3 Clinical pathway of care and durvalumab place in therapy

Guidelines for the management of patients with SCLC include those of the NCCN, published in November 2021[5] and ESMO published in 2021[4] (Table 7). Both guidelines now recommend IO agents such as durvalumab or atezolizumab (+ EP) as primary or preferred first-line treatment options for ES-SCLC. The UK NICE guidelines for the diagnosis and management of lung cancer (NG122) has not yet been updated to reflect the recommendation of atezolizumab + EP in ES-SCLC.[37]

Atezolizumab + EP is preferred in first-line in the UK, followed by maintenance with atezolizumab alone. Chemotherapy is an option in patients who have contraindication to immunotherapy or have a high performance status (usually 3 or above).[2].

Within 2nd line ES-SCLC, clinicians in the UK typically treat patients with cyclophosphamide, doxorubicin and vincristine (CAV) combination therapy or rechallenge with carboplatin and etoposide, with the decision depending on individual clinician preference and patient eligibility factors.[2]

Durvalumab + EP is anticipated to be used as an alternative to atezolizumab + EP in the first-line treatment in patients with ES-SCLC (Figure 2), and as maintenance monotherapy every 4 weeks until disease progression or until unacceptable toxicity. Results from an indirect treatment comparison (ITC) (see Section B.3.9) suggest that durvalumab + EP offers a benefit over atezolizumab + EP, indicated by a directional improvement in the hazard ratios (HR) across OS (HR, [redacted] [redacted]), overall Grade 3/4 treatment-related AEs (OR, [redacted] [redacted]), and serious treatment-related AEs (OR, [redacted] [redacted]). However, in the absence of statistically significant results, a conservative assumption of equivalent efficacy can be assumed for the purpose of cost-comparison.

Table 7. Selected guidelines for the treatment of ES-SCLC

Treatment setting	Guideline (publication date)	
	NCCN (November 2021)[5]	**ESMO (2021)[4]**
First-line	**Extensive-stage disease** Defined as AJCC stage IV If no localized symptomatic sites or brain metastasis, good ECOG PS (0–2) or poor PS (3–4) due to SCLC[a] • Systemic therapy[b,c] *Preferred regimens:* durvalumab + EP and durvalumab maintenance, *or* atezolizumab + EP (4 cycles) and atezolizumab maintenance *Other recommended regimens:* EP *Useful in certain circumstances:* cisplatin + irinotecan *or* carboplatin + irinotecan If localized symptomatic sites: • Systemic therapy (as above)[a] +/- RT[d] (to symptomatic sites) If brain metastases: • Systemic therapy (as above) +/- whole brain RT[d]	**Extensive-stage disease** If PS 0–1 and no contraindication for immunotherapy: • Durvalumab + EP (4 cycles) and durvalumab maintenance *or* • Atezolizumab + etoposide + carboplatin b (4 cycles) and atezolizumab maintenance If ECOG PS 0–1 and contraindications for immunotherapy: • Etoposide + carboplatin + (4–6 cycles)[g] *or* carboplatin + topotecan (PO) *or* cisplatin + irinotecan If response PS 0–2, consolidation thoracic RT is an option; if age < 75 years, PCI or MRI surveillance (if no brain metastasis on MRI before PCI) If PS ≥ 2 due to SCLC: • Etoposide + carboplatin (4–6 cycles)[f] *or* carboplatin + gemcitabine (4–6 cycles)[h]

Treatment setting	Guideline (publication date)	
	NCCN (November 2021)[5]	**ESMO (2021)[4]**
		If response PS 0–2, consolidation thoracic RT is an option; if age < 75 years, PCI or MRI surveillance (if no brain metastasis on MRI before PCI) If PS ≥ 2 due to comorbidities: • BSC
Second-line and later	If relapse ≤ 6 months: • **Preferred:** topotecan (PO or IV), lurbinectedin or clinical trial • Paclitaxel, docetaxel, irinotecan, temozolomide, CAV, etoposide (PO), vinorelbine, gemcitabine, nivolumab, pembrolizumab or bendamustine If relapse > 6 months: • **Preferred:** original regimen • Topotecan (PO or IV), paclitaxel, docetaxel, irinotecan, temozolomide, nivolumab, oral etoposide, pembrolizumab, vinorelbine, gemcitabine, CAV, lurbinectedin or, bendamustine	If platinum-resistant relapse (< 3 months TFI) and refractory and/or PS > 2: • BSC *or* lurbinectedin If platinum-resistant relapse (< 3 months TFI) and PS 0–2: • Topotecan (PO or IV) *or* CAV *or* lurbinectedin If platinum-sensitive relapse (≥ 3 months TFI): • Rechallenge with platinum + etoposide *or* topotecan (PO or IV) *or* CAV

[a]If PS (3–4) not due to SCLC then individualized therapy including palliative care, see NCCN guidance 'palliative care' version 2.2021.[38]

[b]NCCN recommend that treatment response should be assessed after every 2–3 cycles of systemic therapy and at completion of therapy.

[b]Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles

[d]If spinal cord compression, RT to symptomatic sites before systemic therapy, unless immediate systemic therapy is indicated.

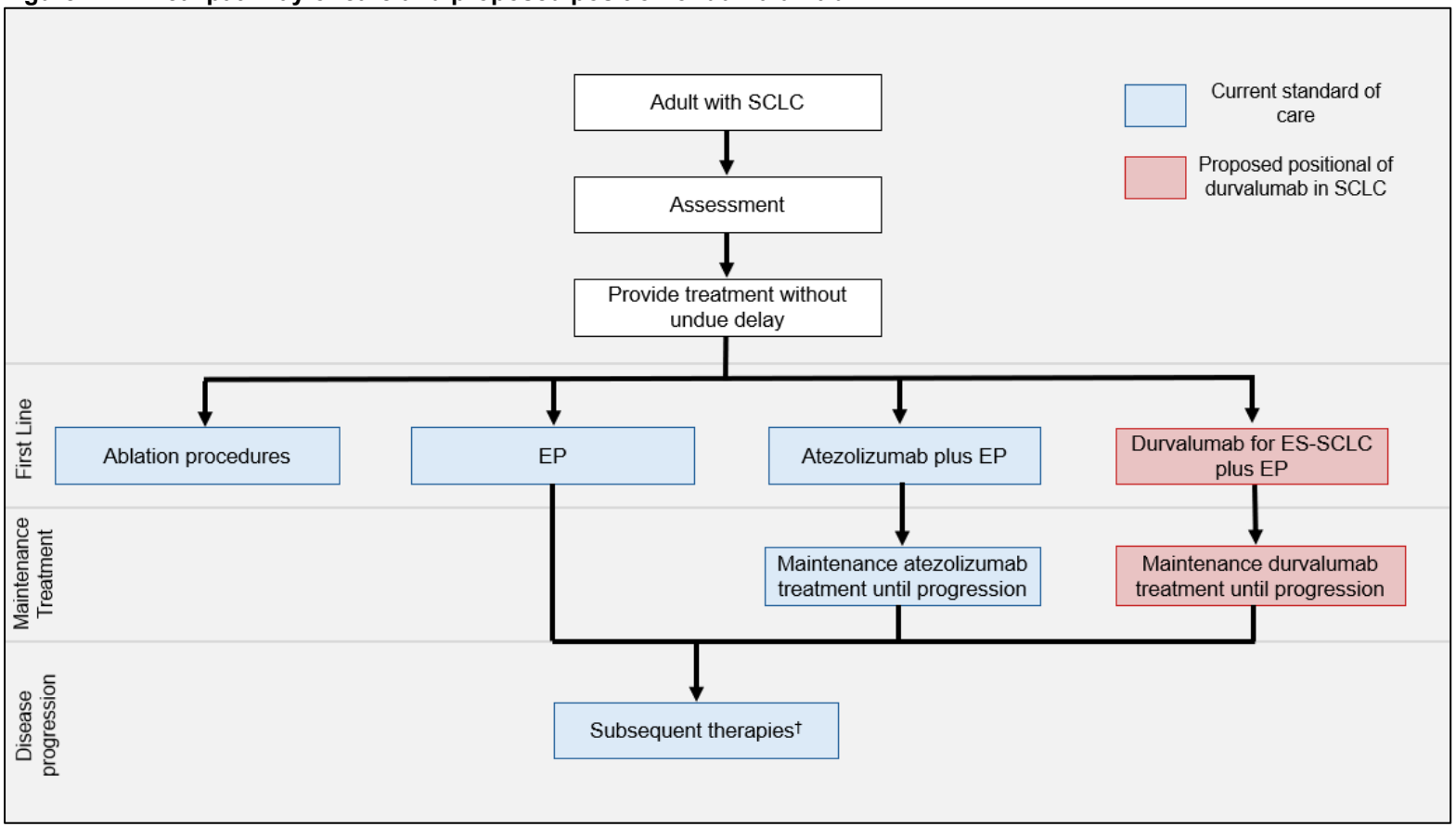
[e]If asymptomatic, systemic therapy first; if symptomatic, whole brain RT before systemic therapy, unless immediate systemic therapy is indicated.

[f]Carboplatin may be replaced by cisplatin in patients < 70 years of age or based on the toxicity profile.

[g]In patients with a PS of ≥ 2, consider chemotherapy dose reduction and/or G-CSF prophylaxis.

BSC, best supportive care; CAV, cyclophosphamide/doxorubicin/vincristine; ECOG, Eastern Cooperative Oncology Group; EP, etoposide plus platinum therapy; ESMO, European Society for Medical Oncology; G-CSF; granulocyte colony-stimulating factor; IV, intravenous; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PCI, prophylactic cranial irradiation; PO, *per os* (oral); PS, performance status; RT, radiation therapy; SCLC, small-cell lung cancer; TFI, treatment-free interval.

Figure 2. Clinical pathway of care and proposed position of durvalumab



Abbreviations: EP, etoposide plus platinum-based chemotherapy; ES-SCLC, extensive-stage small-cell lung cancer; SCLC, small-cell lung cancer.
†Patients may be offered an anthracycline-containing regimen or further treatment with a platinum-based regimen if chemotherapy isn't suitable. Patients may also be offered radiotherapy for palliation of local symptoms. Oral topotecan is recommended as an option only for people with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate and the combination of cyclophosphamide, doxorubicin and vincristine (CAV) is contraindicated.

B.1.3.3.1 Life expectancy

Survival from SCLC in England is worse than in some European countries,[39-41] with life expectancy being particularly poor for patients with ES-SCLC at diagnosis. SCLC is associated with a 5-year OS of approximately 5% to 6%.[10,11] For comparison, 5-year survival rates for NSCLC is estimated to be 24.6%.[10] Median survival is estimated at 12.3 months with atezolizumab + EP in ES-SCLC.[13]

The number of people with untreated ES-SCLC, is estimated to be 1,329 (see Section B.1.3.1.2).

B.1.3.3.2 Issues relating to current clinical practice and unmet need

Despite >40 clinical trials involving >60 agents, atezolizumab + EP is the only IO option to be approved in recent years (see Section B.1.3.3). As outlined in Sections B.1.3.2 and B.1.3.3.1, patients face a short life expectancy and debilitating disease burden. Despite the availability of atezolizumab + EP, EP alone remains the only alternative option for patients. UK oncologists (n=6) stated that ES-SCLC patients are not considered to be a homogenous patient group.[2] Given the rapidly progressive nature of the disease, patients present with varying performance statuses, co-morbidities, clinical symptoms, and therefore require a range of treatment options. Clinicians highlighted the value of having an additional IO option to treat the diverse needs of patients.[2]

Following relapse, treatment options are limited[42] and response rates are low. Median survival is approximately 12.3 months for those who receive atezolizumab + EP.[13] Due to the treatment limitations and aggressive nature of the disease, the prognosis remains poor.

Despite treatment success of atezolizumab + EP in this indication, the OS benefit and tolerability of the combination remains unclear beyond 2 years and there is a clear need for further treatment options to improve the outlook and burden for patients with ES-SCLC. Durvalumab + EP offers a safe and effective IO option demonstrating sustained OS and tolerability over 3 years, which was considered to provide clinical confidence by UK oncologists.[2] The ITC results (see Section B.3.9) suggest that durvalumab + EP offers a benefit over atezolizumab + EP, indicated by a directional improvement in the HR across OS and safety measures. However, in the absence of statistically significant results, a conservative assumption of equivalent efficacy can be assumed for the purpose of cost-comparison.

B.1.4 *Equality considerations*

No equality issues are anticipated.

B.2 Key drivers of the cost-effectiveness of the comparator(s)

- **Only one NICE technology appraisal, TA638, has been published for the treatment of ES-SCLC, examining the cost-effectiveness of atezolizumab + EP for untreated ES-SCLC versus EP alone[3]**
- In TA638, the co-primary clinical outcomes assessed were PFS and OS, both of which were considered in the NMA for this appraisal
- Costs in TA638 included drug acquisition and administration for primary and subsequent therapies, resource use, adverse events, and terminal care
- The NICE committee had no concerns regarding the clinical outcomes and types of costs evaluated in TA638
- The committee concluded that the curve-fitting and the extrapolation of OS had a large impact on the results

B.2.1 *Clinical outcomes and measures*

The only relevant comparator for durvalumab + EP in this appraisal is atezolizumab + EP (TA638),[3] since treatment with IO, such as atezolizumab, is considered SoC for ES-SCLC patients not contraindicated to IO (see Section B.1.1). Further details about this comparator are available in Section B.1.1.

In the TA638 appraisal, the key clinical outcomes used in the cost-effectiveness analyses were:

- Progression-free survival
- Overall survival

No concerns were raised by the appraisal committee on the suitability of the selected clinical outcome measure(s) in the appraisal.[3] The indirect treatment comparison (ITC) conducted between durvalumab + EP and atezolizumab + EP for this appraisal included PFS and OS as clinical outcomes (Section B.3.9).

B.2.2 *Resource use assumptions*

The resource use and associated costs considered in the technology appraisal for atezolizumab + EP were (Table 7):

- Drug acquisition costs
- Drug administration costs
- Radiotherapy costs
- Healthcare resource use costs

- Adverse events costs
- Terminal care costs

All these cost types were included in the cost-comparison analysis for durvalumab + EP versus atezolizumab + EP in ES-SCLC (see Section B.4.3).

Table 7. Resources and associated costs appraised in published NICE guidance for the comparator

Appraisal	Cost category	Item: Unit cost (£)*	Manufacturer's assumptions	Committee's preferred assumptions
TA638[3]	Drug acquisition costs	Atezolizumab with PAS: Confidential Carboplatin 50 mg: £3.18 Carboplatin 600 mg: £28.24 Etoposide 100 mg: £2.30 Etoposide 500 mg: £9.65 Cisplatin 10 mg: £1.84 Cisplatin100 mg: £10.13	Derived from BNF and eMIT 2018	No comment was made by the Committee.
	Drug administration costs	Daycase and Reg Day/Night: Deliver more Complex Parenteral Chemotherapy at First Attendance: £309.22 Deliver complex chemotherapy, day case, standard infusion rate for subsequent treatment: £312.34 Deliver simple parenteral chemotherapy at first attendance as outpatient: £173.99 Daycase and Reg Day/Night: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment at First Attendance: £374.52	Derived from NHS reference costs 2017-2018	No comment was made by the Committee.
	Radiotherapy (PCI) costs	Radiotherapy preparation: £375.00 Radiotherapy delivery: £113.00	Derived from NHS reference costs 2017-2018	The ERG was unable to validate the frequency of PCI that had been incorporated in the model.
	Healthcare resource use costs	Outpatient follow-up visit: £140.87 GP surgery visit: £37.40 GP home visit: £93.28	Derived from NHS reference costs 2017-2018 and PSSRU 2018	No comment was made by the Committee.

Appraisal	Cost category	Item: Unit cost (£)*	Manufacturer's assumptions	Committee's preferred assumptions
		Cancer nurse visit: £42.02 Community nurse visit: £63.00 ECG: £250.10 Chest X-ray: £106.88 CT scan: £106.88 MRI scan: £202.64 Blood tests: £2.51		
	Adverse events costs	Anemia: £2,749 Diarrhoea: £182 Febrile neutropenia: £7,097 Infusion-related reaction: £0 Leukopenia: £377 Neutropenia: £601 Neutrophil count decreased: £449 Pancytopenia: £601 Platelet count decreased: £449 Pneumonia: £2,784 Thrombocytopenia: £124 Vomiting: £182 White blood cell count decreased: £449	Derived from previous submissions, published literature, NHS reference costs 2017-2018 and inflated to 2018 prices using the PSSRU HCSC index where necessary.	The ERG had concerns about the unit costs used for adverse events but acknowledged that using different cost estimates would only have minimal impact on the final ICER.
	Terminal care costs	Palliative care: £6,174.81	Published literature inflated to 2018 prices using the PSSRU inflation index for HCHS	At the clarification stage, the ERG requested the company to review how terminal care costs were integrated into the model. The ERG was satisfied with the responses provided.

* Unit costs are in 2018 prices.

Abbreviations: ERG, evidence review group; HCHS, Hospital and Community Health Services; ICER, incremental cost-effectiveness ratio; PCI, prophylactic cranial irradiation; PSSRU, Personal Social Services Research Unit; TA, technology appraisal

B.3 Clinical effectiveness

The clinical data show that the addition of durvalumab to EP results in significantly improved OS, clinically meaningful prolongation of PFS, and improved quality of life

- CASPIAN is a phase 3, randomised, open-label, multicentre study that evaluates the efficacy and safety of durvalumab with etoposide and carboplatin or cisplatin (EP) versus EP alone as first-line treatment in adult patients with extensive-stage small cell lung cancer (ES-SCLC)[27]
- Durvalumab + EP is the only IO combination in ES-SCLC to demonstrate sustained improvement in OS at 3 years, which was considered to provide clinical confidence by UK oncologists[2]
- Durvalumab + EP is anticipated to be used as an alternative to atezolizumab + EP in the first-line treatment in patients with ES-SCLC (Figure 2), and as maintenance monotherapy every 4 weeks until disease progression or until unacceptable toxicity
- At the 3-year follow-up analysis for the primary endpoint of OS (data cut-off [DCO] 22 March 2021), the addition of durvalumab to EP significantly reduced the risk of death by 29% compared with EP alone (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.595, 0.858; p=0.0003)
  - The median OS for durvalumab + EP was 12.9 months (95% CI, 11.3, 14.7) compared with 10.5 months (95% CI, 9.3, 11.2) for EP alone
  - A higher percentage of patients were alive in the durvalumab + EP arm than EP alone arm at 12 months (52.8% versus 39.3%), 18 months (32.0% versus 24.8%), 24 months (22.9% versus 13.9%) and 36 months (17.6% versus 5.8%)
  - The HRs for OS were consistently in favour of durvalumab + EP when compared with EP alone across different patient subgroups, including in patients with treated or asymptomatic brain metastases and irrespective of performance status (0 or 1) at baseline
- At the 2-year follow-up analysis (DCO 27 January 2020):
  - The addition of durvalumab to EP provided a clinically meaningful prolongation of PFS compared with EP alone, resulting in a 20% reduction in the risk of disease progression or death (HR, 0.80; 95% CI, 0.665, 0.959; nominal p=[redacted])
  - The addition of durvalumab to EP was associated with an increase in confirmed and unconfirmed objective response rate (ORR) of approximately 10% (confirmed ORR, 68% versus 58%; odds ratio [OR], 1.53; 95% CI, 1.08, 2.19; nominal p=[redacted])
  - At 24 months, 13.5% of the responders in the durvalumab + EP group remained in confirmed response, compared with 3.9% of the responders in the control group
- Results from an ITC suggest that durvalumab + EP offers a directional benefit over atezolizumab + EP in OS (HR, [redacted] [[redacted], [redacted]]). However, in the absence of statistically

significant results, a conservative assumption of equivalent efficacy can be assumed for the purpose of cost-comparison.

- Additionally, the ITC analyses demonstrate a numerical benefit in favour of durvalumab + EP with regards to overall Grade 3/4 treatment-related AEs (OR, [redacted] [redacted], [redacted]), and serious treatment-related AEs (OR, [redacted] [redacted], [redacted]), presenting a potentially less toxic IO option in ES-SCLC.
- Results for patient assessments of HRQoL and symptoms, measured at the DCO 27 January 2020 (2-year follow-up analysis), showed longer time to deterioration for patient-reported global health status/quality of life (QoL), and significant improvements for all functioning and symptom scales in favour of durvalumab + EP versus EP
- The time to deterioration was significantly shorter for durvalumab + EP versus EP alone for the different domains of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) (p<[redacted])

The addition of durvalumab to EP did not lead to a notable increase in toxicities at the DCO 27 January 2020 (2-year follow-up) and DCO 22 March 2021 (3-year follow-up) analyses for OS

- There was no particular pattern in the type of AEs that lead to treatment discontinuation or death
    - The rate of Grade 3/4 AEs and AEs leading to discontinuation was similar between treatment arms, demonstrating that the addition of durvalumab to current SoC therapy offers significant and clinically meaningful benefits without adding significant toxicities
- Adverse events of special or potential interest, as well as immune-mediated AEs were numerically higher in the durvalumab + EP group compared with the EP group, driven by Grade 1/2 thyroid endocrinopathy and rash events

B.3.1 *Identification and selection of relevant studies*

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.3.2 *List of relevant clinical effectiveness evidence*

The systematic review identified a single randomised controlled trial (RCT) of durvalumab in the population of interest to this submission (CASPIAN) (Table 8). A more detailed trial overview is presented in Table 9.

Table 8. List of relevant clinical evidence

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Refs identified but not used further	Is study excluded from further discussion? If yes state rationale
CASPIAN	Adults (aged ≥18 years) with histologically or cytologically documented ES-SCLC, or T3-4. WHO/ECOG PS of 0 or 1 and life-expectancy of >12 weeks	Durvalumab + EP	EP	Paz-Ares *et al.* 2019[27] Goldman *et al.* 2021[43]	Paz-Ares *et al.* 2024[44] Paz-Ares *et al.* 2022[45] Garassino *et al.* 2021[46] Hotta *et al.* 2021[47] Goldman *et al.* 2020[48] Paz-Ares *et al.* 2020[49] Reinmuth *et al.* 2022[50]	No

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EP, etoposide and platinum-based chemotherapy; ES, extensive-stage; NA, not applicable; PS, performance status; SCLC, small-cell lung cancer, WHO, World Health Organization

Table 9. Clinical effectiveness evidence

Study	CASPIAN				
Study design	Phase III, randomised, open-label, comparative, multicentre study				
Population	Adults (aged ≥18 years) with histologically or cytologically documented treatment-naïve ES-SCLC, or T3-4. WHO/ECOG PS of 0 or 1 and life-expectancy of >12 weeks.				
Intervention(s)	Durvalumab + etoposide + carboplatin or cisplatin				
Comparator(s)	Etoposide + carboplatin or cisplatin				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	x
	No			No	
Rationale if trial not used in model	NA				
Reported outcomes specified in the decision problem (available DCO for outcome)	**OS (DCO 22 March 2021 [3-year follow-up])** **PFS (DCO 27 January 2020 [2-year follow-up])** Response rates (DCO 27 January 2020 [2-year follow-up]) **Adverse effects of treatment (DCO 22 March 2021 [3-year follow-up])** HRQoL (DCO 27 January 2020 [2-year follow-up])				
All other reported outcomes	PK parameters of durvalumab Blood concentrations of durvalumab and EP Anti-drug antibody assessment Patient-level discontinuation data were used as the basis for time to discontinuation in the economic model Percentage and mean duration of subsequent therapy use				

Bold indicates that these outcomes are used in the economic model

Abbreviations: DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; EP, etoposide and platinum-based chemotherapy; ES, extensive stage; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PS, performance status; SCLC, small-cell lung cancer, WHO, World Health Organization.

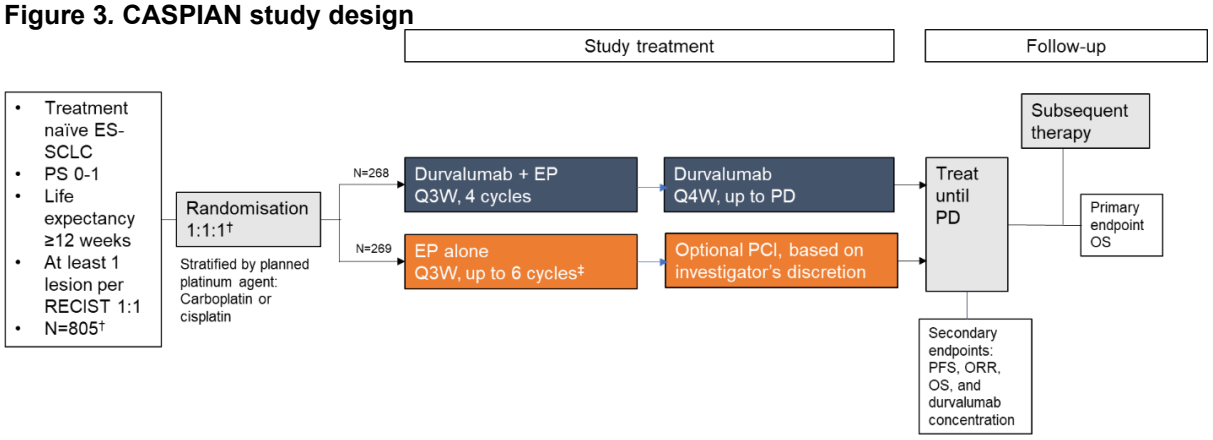
B.3.3 *Summary of methodology of CASPIAN*

B.3.3.1 Summary of methodology

CASPIAN (NCT03043872) is a Phase 3, randomised, open-label, multicentre study to examine the efficacy and safety of durvalumab ± tremelimumab + EP versus EP alone as first-line treatment in adult patients with ES-SCLC.[27] The results of the DCO 27 January 2020 (2-year follow-up) and DCO 22 March 2021 final (3-year follow-up) analysis for the durvalumab + EP and EP arms are reported here and form the basis of this submission. The most recent DCO available for each outcome used in this submission is shown in Table 9 above.

The tremelimumab arm is ongoing[3] and is not relevant to the decision problem or the indication under review by the European Medicines Agency (EMA). Therefore, from this point forward, only the methods and results from the durvalumab + EP and EP arms will be described. The trial design is summarised in Figure 3 and Table 10, with inclusion and exclusion criteria summarised in Table 11.

Figure 3. CASPIAN study design



EP consisted of etoposide 80–100 mg/m2 with either carboplatin AUC 5 to 6 or cisplatin 75–80 mg/m2.

Abbreviations: ES, extensive-stage; EP, etoposide and platinum-based chemotherapy; ORR, objective response rate; OS, overall survival; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; Q4W, every 4 weeks; RECIST Response Evaluation Criteria in Solid Tumors; SCLC, small-cell lung cancer

†This includes the tremelimumab + EP arm, which is not part of this submission.

‡Patients in the EP only arm were permitted an additional two cycles of EP (up to six cycles total) as per the investigator's discretion.

Source: CASPIAN CSR 2019[52]

[3] Initial analysis has shown that tremelimumab did not meet its primary endpoint of OS.51.

AstraZeneca. Imfinzi confirmed a sustained overall survival benefit in final analysis of the Phase III CASPIAN trial in 1st-line extensive-stage small cell lung cancer. Press release. 17 March 2020. https://www.astrazeneca.com/media-centre/press-releases/2020/imfinzi-confirmed-a-sustained-overall-survival-benefit-in-final-analysis-of-the-phase-iii-caspian-trial-in-1st-line-extensive-stage-small-cell-lung-cancer.html Last accessed 27 March 2020.

Table 10. Summary of CASPIAN trial methodology

Trial number (acronym)	CASPIAN
Location	209 sites in 23 countries across Europe, Asia, North America, and South America
Trial design	Randomised, open-label, parallel-group, active-controlled, multicentre, global study
Eligibility criteria for participants	Adult patients (aged ≥18 years) with untreated, histologically or cytologically documented ES disease (as defined by AJCC staging system (7th edition) stage IV SCLC [T any, N any, M1 a/b]), or T3–4 due to multiple lung nodules that are too extensive or have tumour/nodal volume that is too large to be encompassed in a tolerable radiation plan, and WHO/ECOG Performance Status of 0 or 1
Sample size	Planned 795 eligible patients (~265 per arm) Number of randomised patients: • Durvalumab + EP, n=268 • EP, n=269
Planned analysis	1-year interim OS analysis (DCO 11 March 2019): An interim OS was planned to be calculated when at least 318 deaths (about 60% maturity) had occurred in both the durvalumab + tremelimumab + EP and EP alone treatment arms and in the durvalumab + EP and EP alone treatment arms. At the time of the OS interim analysis, 336 death events had occurred (62.6% maturity for OS overall). Outcomes included in this analysis were OS, PFS, response rates, HRQoL, and safety. 2-year follow-up analysis (DCO 27 January 2020): The primary OS analysis (final analysis) was planned to occur when 425 OS events had occurred (about 80% maturity) in the durvalumab + EP and EP alone treatment arms. At the time of final analysis 441 death events had occurred between the durvalumab + EP and EP treatment arms (82.1% maturity if OS overall). Outcomes included in this analysis were OS, PFS, response rates, HRQoL, and safety. 3-year follow-up analysis (DCO 22 March 2021): A long-term follow-up OS analysis was pre-specified to occur approximately 1 year after the DCO date of the final OS analysis, to provide a median survival follow-up of approximately 3 years. At the time of the long-term follow-up analysis, 469 death events had occurred between the durvalumab + EP and EP groups (87.4% maturity for OS overall). Only OS and safety outcomes were included in this analysis.
Trial drugs (the interventions for each group with sufficient details to allow replication, including	**Arm 1** (not relevant to this submission) **Arm 2; ITT population (n=268)**

how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	• During chemotherapy: durvalumab 1500 mg + etoposide 80 to 100 mg/m^2 + carboplatin AUC 5-6 or cisplatin 75 to 80 mg/m^2; Q3W for four cycles • After chemotherapy: durvalumab 1500 mg Q4W until disease progression **Arm 3; ITT population (n=269)** • During chemotherapy: etoposide 80 to 100 mg/m^2 + carboplatin AUC 5-6 or cisplatin 75 to 80 mg/m^2; Q3W for four cycles (can be given for an additional two cycles Q3W on weeks 12 and 15 (i.e. total of six cycles post-randomisation at investigator's discretion) • Prophylactic cranial irradiation, if clinically indicated • After chemotherapy: no active treatment until progression
Permitted and disallowed concomitant medication and treatments	**Disallowed concomitant medications – all treatment arms** Any investigational anticancer therapy other than those under investigation in this study mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study Live attenuated vaccines **Disallowed concomitant medications – durvalumab arm** 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 Drugs with laxative properties and herbal or natural remedies for constipation Sunitinib EGFR TKIs Herbal and natural remedies which may have immune-modulating effects Other medication considered necessary for the subject's safety and well-being could be given at the discretion of the investigator(s), for example: 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," as listed above

	Best supportive care (including antibiotics, GCSF and other hematopoietic factors, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc]) Inactivated viruses, such as those in the influenza vaccine PCI was not allowed in the intervention arms (Arm 1 or Arm 2), but could be given at the investigator's discretion in the control arm (Arm 3)
Primary outcomes (including scoring methods and timings of assessments)	OS assessed as the time from the date of randomisation until death due to any cause. The interim analysis of OS was planned to take place when approximately 318 OS events had occurred (60% maturity) in the durvalumab + EP and EP treatment arms. The primary OS analysis was planned after 425 OS events (80% maturity) across the durvalumab + EP and EP alone treatment groups, with the long-term follow-up OS analysis planned for 1 year post the DCO date of the final analysis to achieve a median survival follow-up of 3 years.
Other outcomes	**Secondary endpoints** • PFS per RECIST v1.1 using investigator assessments† • Objective response rate‡ • PFS at 6 and 12 months§ • OS at 18 months¶ Concentration of durvalumab in blood, and non-compartmental PK parameters, such as peak concentration and trough (as data allow; sparse sampling) **Other endpoints** • HRQoL, as assessed using the: o EORTC QLQ-C30 v3 (core) o EORTC QLQ-LC13 (lung cancer module) o Patient-reported outcomes version of the CTCAE o Patient's Global Impression of Change o 5-dimension, 5-level EuroQol questionnaire (exploratory endpoint) • Hospital attendance and length of hospital/intensive care unit stay

Other outcomes used in the economic model/specified in the scope	• Adverse events • Patient-level EQ-5D data were used to derive utilities • Time to discontinuation, based on patient-level data • Percentage and mean duration of subsequent therapy use
Pre-planned subgroups	Pre-specified subgroup analyses were performed to investigate the consistency of treatment effect across pre-specified stratification factors and subgroups based on demographics, geographical region, carboplatin or cisplatin use, and disease characteristics, although the study was not sized for any of the individual subgroup evaluations and no adjustments were made for multiple testing subgroup analyses (see Section B.3.4).

Abbreviations: AJCC, American Joint Committee on Cancer; AUC, area under the curve; CTCAE, common terminology criteria for adverse events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG, Eastern Cooperative Oncology Group; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EP, etoposide plus platinum-based chemotherapy; EQ-5D, 5-dimension EuroQol questionnaire; ES, extensive-stage; GCSF, granulocyte-colony stimulating factor; HRQoL, health-related quality of life; ITT, intention-to-treat; M, metastases; mAb, monoclonal antibody; N, lymph nodes; OS, overall survival; PCI, prophylactic cranial irradiation; PD-1, programmed death protein 1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PK, pharmacokinetic; Q3W, every 3 weeks; Q4W, every 4 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SCLC, small-cell lung cancer; T, tumour size; WHO, World Health Organization

†The time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression); ‡The number (%) of patients with at least one visit assessment of complete response or partial response

§The Kaplan–Meier estimate of PFS at 6 and 12 months

¶The Kaplan–Meier estimate of OS at 18 months

Source: Paz-Ares et al, 2019,[27] CASPIAN study protocol[53]

Table 11. Key inclusion and exclusion criteria for CASPIAN

Inclusion criteria
Male or female ≥18 years old (≥20 years old in Japan)
Histologically or cytologically documented ES-SCLC[†] Brain metastases; must be asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment
Suitable to receive standard first-line platinum-based chemotherapy
Life expectancy ≥12 weeks at Day 1
WHO PS 0 or 1 at enrolment
Body weight >30 kg
Having measurable disease per RECIST v1.1
Adequate organ and bone marrow function
No prior exposure to immune-mediated therapy
Exclusion criteria
Active or documented autoimmune or inflammatory disorders
Uncontrolled intercurrent illness, such as ongoing or active infection, interstitial lung disease, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia or serious chronic gastrointestinal condition
A history of another primary malignancy
Active infection including tuberculosis, hepatitis B or C, or HIV
Any history of radiotherapy to the chest prior to systemic therapy or planned consolidation chest radiation therapy (except palliative care outside of the chest)

Abbreviations: ES, extensive-stage; HIV, human immunodeficiency virus; PS, performance status; RECIST v1.1, response evaluation criteria in solid tumours, version 1.1; SCLC, small-cell lung cancer; WHO, World Health Organization.

[†] Biopsy was not mandated but required if available

Source: Paz-Ares et al, 2019[27]

B.3.3.2 Patient baseline characteristics

From 27 March 2017, 268 patients were randomised in the durvalumab + EP group and 269 in the control group. Patients with ES-SCLC were recruited from 209 sites in 23 countries across Europe, Asia, North America, and South America. Key patient demographics and baseline characteristics are summarized in Table 12. Most (>80%) patients were white, approximately two-thirds were male, and the median age was 62–63 years. Most (>90%) were current or ex-smokers. Approximately 10% had brain or central nervous system (CNS) metastases at baseline and approximately 40% had liver metastases at baseline. The two treatment groups were generally well-balanced and the disease characteristics (Table 13) were consistent and representative of patients with ES-SCLC receiving first-line therapy.

Table 12. Key patient demographics and baseline characteristics in CASPIAN

Characteristic (ITT population)	Durvalumab + EP n=268	EP n=269
Median age, years (range)	62 (28–82)	63 (35–82)
Male gender, n (%)	190 (70.9%)	184 (68.4%)
Race, %		
White	85.4	82.2
Asian	13.4	15.6
Other	1.1	2.2
Smoking status, n (%)		
Non-smoker	22 (8.2%)	15 (5.6%)
Ex-smoker	126 (47.0%)	128 (47.6%)
Current smoker	120 (44.8%)	126 (46.8%)
AJCC stage IV, n (%)	240 (89.6%)	245 (91.1%)
Brain metastases at baseline, n (%)	28 (10.4%)	27 (10.0%)

Abbreviations: AJCC, American Joint Committee on Cancer; EP, etoposide plus platinum-based chemotherapy; ITT, intention-to-treat; WHO, World Health Organization.

Source: Paz-Ares et al, 2019[27]

Table 13. Baseline disease characteristics in CASPIAN

Characteristic (ITT population)	Durvalumab + EP n=268	EP n=269
WHO/ECOG PS, n (%)		
(0) Normal activity	99 (36.9%)	90 (33.5%)
(1) Restricted activity	169 (63.1%)	179 (66.5%)
Primary tumour location,† n (%)		
Lung	268 (100.0%)	269 (100.0%)
AJCC staging,†‡ n (%)		
III§	1 (0.4%)	0
IIIA	5 (1.9%)	3 (1.1%)
IIIB	22 (8.2%)	21 (7.8%)
IV	240 (89.6%)	245 (91.1%)
Histology type,† n (%)		
Small-cell carcinoma (neuroendocrine)	39 (14.6%)	48 (17.8%)
Small-cell carcinoma (combined)¶	229 (85.4%)	220 (81.8%)
Other	0	1 (0.4%)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EP, etoposide plus platinum-based chemotherapy; ITT, intention-to-treat; PS, performance status; SCC, small-cell carcinoma, SCLC, small-cell lung cancer; WHO, World Health Organization

† Primary tumour location, histology and AJCC staging are at diagnosis

‡ AJCC staging: “Stage IV" combines 'Stage IV'/'Stage IVA'/'Stage IVB' from eCRF [PATHGEN] module

§ For the 1 Stage III patient, the TNM indicated Stage IIIb although the data were not reported this way

¶ 'Small-cell carcinoma (combined)' includes SCLC, SCC, SCC oat cell/intermediate/combined oat cell categories listed in the eCRF [PATHGEN] module.

B.3.3.3 Patient disposition

A total of 704 patients were enrolled into the durvalumab + EP and EP groups; of these, 537 were randomised at 209 study centres across 23 countries in North and Latin America, Europe, and Asia Pacific.

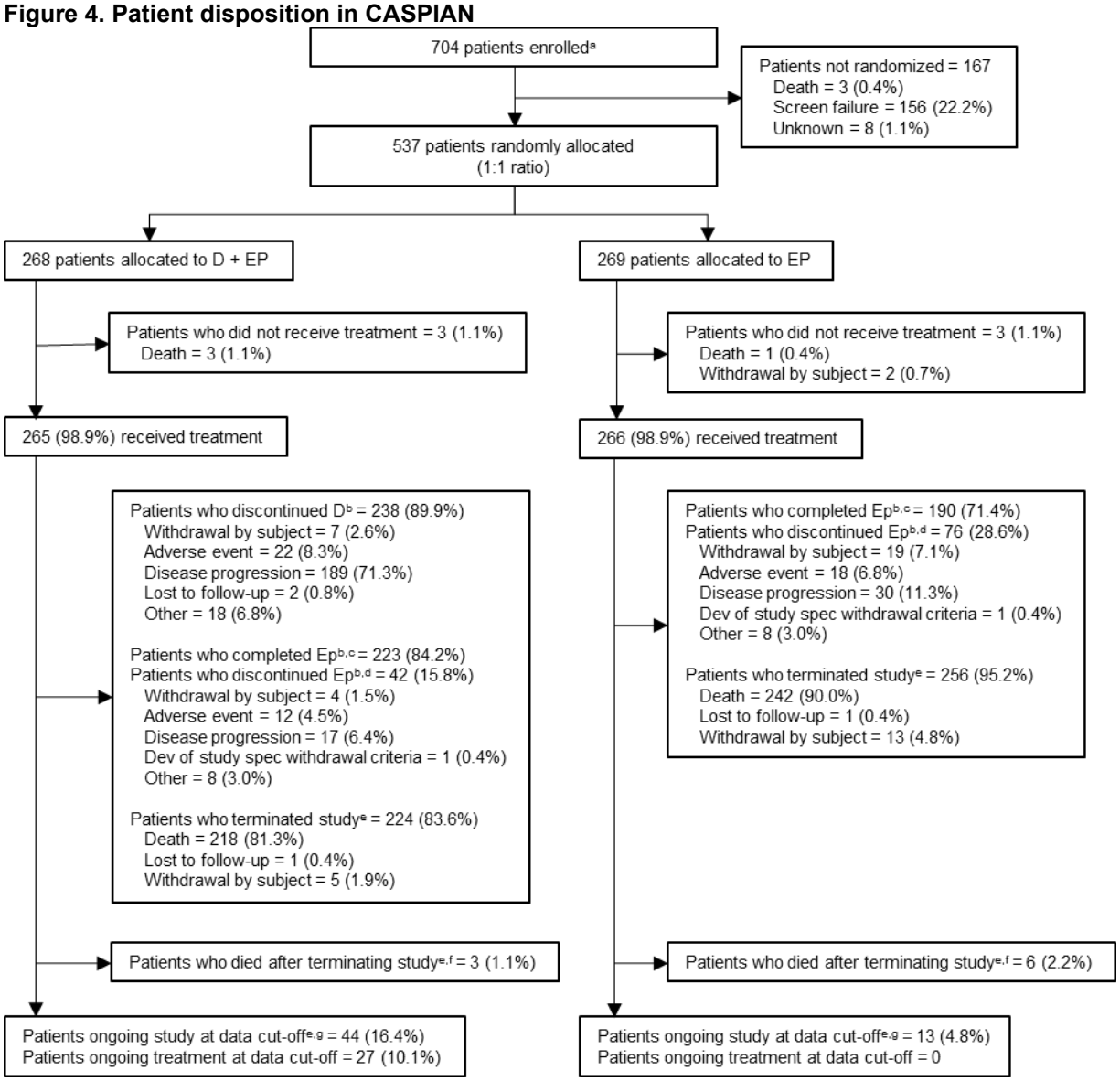
Of the 537 randomised patients, 268 were randomised to the durvalumab + EP group and 269 to the EP group. A total of 265 (98.9%) patients in the durvalumab + EP group and 266 (98.9%) in the EP group received study treatment. In the durvalumab + EP group, 3 (1.1%) randomised patients did not receive any study treatment (2 patients due to death, and 1 patient due to an unknown reason [the recorded reason was unknown; however, this patient was verbally reported to be too sick after randomisation to receive study medication]). In the EP group, 3 (1.1%) randomised patients did not receive any study treatment (1 patient due to death, and 2 patients withdrew consent).

In the durvalumab + EP group, 222 (83.8%) patients discontinued durvalumab; the most frequently reported reasons for discontinuing study treatment were due to disease progression (66.8%), due to an AE (6.8%) and due to other reasons (6.8%).

A total of 222 (83.8%) patients in the durvalumab + EP group and 190 (71.4%) patients in the EP group completed EP treatment (1 patient for EP completion in the durvalumab + EP group is missing due the entry not being recorded on the electronic case report form [eCRF] in error). A total of 42 (15.8%) patients in the durvalumab + EP group and 76 (28.6%) patients in the EP group discontinued EP. The most frequently reported reasons for discontinuing EP in the durvalumab + EP and EP groups were due to disease progression (6.4% and 11.3%, respectively), due to an AE (4.5% and 6.8%, respectively) and withdrawal by the patient (1.5% and 7.1%, respectively). At DCO 22 March 2021 (3-year follow-up), 44 (16.4%) patients in the durvalumab + EP group and 13 (4.8%) patients in the EP group remained in the study.

Three patients (1.1%) in the durvalumab + EP group and 6 (2.2%) patients in the EP group died after terminating the study. A flow diagram of patient disposition is presented in Figure 4.

Figure 4. Patient disposition in CASPIAN



Patient disposition is based on the global cohort.

Abbreviations: D, durvalumab; EP, etoposide and platinum-based chemotherapy.

[a] Patients giving informed consent. Any re-screened patients are counted once.

[b] Percentages are calculated from number of patients who received treatment.

[c] Patients who completed T had "Maximum cycle of immunotherapy reached" reported on the eCRF. Patients who completed EP had "Maximum cycle of chemotherapy reached" reported for any EP molecule on the eCRF.

[d] A patient was considered as having discontinued EP combination when all molecules were discontinued. If different reasons for discontinuation were collected, the last discontinuation reason by date was selected.

[e] Percentages were calculated from number of patients who were randomized.

[f] Obtained from public records or survival follow-up.

[g] Patients ongoing study consisted of those randomized patients still receiving treatment, those randomized patients who completed treatment and were in safety follow-up, or those randomized patients who were still in survival follow-up regardless of whether they were administered treatment or not.

Source: CASPIAN CSR 2021[54]

B.3.4 *Statistical analysis and definition of study groups in CASPIAN*

Approximately 795 patients were needed for 1:1:1 randomisation to obtain 425 events in the durvalumab + EP and EP groups combined (80% maturity) for the analysis of OS at DCO 27 January 2020 (2-year follow-up) and DCO 22 March 2021 (3-year follow-up). Sample size assumptions are detailed in Table 14. The interim analysis of OS was planned when approximately 318 events had occurred both in the durvalumab + EP and EP groups combined (60% maturity). Based on an assumed OS HR of 0.71, it was estimated that the trial would have 71% power to demonstrate statistical significance at the interim analysis with a two-sided significance level of 1.43% (for overall α of 4%) for the comparison of durvalumab + EP versus EP, although the actual α spend was to be based on the observed number of events at data cut-off.

Table 14. Sample size assumptions

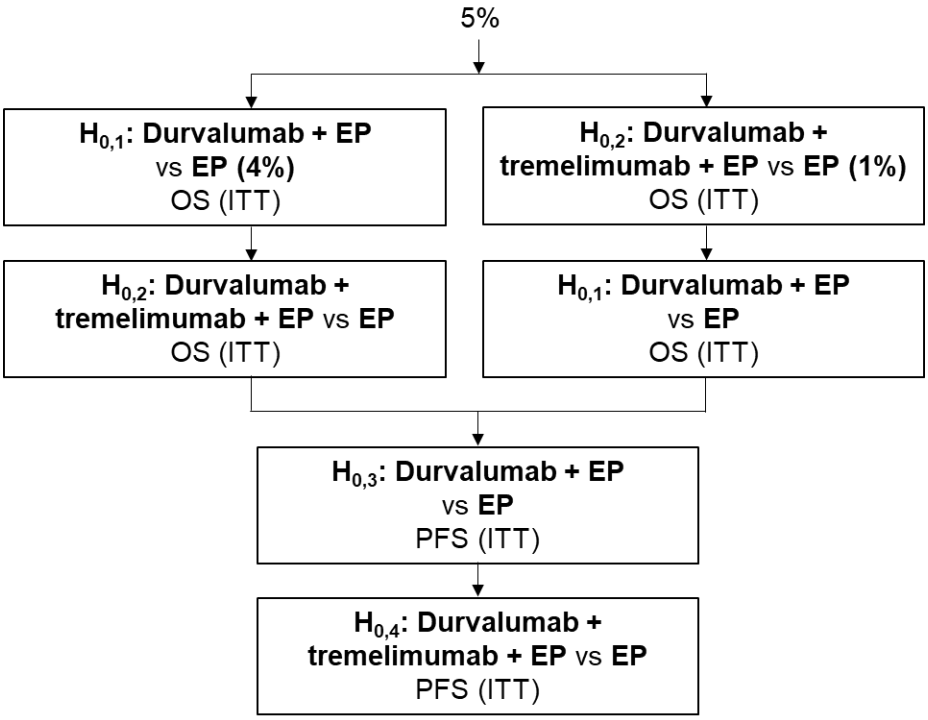
Primary endpoint	Power (%)	HR	Events	Overall 2-sided significance level (%)
OS (durvalumab + EP versus EP)	96	0.69	425	4†

Abbreviations: EP, etoposide and platinum-based chemotherapy; HR, hazard ratio; OS, overall survival.

† Adjusting for one interim analysis of OS planned when 75% of target OS events had occurred and primary analysis of OS, using the Lan–DeMets spending function that approximates an O'Brien-Fleming approach to account for multiple comparisons.[55]

The study was considered to be positive (i.e. the primary hypothesis was met) if OS was significantly longer with durvalumab + EP compared with EP alone. To control the type I error at 5% (two-sided), a hierarchical multiple-testing procedure with a gatekeeping strategy was used across the primary OS analyses and secondary PFS analyses (Figure 5). A 4% α was allocated to OS for durvalumab + EP versus EP. Progression-free survival was only to be formally tested within the multiple testing procedure if both OS primary analyses were significant.

Figure 5. Hierarchical multiple testing procedure



A hierarchical multiple testing procedure with a gatekeeping strategy was used to control the type I error at a two-sided 5% significance level. The hypotheses were to be tested using a multiple testing procedure with an alpha-exhaustive recycling strategy.1 This strategy was used to test the two primary analyses of OS and two secondary analyses of PFS. PFS was therefore only to be tested within the multiple testing procedure if both OS primary analyses achieved significance. The overall 5% alpha was split between the primary endpoints: an alpha level of 4% was allocated to the analysis of OS for durvalumab + EP versus EP, and an alpha level of 1% for the analysis of OS for durvalumab + tremelimumab + EP versus EP.
Abbreviations: EP, etoposide and platinum-based chemotherapy; H, hypothesis; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

Overall survival and PFS were analysed using a stratified log-rank test adjusting for planned platinum (carboplatin or cisplatin), with HRs and 95% CIs estimated using a Cox proportional hazards model. The Kaplan-Meier method was used to estimate OS, PFS, and duration of response (DoR). A pre-specified subgroup analysis of OS was done to establish the consistency of the treatment effect according to predefined baseline characteristics of planned platinum (carboplatin versus cisplatin), age (<65 years versus ≥65 years), sex (women versus men), World Health Organization (WHO) performance status (0 versus 1), smoking status (smoker versus non-smoker), brain or CNS metastases (yes versus no), disease stage at diagnosis (Stage III versus Stage IV), race (Asian versus non-Asian), and region (Asia versus Europe versus North and South America). HRs and 95% CIs for patient subgroups were calculated using an unstratified Cox proportional hazards model with treatment as the only covariate. Sensitivity analyses for OS included assessment of the effect of additional predefined covariates (the same as those included in the subgroup analysis) on the HR estimate. A further sensitivity analysis of OS was done to examine the censoring patterns to identify potential attrition bias, using a Kaplan-Meier plot of time to censoring, where the censoring indicator of OS was reversed. Odds ratios and 95% CIs for comparing the

proportion of patients with an objective response between treatment groups were calculated using a logistic regression model, adjusted for planned platinum therapy.

Data queries were raised for inconsistent, impossible, or missing data. All entries to the study database are available in an audit trail. Patients with missing data for a subgroup variable were excluded from the analysis for that subgroup only. If some lesion measurements were missing but all other lesions meet the complete response criteria (i.e. 0 mm or <10 mm for lymph nodes) then response was set to not evaluable irrespective of whether, when referencing the sum of TL diameters, the criteria for progressive disease are also met. For patient-reported outcomes, visits with excessive missing data (defined as >75% missing data) were excluded.

B.3.4.1 Definition of study groups

Efficacy data were analysed on an intention-to-treat (ITT) basis, including all randomised patients, regardless of whether they received treatment. All patients who received at least one dose of study treatment were included in safety analyses.

Periodic safety monitoring and interim efficacy assessments were done by an independent data monitoring committee.

B.3.5 *Critical appraisal of the relevant clinical effectiveness evidence*

A quality assessment of all trials identified in the clinical systematic review can be found in Appendix D.1.7 (separate Appendices document). The quality assessment for the CASPIAN study, which is the only clinical study relevant to this submission, is presented in Table 15.

Table 15. Quality assessment results for CASPIAN

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	IVRS/IWRS was used for randomisation. A blocked randomisation list was produced for each of the strata.	Yes
Was the concealment of treatment allocation adequate?	Open-label study The AstraZeneca study team was blinded to aggregate treatment information.	NA
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (see Section B.3.3.2, Table 14)	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	The sponsor was blinded to treatment allocation. During the programming and preparation of statistical outputs, data were dummy blinded.	No

	How is the question addressed?	Grade (yes/no/unclear/NA)
Were there any unexpected imbalances in drop-outs between groups?	No (see Section B.3.3.3)	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, the pre-specified outcomes are reported in the CSR	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Abbreviations: CSR, clinical study report; IVRS, Interactive Voice Response System; IWRS, Interactive Web Response System; NA, not applicable.

Source: CASPIAN CSR 2019[52]

B.3.6 *Clinical effectiveness results of CASPIAN*

The results presented for the primary endpoint of OS are based on the DCO 27 January 2020 (2-year follow-up) and DCO 22 March 2021 (3-year follow-up) analyses, whereas the results for the secondary outcomes are solely based on the analysis at DCO 27 January 2020 (2-year follow-up). At the time of the OS DCO 22 March 2021 (3-year follow-up) analysis, [redacted] deaths had occurred between both the durvalumab + EP and EP groups ([redacted] % maturity overall for OS). The OS analysis at DCO 27 January 2020 (2-year follow-up), between the durvalumab + EP and EP groups, took place at 82.1% maturity, after 441 death events had occurred.

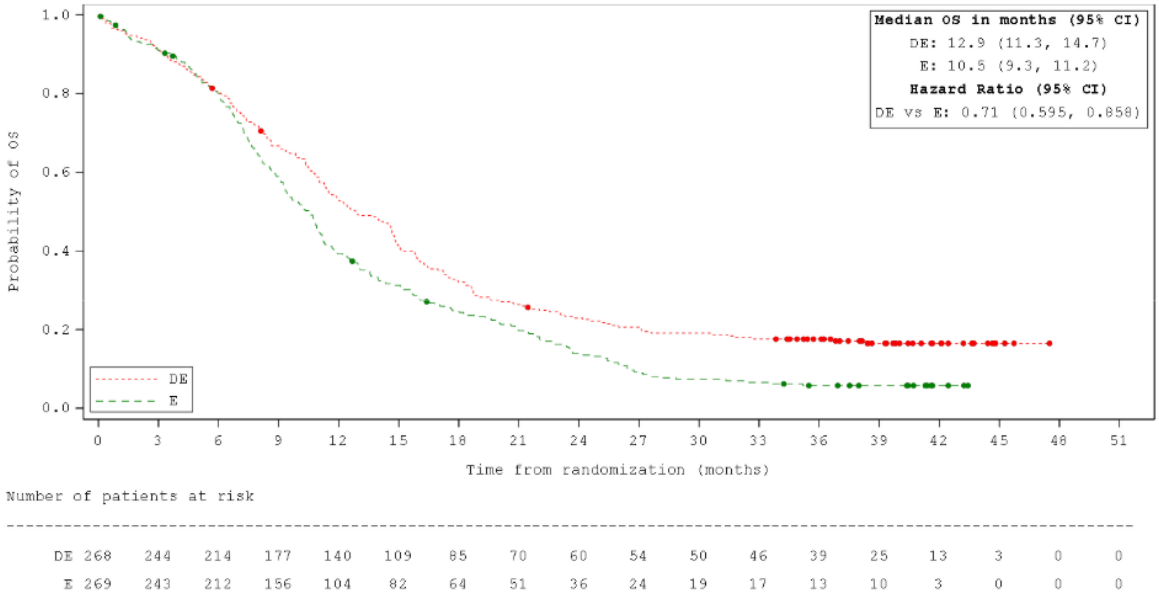
The analysis of OS met the prespecified O'Brien Fleming type boundary for declaring statistical significance between the durvalumab + EP versus EP groups (based on the Lan-DeMets alpha spending function to ensure strong control of the Type 1 error for interim and primary analysis with 2-sided interim p-value <0.0178 for the durvalumab + EP versus EP alone comparison).

B.3.6.1 Primary efficacy outcome: Overall survival, DCO 22 March 2021 (3-year follow-up), [redacted]% maturity

The addition of durvalumab to EP significantly improved OS, reducing the risk of death by 29% compared with EP alone (HR, 0.71; 95% CI, 0.595, 0.858; p=0.0003, Figure 6). The results of the analysis at DCO 22 March 2021 (3-year follow-up) are consistent with the OS analysis at DCO 27 January 2020 (2-year follow-up) (HR, 0.75; 95% CI, 0.625, 0.910; p=0.0032). The HR from the 3-year follow-up corresponded to an increase in median OS of 2.4 months, from 10.5 to 12.9 months. The difference between treatment groups was sustained over the follow-up period, as observed at 12 months (52.8% versus 39.3%) and 18 months (32.0% versus 24.8%), 24 months (22.9% versus 13.9%) and 36 months (17.6% versus 5.8%).

The OS benefit was consistent across all pre-specified subgroups at the DCO 22 March 2021 (3-year follow-up) analysis, favouring durvalumab +EP, providing confidence in the applicability of the results to patients in UK clinical practice. For example, consistent with the OS subgroup analysis at DCO 27 January 2020 (2-year follow-up), there were no differences between subgroups based on performance status or the presence of brain/CNS metastases at baseline (Figure 7).

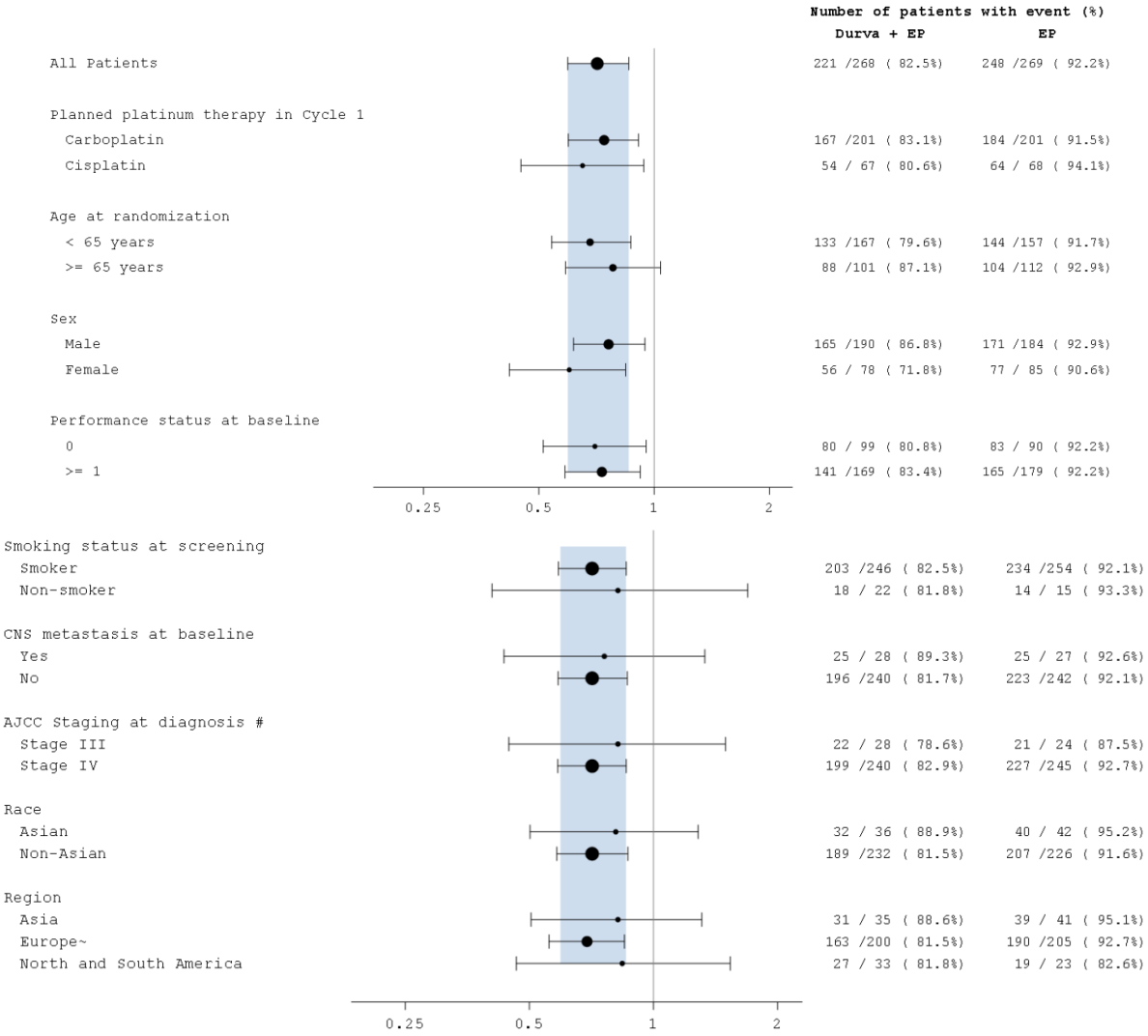
Figure 6. Overall survival in CASPIAN; DCO 22 March 2021 (3-year follow-up) (Full Analysis Set)



Abbreviations: CI, confidence interval; D + E/P/DE, durvalumab + etoposide and platinum-based chemotherapy; EP, etoposide plus platinum-based chemotherapy; HR, hazard ratio; (m)OS, (median) overall survival.

Source: CASPIAN CSR 2021[54]

Figure 7. Subgroup analysis of OS for CASPIAN; DCO 22 March 2021 (3-year follow-up) (Full Analysis Set)



Size of circle is proportional to the number of events across both treatment groups. Gray band represents the 95% CI for the overall (all patients) hazard ratio. For the "All Patients" analysis: same model as the main analysis. For the subgroup analysis: the HR and CIs were calculated using an unstratified Cox proportional hazards model, with treatment as only covariate and ties handled by Efron approach. A HR < 1 favours Durva + EP to be associated with a longer OS than EP.

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; CNS, central nervous system; EP, etoposide plus platinum-based chemotherapy; HR, hazard ratio; OS, overall survival.

Source: CASPIAN CSR 2021[54]

B.3.6.1.1 Sensitivity analysis

In the analysis conducted at DCO 22 March 2021, a sensitivity analysis was performed for OS to assess censoring patterns and identify potential attrition bias. This involved generating a Kaplan-Meier plot of time to censoring, where the censoring indicator for

OS was reversed. The analysis did not show evidence of differential censoring patterns between the treatment groups.

B.3.6.2 Secondary analysis of primary outcome

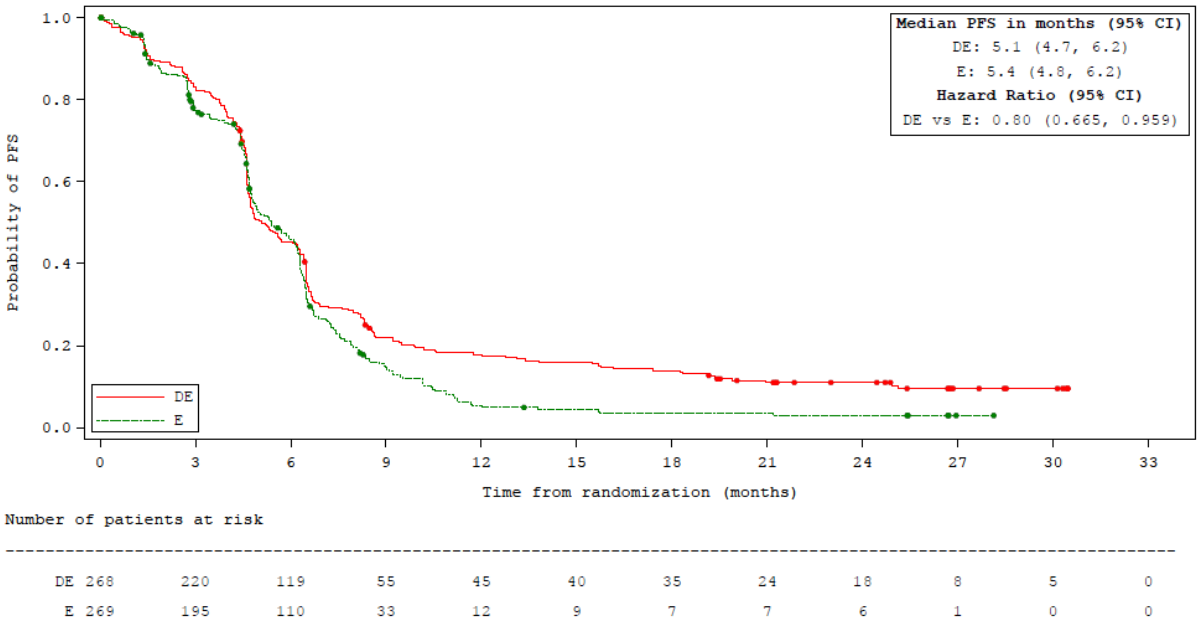
A secondary analysis of the primary outcome was only planned for durvalumab + tremelimumab + EP versus durvalumab + EP and is therefore not available for this analysis.

B.3.6.3 Secondary efficacy outcomes

B.3.6.3.1 Progression-free survival

Measured at DCO 27 January 2020 (2-year follow-up), the addition of durvalumab to EP also provided a clinically meaningful prolongation of PFS compared with EP alone (HR: 0.80; 95% CI: 0.665, 0.959; p value=[redacted]). Treatment with durvalumab + EP reduced the overall risk of progression or death by an average of 20% compared with EP alone. The Kaplan-Meier (KM) plots for the two treatment groups are similar over the first six months, possibly reflecting the fact that over half (56.8%) of patients in the control group received six cycles of EP (while patients in the durvalumab + EP group could only receive up to four cycles).[56] Delayed treatment effects are not uncommon in IO.[57-60] However, beyond six months the KM curves separate, showing an advantage for the durvalumab + EP group, resulting in a [redacted]% reduction in the risk of disease progression or death (HR, [redacted]; 95% CI, [redacted], [redacted]; nominal p=[redacted]). At 12 months, 17.5% of patients in the durvalumab + EP group remained free of progression, compared with 4.7% in the control group (Figure 8). According to subgroup analyses, PFS was consistently [redacted] in the durvalumab + EP group compared with the control group, except for [redacted]. However, the subgroups were not powered to detect significant differences. Therefore, these data should be interpreted with caution.

Figure 8. PFS in CASPIAN: DCO 27 January 2020 (2-year follow-up)



Abbreviations: CI, confidence interval; EP, etoposide plus platinum-based chemotherapy; HR, hazard ratio; (m)PFS, (median) progression-free survival; RECIST v1.1, response evaluation criteria in solid tumors, version 1.1. *Investigator assessed per RECIST v1.1

Source: CASPIAN CSR 2020[56]

B.3.6.3.2 Objective response rate and duration of response

At DCO 27 January 2020 (2-year follow-up), the addition of durvalumab to EP was associated with an increase in unconfirmed objective response rate (ORR) of approximately [redacted]% (unconfirmed ORR [redacted]% versus [redacted] %; OR [redacted], 95% CI [redacted], [redacted], nominal p=[redacted]). The analysis of unconfirmed ORR was pre-specified in the protocol. The addition of durvalumab to EP was associated with an increase in confirmed ORR of approximately 10% (confirmed ORR 67.9% versus 58.0%; OR 1.53, 95% CI 1.078, 2.185, nominal p=[redacted]; Figure 9a).[56] The analysis of confirmed ORR was conducted post hoc.

At DCO 27 January 2020 (2-year follow-up), the median DoR (post-hoc analysis) was 5.1 months in both groups, but, as for PFS, the difference between treatment groups emerged after the first 6 months, with the result that at 12 months, 23.2% of responders in the durvalumab + EP group remained in confirmed response, compared with 7.3% of responders in the control group (Figure 9b). This difference was sustained at 24 months, at 13.5% and 3.9% respectively for the durvalumab + EP and EP alone group.

Figure 9. Confirmed ORR and DoR in CASPIAN: final analysis

a)

Objective Response Rate*	Durvalumab + EP (n=268)	EP (n=269)
Patients with response (%)	67.9%	58.0%

Odd Ratio (95% CI)	1.53 (1.078, 2.185)
p-value	P=

b)

a) Confirmed ORR and b) DoR in CASPIAN: final analysis

Abbreviations: CI, confidence interval; DCO, data cut-ff; DoR, duration of response; EP, etoposide plus platinum-based chemotherapy; ORR, objective response rate; RECIST v1.1, response evaluation criteria in solid tumors, version 1.1.

*Investigator assessed per RECIST v1.1

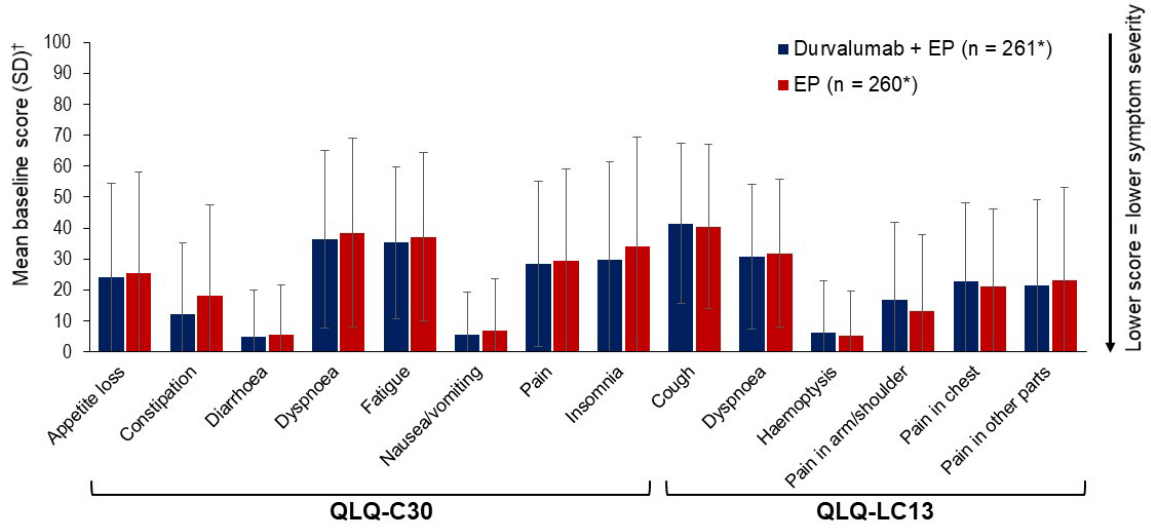
Source: CASPIAN CSR 2020[56]

B.3.6.4 Patient-reported outcomes

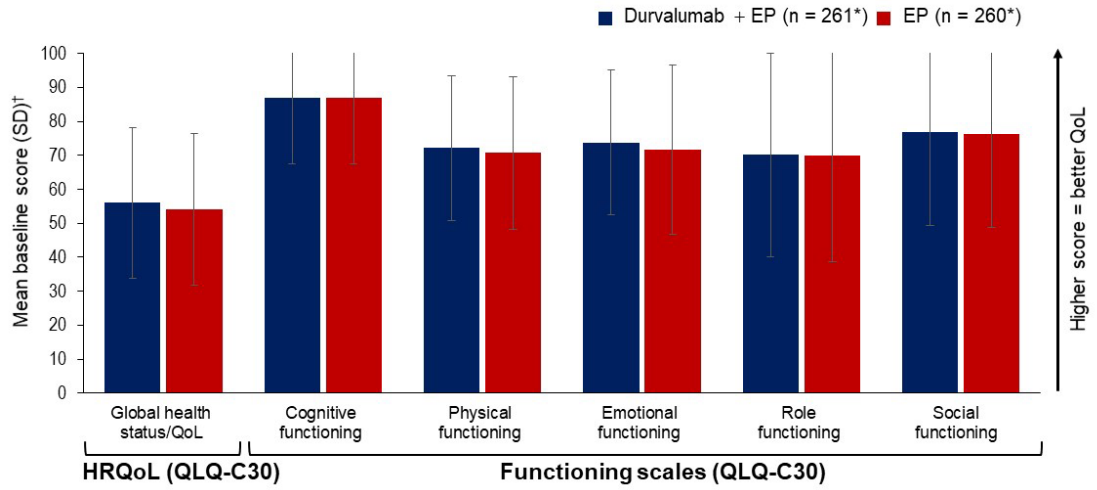
Compliance with EORTC QLQ assessments was high at baseline (> %) and in both the durvalumab + EP and EP groups.[31] Compliance remained > % up to Week 84 (i.e. end of Cycle 28) in the durvalumab + EP group and up to 20 weeks (i.e. end of Cycle 6) in the EP group. Baseline scores were comparable for the two treatment groups, with symptom scores of at least 30 being seen for fatigue, insomnia, dyspnoea (EORTC QLQ-C30 and QLQ-LC13) and cough, and <10 for nausea/vomiting, diarrhoea, haemoptysis, sore mouth, dysphagia, and alopecia (Figure 10a). Mean baseline scores for GHS and EORTC QLQ-C30 functioning domains were also similar for the two groups and were indicative of a poor HRQoL compared with the general population (approximately 54 and 56, respectively, versus 66 for the general population).[29] A greater impact of the disease on role functioning (approximately 70 versus 84 for the general population) and physical functioning (71 and 72, respectively, versus 85) was seen compared with social functioning (76 and 77, respectively, versus 86), cognitive functioning (87 versus 85) and emotional functioning (72 and 74, respectively, versus 74, Figure 10b).

Figure 10. Baseline HRQoL, functional domains and symptom scores for patients in CASPIAN

a)



b)



Abbreviations: SD, standard deviation; EP, etoposide plus platinum-based chemotherapy; HRQoL, health-related quality of life; PRO, patient-reported outcome; QLQ, Quality of Life Questionnaire; QoL, quality of life.

*Patients evaluable for PROs; 245 patients in each arm had baseline data available

†Symptoms/global health status/QoL and functioning are scored on 0–100-point scale

Source: Paz-Ares et al, 2019[31]

At DCO 27 January 2020 (2-year follow-up analysis), results for patient assessments of HRQoL and symptoms showed [redacted] time to deterioration for patient-reported global health status/QoL, and significant [redacted] for all functioning and symptom scales in favour of durvalumab + EP versus EP (Figure 11).[52,61] Statistically significant differences in time to deterioration between treatment groups were also seen for [redacted] (Figure 11b). The time to deterioration was [redacted] months (durvalumab + EP) versus [redacted] months (EP) for physical functioning (p=[redacted]), [redacted] versus [redacted] months for role

functioning (p=[redacted]), [redacted] versus [redacted] months for emotional functioning (p=[redacted]), [redacted] versus [redacted] months for cognitive functioning (p<[redacted]) and [redacted] versus [redacted] months for social functioning (p=[redacted]).

Figure 11. Time to deterioration in a) EORTC QLQ-C30 functioning and HRQoL subscales/items and b) symptom subscales/items (EORTC QLQ-C30 and QLQ-LC13) for durvalumab + EP versus EP alone (DCO 27 January 2020)

Abbreviations: CI, confidence interval; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EP, etoposide plus platinum-based chemotherapy; HR; hazard ratio; HRQoL, health-related quality of life
Source: CASPIAN CSR 2020[56]

Clinically relevant improvements in the pre-defined key symptoms were observed in [redacted] between baseline and 2 years follow-up and in some cases occurred earlier in the durvalumab + EP group.[56] Reductions in other symptoms ([redacted] as measured by EORTC QLQ-C30 and, [redacted] as measured by EORTC QLQ-LC13) [redacted] significantly between treatment groups.

B.3.6.5 Conclusion

The randomised, open-label, phase 3 CASPIAN trial demonstrated that the addition of durvalumab to EP as first-line treatment for ES-SCLC resulted in significantly longer OS than versus the control group.

The addition of durvalumab to EP demonstrated a statistically significant and clinically meaningful improvement in OS compared with EP alone (HR 0.71; 95% CI, 0.595, 0.858; p=0.0003) based on the DCO 22 March 2021, representing 3-year follow-up. The treatment effect was sustained over time, as shown by the OS results at 12,18, 24 and 36 months, and the pre-specified sensitivity analyses supported the primary OS analysis. With 3 years of follow-up, the CASPIAN trial has the longest phase 3 trial follow-up period of any IO in this setting.[13,54] The OS benefit was observed against a robust control group which allowed PCI, and up to six cycles of EP. The subgroup analyses of OS demonstrated that the OS benefits favouring the durvalumab + EP treatment were consistent across all pre-specified stratification factors and subgroups, including by performance status and the presence of brain metastases, underlining the applicability of the results to UK clinical practice. The overall risk of death was reduced by an average of 29% after 3 years.

Durvalumab + EP demonstrated a sustained improvement in PFS with nearly four times the number of patients progression-free at 24 months versus EP and ~10.1% of patients with ongoing treatment at 3 years.

Addition of durvalumab to EP provided an improvement in QoL by delaying worsening of patient-reported symptoms, functioning, and HRQoL compared with EP alone.

B.3.7 *Subgroup analysis*

Please see Section B.3.6.1 for subgroup analyses.

B.3.8 *Meta-analysis*

Since only a single relevant RCT for durvalumab + EP in the treatment of ES-SCLC is available (see Section B.3.2), no meta-analysis could be performed.

B.3.9 *Indirect and mixed treatment comparisons*

As described in Section B.1.1, atezolizumab + EP is recommended by NICE and considered the current SoC for first-line ES-SCLC. In the absence of a study directly comparing durvalumab + EP and atezolizumab + EP for the first-line treatment of patients with ES-SCLC, an ITC has been conducted.

As described in section D.1 of the appendices, a systematic literature review (SLR) of phase II-IV RCTs assessing the efficacy and safety of first-line treatment strategies for adult patients with ES-SCLC was performed in October 2018 and updated in September 2019 and May 2024. In combination with the original SLRs, 51 studies in 68 publications were identified. The CASPIAN and IMpower133 studies were the studies of interest for

the ITC given that they are of most relevance to this submission. The comparability of the CASPIAN and IMpower133 trials was assessed and overall, the trials were similar, except for the platinum-based chemotherapy used. Participants of IMpower133 received atezolizumab with etoposide and carboplatin.[62] In CASPIAN,[63] participants were given either etoposide and carboplatin or etoposide with cisplatin based on investigator's choice with or without durvalumab. Thus, the studies were connected via the common comparator etoposide and carboplatin. After an assessment of equivalence between etoposide with cisplatin and etoposide with carboplatin (see Appendix D.3.1.2.7), the base case analysis was based on assuming equivalence (pooling the therapies, etoposide with cisplatin and carboplatin). Sensitivity analyses adopting the more conservative approach assuming that cisplatin and carboplatin were not equivalent were also conducted. Please see Appendix D for the results of the analyses under the assumption of non-equivalence.

The ITC was performed using the Frequentist Bucher approach.[64] The efficacy of durvalumab + EP vs atezolizumab + EP for first-line ES-SCLC was assessed based on OS, PFS, and safety outcomes. The ITC was originally conducted on efficacy and safety outcomes from the DCO 27 January 2020, at around 2 years of follow-up. The ITC was subsequently updated with the inclusion of the CASPIAN trial results for the OS outcome based on the DCO 22 March 2021 (3-year follow-up).

The DCO used in each analysis was dependent on availability of data for each respective outcome. Overall survival analyses were based on the 3-year follow-up analysis (DCO 22 March 2021) of CASPIAN[45,54] and the 2-year data analysis from IMPower133 (median follow-up of 22.9 months),[13] whilst PFS and safety analyses are based on the 2-year follow-up analysis (DCO 27 January 2020) of CASPIAN[43,56] and results from IMpower133 with a median follow-up of 13.9 months.[62] The IMpower133 publication used to inform atezolizumab + EP efficacy in the latest OS analyses also reported 2-year follow-up for PFS and safety outcomes however, the point estimate for the PFS HR (HR: 0.77 [0.63, 0.95] did not change from the primary analysis.[62,65] Therefore, the primary IMpower133 publication was used for the PFS and safety analyses, as it would not have materially impacted the results.

Given the poor prognosis of ES-SCLC patients and its designation as a primary endpoint in the CASPIAN and IMPower133 studies, OS was considered the most relevant outcome. See Appendix D for the full ITC methods.

The network for the ITC of durvalumab versus atezolizumab is provided in Figure 12.

Figure 12. Network for the ITC of durvalumab versus atezolizumab

Abbreviations: AT, atezolizumab; CAR, carboplatin; CIS, cisplatin; DUR, durvalumab; ET, etoposide
*The base case network assumed equivalence between etoposide with cisplatin and etoposide with carboplatin

B.3.9.1 Results

B.3.9.2 Overall survival

Overall survival analyses were conducted based on the 3-year follow-up results (DCO 22 March 2021, median follow-up of 39.4 months) for the CASPIAN trial,[45,54] and OS data with a median follow-up of 22.9 months for atezolizumab in the IMpower133 trial.[13]

Results based on the DCO of 22 March 2021 indicate that durvalumab + EP offers a benefit in OS over atezolizumab +EP (HR: [redacted] [redacted], [redacted]]) (Table 16). However, in the absence of statistically significant results, a conservative assumption of equivalent efficacy can be assumed.

Table 16. Data informing and results of the ITC for OS*

Study	Treatment 1	Treatment 2	Within-trial HR (95% CI) Trt 1 versus Trt 2	ITC (between trial) HR (95% CI) durvalumab + EP versus atezolizumab + EP
CASPIAN[54]	durvalumab + EP	EP	0.71 (0.6, 0.86)	[redacted] ([redacted], [redacted])
IMpower133[13]	atezolizumab + EP	EP	0.76 (0.60, 0.95)	

Abbreviations: CI, confidence interval; EP, etoposide + platinum-based chemotherapy; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; Trt, treatment
*Analysis based on the assumption of equivalence between cisplatin and carboplatin

B.3.9.3 Progression-free survival

Analyses for PFS were conducted based on the DCO of 27 January 2020 (2-year follow-up, median follow-up time of 25.1 months) for the CASPIAN trial,[43,56] and atezolizumab data from the IMpower133 trial at a median follow-up of 13.9 months.[62] Results of the PFS analyses indicate no significant difference between durvalumab + EP and atezolizumab + EP (HR: [redacted] [redacted], [redacted]]) (Table 17).

Table 17. Data informing and results of the ITC for PFS*

Study	Treatment 1	Treatment 2	Within-trial HR (95% CI) Trt 1 versus Trt 2	ITC (between trial) HR (95% CI) durvalumab + EP versus atezolizumab + EP
CASPIAN[56]	durvalumab + EP	EP	0.80 (0.67, 0.96)	[redacted] ([redacted], [redacted])
IMpower133[62]	atezolizumab + EP	EP	0.77 (0.62, 0.96)	

Abbreviations: CI, confidence interval; EP, etoposide + platinum-based chemotherapy; HR, hazard ratio; ITC, indirect treatment comparison; PFS, progression-free survival; Trt, treatment

*Analysis based on the assumption of equivalence between cisplatin and carboplatin

B.3.9.4 Safety endpoints

Analyses for safety outcomes were conducted based on the DCO of 27 January 2020 (2-year follow-up) for the CASPIAN trial,[43,56] and atezolizumab data from the IMpower133 trial at a median follow-up of 13.9 months.[62]

The results for overall grade 3-4 and serious treatment-related AEs indicate no significant difference between durvalumab + EP and atezolizumab + EP (Table 18). Durvalumab + EP seems to perform better than atezolizumab + EP in reducing overall grade 3-4 treatment-related AEs (OR: [redacted] [[redacted], [redacted]]). Additionally, durvalumab + EP reduced the risk of serious treatment-related AEs compared to atezolizumab + EP (OR: [redacted] [[redacted], [redacted]]). Both results were not statistically significant and were consistent with the ITCs without the assumption of equivalence. The results for specific grade 3-4 treatment-related AEs are presented in Appendix D.4.

Table 18. Data informing and results of the ITCs for treatment-related AEs*

Study	Treatment 1	Treatment 2	Within trial			ITC (between trial) OR (95% CI) DUR + EP vs AT + EP
			% (n/N)		OR (95% CI)	
			Trt 1	Trt 2	Trt 1 vs Trt 2	
Grade 3-4 treatment-related AEs						
CASPIAN[56]	durvalumab + EP	EP	45.7 (121/265)	51.9 (138/266)	0.78 (0.55, 1.10)	[redacted] ([redacted], [redacted])
IMpower133 [62]	atezolizumab + EP	EP	56.6 (112/198)	56.1 (110/196)	1.02 (0.68, 1.52)	
Serious treatment-related AEs						
CASPIAN[56]	durvalumab + EP	EP	13.2 (35/265)	18.8 (50/266)	0.66 (0.41, 1.05)	[redacted] ([redacted], [redacted])
IMpower133 [62]	atezolizumab + EP	EP	22.7 (45/198)	18.9 (37/196)	1.26 (0.78, 2.06)	

Abbreviations: AE, adverse event; AT, atezolizumab; CI, confidence interval; DUR, durvalumab; EP, etoposide + platinum-based chemotherapy; ITC, indirect treatment comparison; OR, odd ratio; Trt, treatment

*Analysis based on the assumption of equivalence between cisplatin and carboplatin

B.3.9.5 Strengths and uncertainties in the ITC

Overall, the ITC demonstrates similar efficacy and safety between durvalumab + EP and atezolizumab + EP in patients with ES-SCLC, with a directional improvement in OS and safety endpoints in favour of durvalumab + EP.

The CASPIAN and IMpower133 trials are similar in design, patient population, eligibility criteria, and baseline characteristics. The platinum-based chemotherapy differs between the trials. The CASPIAN trial is well balanced with respect to the cisplatin and carboplatin treatment arms given this was a stratification factor, therefore, the potential bias in the CASPIAN trial is expected to be minimal. Steps were also taken to evaluate equivalence of cisplatin and carboplatin (see Appendix D.3.1.2.7), and ITC analyses were performed with and without assuming equivalence of cisplatin and carboplatin. The results of the analyses are consistent, indicating that although the choice of platinum-based chemotherapy differs between trials, this does not have an important impact on the results.

A feasibility assessment was conducted that included an assessment of potential treatment effect modifiers. The ad-hoc targeted review showed treatment effect modifiers in ES-SCLC are not widely reported in the literature. Additionally, analyses of the CASPIAN trial did not identify any statistical evidence of treatment effect modifiers. Since

the patient baseline characteristics were balanced between CASPIAN and IMpower133, any treatment effect modifiers would have a minor impact on the relative treatment effects and the validity of the ITC.

A conservative assumption of equivalent efficacy can therefore be assumed for the purpose of cost-comparison. The results from the ITC analyses were further validated by UK oncologists (N=6), all of whom stated that they would expect durvalumab + EP to have a comparable efficacy to atezolizumab + EP in ES-SCLC.[2]

B.3.10 *CASPIAN adverse reactions*

B.3.10.1 Exposure

In both treatment groups, approximately a quarter of patients received cisplatin and the remainder received carboplatin,[27] which is largely in line with UK clinical practice.[2] The median (range) number of EP cycles received was 4 (1–6) in the durvalumab + EP group and 86.8% of patients received 4 cycles or more, indicating that the addition of durvalumab did not compromise the delivery of EP (given that the planned number of cycles to be delivered was 4). In the control group, the median number of EP cycles received was six and 56.8% of patients received six cycles. Although up to six cycles of EP therapy are recommended by NICE,[66] UK clinicians have advised that not all patients would receive six cycles,[67] and the clinical data indicate that further cycles of EP (beyond four cycles) do not offer an OS benefit.[68]

The median duration of exposure to durvalumab was 28 weeks and was thus long enough to evaluate the safety profile of the combination regimen.[52] At the time of the long-term follow-up analysis, patients in the durvalumab + EP group received a median (range) of 7 (1–52) doses of durvalumab and 32 (12.1%) patients received at least 28 cycles of durvalumab, representing 2 years of dosing, and 20 (7.5%) patients received at least 41 cycles which represent approximately 3 years of dosing. Approximately 50% of patients in both groups required dose delays, largely due to AEs.

B.3.10.2 Adverse event overview

Safety analyses were conducted at DCO 11 March 2019 (1-year follow-up), DCO 27 January 2020 (2-year follow-up) and DCO 22 March 2021 (3-year follow-up) and included 265 patients from the durvalumab + EP group and 266 patients from the EP group. The results from DCO 27 January 2020 and DCO 22 March 2021 (the 2- and 3-year follow-ups) are presented and form the focus of this submission unless stated otherwise. The results presented from the DCO 27 January 2021 (2-year follow-up) analysis include all AEs, serious AEs (SAEs) and deaths. The safety analyses at the 3-year follow-up (DCO 22 March 2021) only reported an update for SAEs and deaths as all additional events occurred in patients who were still receiving durvalumab (or were within 90 days of treatment discontinuation).

The overall safety profile in the CASPIAN trial was comparable between the durvalumab + EP and EP groups and was consistent with the known safety profile of individual

treatment components. At the 3-year follow-up (DCO 22 March 2021), there were no new safety signals identified or significant changes in the safety profile for durvalumab + EP compared to EP alone, demonstrating consistency in patient tolerability. Changes in AEs between the 3-year follow-up (DCO 22 March 2021) and the 2-year follow-up (DCO 27 January 2020) analysis were numerical in nature (Table 19, bold text representing changes at the 3-year follow-up). Most patients experienced at least one AE, and approximately 60% of patients experienced Grade 3/4 AEs, with only 10.2% and 9.4% of patients discontinuing therapy due to AEs in the durvalumab + EP and EP group respectively (Table 19).[54,56]

At the 2-year follow-up (DCO 27 January 2020), the incidence of AEs leading to death was slightly higher in the control versus the intervention group (5.6% versus 4.9%), as was the incidence of SAEs, reflecting the longer duration of chemotherapy (i.e. six versus four cycles) in the control group. These results were reflected in the 3-year follow-up (DCO 22 March 2021), with the incidence of AEs leading to death of 6.0% versus 5.3% for the control group and durvalumab + EP respectively. Incidences of SAEs were also slightly higher in the control versus intervention groups (36.5% versus 32.5%) at the long-term follow-up analysis. Also at the time 2-year follow-up analysis (DCO 27 January 2020), the incidence of AEs leading to treatment delay or interruption was slightly higher in the durvalumab + EP group ([redacted]% versus [redacted] % for the EP group) and may reflect the longer overall duration of therapy (i.e. inclusion of durvalumab maintenance therapy).

The incidence of AEs of special interest (AESIs) was numerically higher in the durvalumab + EP group ([redacted] % versus [redacted] %) due to a higher incidence of thyroid endocrinopathy events at DCO 27 January 2020 (2-year follow-up). This is consistent with the known safety profile of durvalumab and was manageable with the use of steroids or endocrine therapy.

Table 19. Summary of the evidence of AEs in CASPIAN- DCO 27 January 2020, with numerical changes from DCO 22 March 2021 shown in bold

AEs, n (%)	**Durvalumab + EP N=265**	**EP N=266**
Any AE	260 (98.1%)	258 (97.0%)
Grade 3/4 AEs	[redacted]	[redacted]
Serious AEs	**86 (32.5%)**	97 (36.5%)
AEs leading to treatment discontinuation	27 (10.2%)	25 (9.4%)
Immune-mediated AEs†	53 (20.0%)	7 (2.6%)
AEs leading to death	**14 (5.3%)**	**16 (6.0%)**
Treatment-related AEs leading to death	6 (2.3%)	2 (0.8%)
AESIs	[redacted]	[redacted]
Any AE leading to drug delay/interruption	[redacted]	[redacted]

Abbreviations: AE, adverse event; AESI, adverse event of special interest; EP, etoposide plus platinum-based chemotherapy

†An event that is associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is no clear alternate aetiology and the event required treatment with systemic

corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy; the majority of immune-mediated AEs were low grade and thyroid related
Source: Goldman et al, 2021[43]; Paz-Ares et al, 2022[45]; CASPIAN CSR 2021, 2020[54,56]

At DCO 27 January 2020 (2-year follow-up), the most commonly reported AEs (incidence of ≥15%) were consistent with the known safety profile of EP, with haematological AEs being the most frequent (Table 20). [56] The incidence of neutropenia, anaemia and thrombocytopenia was higher in the control group, probably reflecting the longer duration of chemotherapy.

Table 20. Incidence of AEs reported in ≥15% of patients in either treatment group in CASPIAN- DCO 27 January 2020

AEs, n (%)	Durvalumab + EP N=265	EP N=266
Neutropenia	111 (41.9)	124 (46.6)
Anaemia	102 (38.5)	125 (47)
Nausea	89 (33.6)	89 (33.5)
Alopecia	84 (31.7)	91 (34.2)
Constipation	45 (17.0)	51 (19.2)
Decreased appetite	48 (18.1)	46 (17.3)
Thrombocytopenia	41 (15.5)	53 (19.9)
Fatigue	48 (18.1)	45 (16.9)
Asthenia	42 (15.8)	40 (15)
Vomiting	39 (14.7)	44 (16.5)
Leukopenia	40 (15.1)	32 (12)
Diarrhoea	29 (10.9)	30 (11.3)
Pruritus	21 (7.9)	10 (3.8)

Abbreviations: AE, adverse event; EP, etoposide plus platinum-based chemotherapy.
Source: Goldman et al, 2021[43]; CASPIAN CSR 2020[56]

In both treatment groups, at the 2-year follow-up analysis (DCO 27 January 2020), haematological AEs were the most frequently reported Grade 3/4 AEs and the only Grade 3/4 AEs reported in >5% of patients (Table 21). The incidence of Grade 3/4 neutropenia, anaemia and thrombocytopenia were higher in the control group (EP) versus the intervention group. The only Grade 3/4 AEs reported to occur at a higher incidence (difference of ≥1.5%) in the durvalumab + EP group were increased lipase levels, increased amylase levels and hypertension, while pneumonia occurred more frequently in the control group.

Table 21. Incidence of Grade 3/4 AEs reported in at least 2% of patients in either treatment group in CASPIAN- DCO 27 January 2020

AEs, n (%)	Durvalumab + EP N=265	EP N=266
Any Grade 3/4 AEs	[redacted]	[redacted]
Neutropenia	64 (24.2)	88 (33.1)
Anaemia	24 (9.1)	48 (18)
Thrombocytopenia	15 (5.7)	25 (9.4)
Febrile neutropenia	14 (5.3)	17 (6.4)
Neutrophil count decreased	17 (6.4)	17 (6.4)
Leukopenia	17 (6.4)	14 (5.3)
Hyponatraemia	10 (3.8)	7 (2.6)
Pneumonia	5 (1.9)	9 (3.4)
White blood cell count decreased	4 (1.5)	6 (2.3)
Lipase increased	9 (3.4)	4 (1.5)
Platelet count decreased	4 (1.5)	6 (2.3)
Hypertension	8 (3)	1 (0.4)
Amylase increased	6 (2.3)	1 (0.4)

Abbreviations: AE, adverse event; EP, etoposide plus platinum-based chemotherapy
Source: Goldman et al, 2021[43]; CASPIAN CSR 2020[56]

The incidence of individual AESIs reported at the 2-year follow-up (DCO 27 January 2020) was higher in the durvalumab + EP group, largely reflecting the higher incidence of thyroid endocrinopathy and thus consistent with the known safety profile of durvalumab (Table 22).[56] The AESI of dermatitis /rash was also reported at a higher incidence (difference >2%) in the durvalumab + EP group ([redacted]% versus [redacted]%).

Table 22. Incidence of AESIs in CASPIAN- DCO 27 January 2020

AESI, n (%)	**Durvalumab + EP N=265**	**EP N=266**
Any AESI	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Diarrhoea/colitis	[redacted]	[redacted]
Hepatic events	[redacted]	[redacted]
Hypothyroid events	[redacted]	[redacted]
Hyperthyroid events	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]
Dermatitis/rash	[redacted]	[redacted]
Infusion-related reactions	[redacted]	[redacted]
Hypersensitivity/anaphylactic reactions	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]
Type 1 diabetes mellitus	[redacted]	[redacted]

Abbreviations: AESI, adverse event of special interest; EP, etoposide plus platinum-based chemotherapy.
Source: CASPIAN CSR[56]

At the DCO 22 March 2021 (3-year follow-up), SAEs were generally reported in a similar proportion of patients in the durvalumab + EP group compared with the EP control group as that reported at the 2-year follow-up analysis (DCO 27 January 2020), with minor numerical differences. At both data cut off points, the majority of SAEs were haematological, or related to haematological toxicities, and occurred more frequently in the control than the intervention group (Table 23). The only SAEs occurring more frequently in the durvalumab + EP group were chronic obstructive pulmonary disease (1.1% versus 0.4%) and pancytopenia (1.5% versus 1.1%) at both analyses.

Table 23. Incidence of SAEs reported in ≥3% of patients in either treatment group in CASPIAN- DCO 27 January 2020 with DCO 22 March 2021 analysis changes highlighted in bold

SAEs, n (%)	Durvalumab + EP N=256	EP N=266
Patients with any SAE	**86 (32.5)**	97 (36.5)
Pneumonia	6 (2.3)	**11 (4.1)**
Anaemia	5 (1.9)	12 (4.5)
Febrile neutropenia	12 (4.5)	12 (4.5)
Neutropenia	2 (0.8)	7 (2.6)
Pancytopenia	4 (1.5)	3 (1.1)
Thrombocytopenia	1 (0.4)	9 (3.4)
Hyponatraemia	2 (0.8)	4 (1.5)
Pneumonitis	3 (1.1)	3 (1.1)
Diarrhoea	2 (0.8)	4 (1.5)
Vomiting	–	3 (1.1)
Hypokalaemia	–	3 (1.1)
Cerebrovascular accident	–	3 (1.1)
COPD	3 (1.1)	1 (0.4)

Abbreviations: COPD, chronic obstructive pulmonary disease; EP, etoposide plus platinum-based chemotherapy; SAE, serious adverse event.
Source: Paz-Ares et al, 2022[45]; CASPIAN CSR 2021[54]; CASPIAN CSR 2020[56]

By the 3-year follow-up analysis (DCO 22 March 2021), six deaths had occurred in the durvalumab + EP group as a result of AEs that were considered by the investigator as being possibly related to treatment. These AEs were sepsis, pancytopenia, dehydration, cardiac arrest and hepatotoxicity. Two deaths in the EP group were considered by the investigator to be possibly related to treatment; these were one case of pancytopenia and one of thrombocytopenia/haemorrhage.

B.3.11 *Conclusions about comparable health benefits and safety*

The standard of care for first-line treatment of patients with ES-SCLC in the National Health Service (NHS) is currently atezolizumab + EP. However, given the rapidly

progressive nature of the disease, patients with ES-SCLC are heterogeneous patient group with diverse needs.[2,10,11] Clinicians highlighted the value of having an additional IO option to treat the diverse needs of patients.[2] As such, durvalumab + EP is anticipated to be used as an alternative to atezolizumab + EP in the first-line setting.

The randomised, open-label, phase 3 CASPIAN trial has demonstrated that the addition of durvalumab to EP as a first-line treatment for ES-SCLC results in a statistically significant and clinically meaningful improvement in OS compared with EP alone (HR 0.71; 95% CI, 0.595, 0.858; p=0.0003) based on the DCO 22 March 2021, representing 3 years follow-up. Subgroup analyses of OS demonstrated that the OS benefits favouring the durvalumab + EP treatment were consistent across all prespecified stratification factors and subgroups, including by performance status and the presence of CNS metastases, underlining the applicability of the results to UK clinical practice.

Durvalumab + EP demonstrated a sustained improvement in PFS with nearly four times the number of patients progression-free at 24 months versus EP and ~10.1% of patients with ongoing treatment at 3 years.

In the absence of a study directly comparing durvalumab + EP and atezolizumab + EP for the first-line treatment of patients with ES-SCLC, an ITC has been conducted between CASPIAN and the atezolizumab trial IMpower133.[62]

The CASPIAN and IMpower133 trials are similar in design, patient population, eligibility criteria, and baseline characteristics. The platinum-based chemotherapy differs between the trials. Participants of IMpower133[62] received atezolizumab with etoposide and carboplatin, whereas in CASPIAN[63], participants were given either etoposide with carboplatin or etoposide with cisplatin, based on investigator's choice, with or without durvalumab.

The CASPIAN trial is well balanced with respect to the cisplatin and carboplatin treatment arms given this was a stratification factor, therefore, the potential bias in the CASPIAN trial is expected to be small. Steps were also taken to evaluate equivalence of cisplatin and carboplatin, and ITC analyses were performed with and without equivalence of cisplatin and carboplatin. The results of the analyses are consistent, indicating that although the choice of platinum-based chemotherapy differs between trials, this does not have an important impact on the results.

Overall, the ITC results suggest that durvalumab + EP offers a directional benefit over atezolizumab + EP in OS (HR, [redacted] [redacted, redacted]). However, in the absence of statistically significant results, a conservative assumption of equivalent efficacy can be assumed for the purpose of cost-comparison. Additionally, the ITC analyses demonstrate a numerical benefit in favour of durvalumab + EP with regards to overall Grade 3/4 treatment-related AEs (OR, [redacted] [redacted, redacted]), and serious treatment-related AEs (OR, [redacted] [redacted, redacted]), presenting a potentially less toxic IO option in ES-SCLC.

In TA638, the committee highlighted that although atezolizumab with chemotherapy was shown to improve PFS and OS compared with chemotherapy, the long-term benefit was uncertain. The committee decision at that time was based on an April 2018 data cut-off

for IMpower133, at a median follow-up of 13.9 months. Overall survival data from IMpower133 at the 2-year follow-up, which have been used in the ITC, show deterioration in HR (0.70 to 0.76), with convergence of KM curves. Longer follow-up (3-years) is available from the CASPIAN trial, with improvements in OS maintained over the follow-up period (HR 0.71). Therefore, with long term follow-up data used, the results of the ITC provide a more reliable and robust demonstration of efficacy of durvalumab + EP vs EP.

B.3.12 *Ongoing studies*

Ongoing clinical studies of durvalumab in SCLC relevant to this submission are shown in Table 24.

Table 24. Ongoing studies expected to provide additional evidence for durvalumab + EP for the treatment of untreated ES-SCLC in the next 12 months

Study (NCT number)	Title	Design	Estimated completion	Additional evidence expected
CASPIAN (NCT03043872)[69]	Durvalumab ± Tremelimumab in Combination With Platinum Based Chemotherapy in Untreated Extensive-Stage Small Cell Lung Cancer (CASPIAN)	Phase 3, randomised, open-label, multicenter, international study	Dec 2024	CASPIAN is still active; however, all planned analyses have been reported
LUMINENCE (NCT04774380)[70]	Study of Durvalumab in Combination With Platinum and Etoposide for the First Line Treatment of Patients With Extensive-stage Small Cell Lung Cancer (LUMINANCE)	Phase 3b, single arm, international study	Dec 2024	The primary endpoint of this study is safety and tolerability. The key secondary endpoints of ORR, PFS, DOR, and 12-month OS are yet to be reported.

Abbreviations: DOR, duration of response; EP, etoposide plus platinum-based chemotherapy; ES-SCLC, extensive stage-small cell lung cancer; NCT, National Clinical Trial; ORR, overall response rate; OS overall survival, PFS, progression-free survival

Sources: cited in table

B.4 Cost-comparison analysis

- **The ITC results demonstrated similar efficacy between durvalumab + EP and atezolizumab + EP, with a directional improvement in OS for durvalumab + EP. Therefore, a conservative assumption of equal efficacy was made, leading to a cost-comparison analysis between the two treatments for ES-SCLC patients**
- **The cost-comparison analysis results showed that durvalumab + EP is expected to be cost-saving compared to treatment with atezolizumab + EP, when including the confidential commercial access agreement for durvalumab + EP**
- **In the base case, durvalumab + EP demonstrated a cost savings of [redacted] compared to atezolizumab + EP**
- **In all sensitivity analyses and scenarios tested, durvalumab + EP consistently demonstrated cost savings compared to atezolizumab + EP**

B.4.1 *Changes in service provision and management*

Durvalumab + EP is anticipated to be used in the hospital setting, in line with the currently licensed IO therapy for ES-SCLC, atezolizumab + EP. No additional requirements in terms of service provision or disease management are expected.

B.4.2 *Cost-comparison analysis inputs and assumptions*

The aim of this cost-comparison analysis was to estimate the costs related to treatment with durvalumab + EP versus atezolizumab + EP for patients with ES-SCLC, from an UK healthcare system perspective.

B.4.2.1 Features of the cost-comparison analysis

An overview of the features of the cost-comparison analysis is presented in Table 25.

Table 25. Features of the cost-comparison analysis

Component	Approach	Justification
Population	Adults with untreated extensive-stage small-cell lung cancer	Aligned with the current label for durvalumab + EP and as per NICE scope
Intervention	Durvalumab in combination with platinum-based chemotherapy (etoposide with either carboplatin or cisplatin)	As per NICE scope[71]
Comparator(s)	Atezolizumab in combination with platinum-based chemotherapy (etoposide with carboplatin)	As per NICE scope[71]
Outcomes	• Incremental per-patient costs • Total per-patient costs	In line with the NICE user guide for cost-comparison submissions[72]
Perspective	NHS and PSS in England and Wales	In line with the NICE user guide for cost-comparison submissions[72]
Time horizon	Lifetime (15 years) to reflect all costs and outcomes between technologies being compared	In line with the NICE user guide for cost-comparison submissions[72]
Cycle length	1 week (7 days)	As time to progression is relatively short, the cycle length was set to one week to better reflect the progression of the disease and to account for different treatment schedules (every 3 weeks, every 4 weeks, etc). A half-cycle correction was also applied.
Discounting	A 3.5% discount rate is used in the base case	This is considered appropriate because a lifetime time horizon is used. A scenario has been conducted in which no discounting is applied.

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services

B.4.2.1.1 Patient population

The target population was aligned with the intention-to-treat population of the CASPIAN trial,[27] specifically adult patients (aged ≥18 years) with histologically or cytologically documented ES-SCLC due to multiple lung nodules that are too extensive or had tumour/nodal volume that is too large to be encompassed in a tolerable radiation plan (i.e., considered suitable for platinum chemotherapy). This patient population is aligned with the license for durvalumab in ES-SCLC and is consistent with the NICE decision problem described in Section B.1.1.

Baseline patient characteristics used in the economic analysis were based on the CASPIAN trial population.[27] Patients entering the model had a median baseline age of

62.4 years, a mean weight of 73.1 kg, and 69.6% of the CASPIAN trial population were male.

B.4.2.1.2 Model structure

A cost-comparison model was developed in Microsoft Excel®. The model structure is a three-state area under the curve (AUC) model, also known as a partitioned survival analysis or partitioned survival model (PartSA). The model structure was selected based on the following reasons.

- The PartSA approach is widely utilised in oncology modelling, leveraging commonly available clinical trial outcomes (OS and PFS) to provide a comprehensive representation of disease progression and disease management.
- The structure is consistent with approaches adopted in numerous economic evaluations submitted to NICE for the treatment of IO therapies in lung cancer, including SCLC (atezolizumab for ES-SCLC)[3], and NSCLC (nivolumab for previously untreated NSCLC; pembrolizumab for untreated PD-L1-positive metastatic non-small cell lung cancer). [73,74]
- This approach explicitly models health benefits, such as PFS and OS, to appropriately capture the costs associated with different health states when conducting a cost comparison.

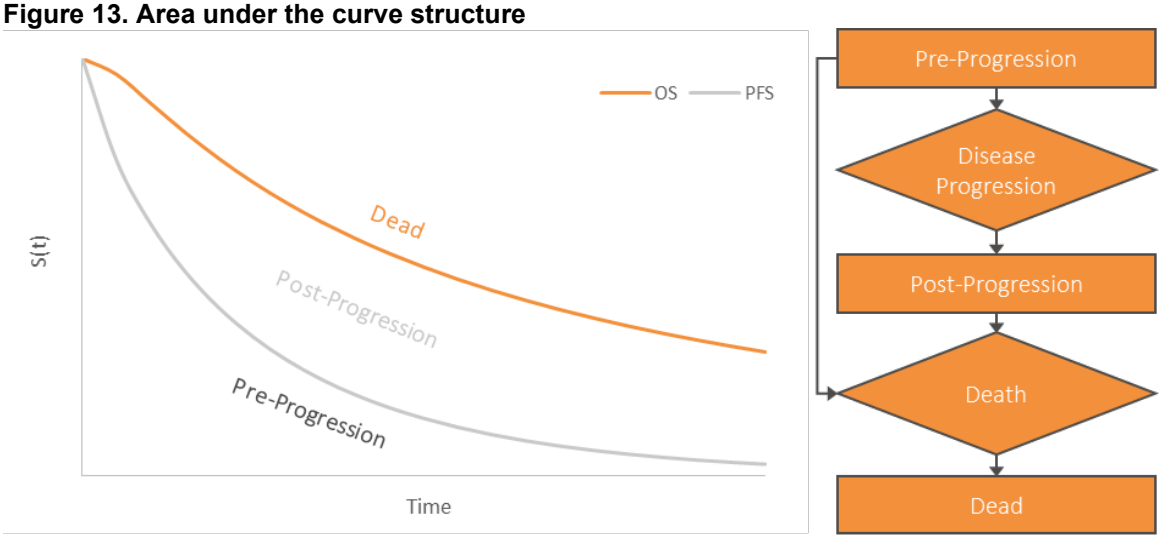
The three health states considered in the model are distinct and mutually exclusive:

- Progression-free survival (PFS)
- Post-progression survival (PPS)
- Death

All patients begin in the PFS state at the start of the analysis. Subsequently, they can move to the PPS state and eventually to the death state. Alternatively, patients may move directly from the PFS state to the death state; once they have progressed, they cannot revert to the PFS state. Within a PartSA approach, individual transition probabilities are not explicitly modelled. Instead, OS and PFS curves are utilised to determine the proportion of patients in each health state.

As shown in Figure 13, the model estimates the proportion of a cohort in each state based upon parametric or non-parametric survival curves, with separate survival functions for OS and PFS.

Figure 13. Area under the curve structure



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

Since both durvalumab + EP and atezolizumab + EP are recommended for use until disease progression and some patients discontinue treatment prior to progression, the model accounts for on versus off treatment. Some patients may also continue treatment post-progression. To accurately capture treatment-related costs, treatment discontinuation was modelled using time to treatment discontinuation (TTD) curve data derived from the CASPIAN trial.[27]

B.4.2.1.3 Intervention technology and comparators

The NICE final scope states that the intervention is durvalumab + EP and the relevant comparator is atezolizumab + EP. This is aligned with UK clinical experts who stated in one-to-one interviews that the SoC for first-line treatment of patients with ES-SCLC in UK clinical practice is atezolizumab + EP.[2,67] Therefore, no other comparators have been considered.

The current pathway of care, including proposed place of durvalumab + EP in ES-SCLC has been previously presented in Figure 2.

B.4.2.1.4 Clinical parameters and variables

B.4.2.1.4.1 Incorporation of the clinical data into the model

The cost-comparison analysis was informed by estimates of OS, PFS, and subsequent treatment data from the CASPIAN trial.[27] Duration of treatment for durvalumab + EP and atezolizumab + EP was based on TTD data, with duration of subsequent treatment based on patient level estimates by treatment class.

The model incorporated the 3-year data (DCO 22 March 2021). At this DCO, [redacted] deaths had occurred in the durvalumab + EP arm, necessitating parametric survival analysis to extrapolate OS, over a lifetime horizon, as per NICE guidelines. This process

involved performing parametric survival modelling of OS, PFS, and TTD, and integrating the resulting survival functions into the model.

Only the data from the durvalumab + EP arm of CASPIAN was considered, based on the assumption of equal efficacy between durvalumab + EP and atezolizumab + EP (section B.3.9) and the fact that the placebo arm (EP alone) of CASPIAN is not a suitable comparator for this decision. Consequently, individual models were developed for each outcome.

In accordance with standard practice and guidance from the NICE DSU, the extrapolation of the survival data used a range of standard parametric survival models including exponential, Weibull, Gompertz, lognormal, loglogistic, and generalised gamma. In addition, the analysis explored flexible spline models using the maximum available Kaplan-Meier data.

The parametric fits were selected, following the NICE DSU guidance, [75] on the basis of:

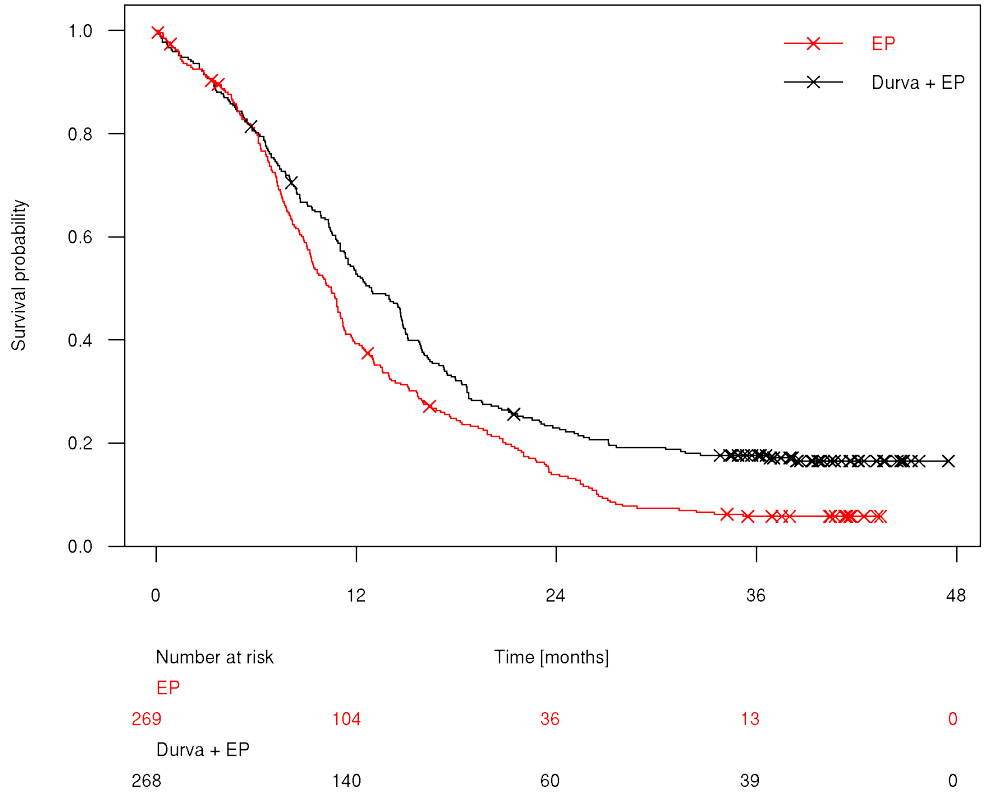
- Assessment of hazard functions
- Statistical fit (Akaike information criterion [AIC]/ Bayesian information criterion [BIC]; model with the best adjustment to the patient level data)
- Visual inspection of the curve fit against the Kaplan-Meier data from the CASPIAN trial
- Clinical plausibility and external validation of long-term projections

Extrapolations from the CASPIAN trial

Overall survival

As described above, only the durvalumab + EP treatment arm of CASPIAN was considered, resulting in an individual OS model using 3-year data from the CASPIAN trial (DCO 22 March 2021). Figure 14.

Figure 14. OS Kaplan Meier curve of the CASPIAN trial

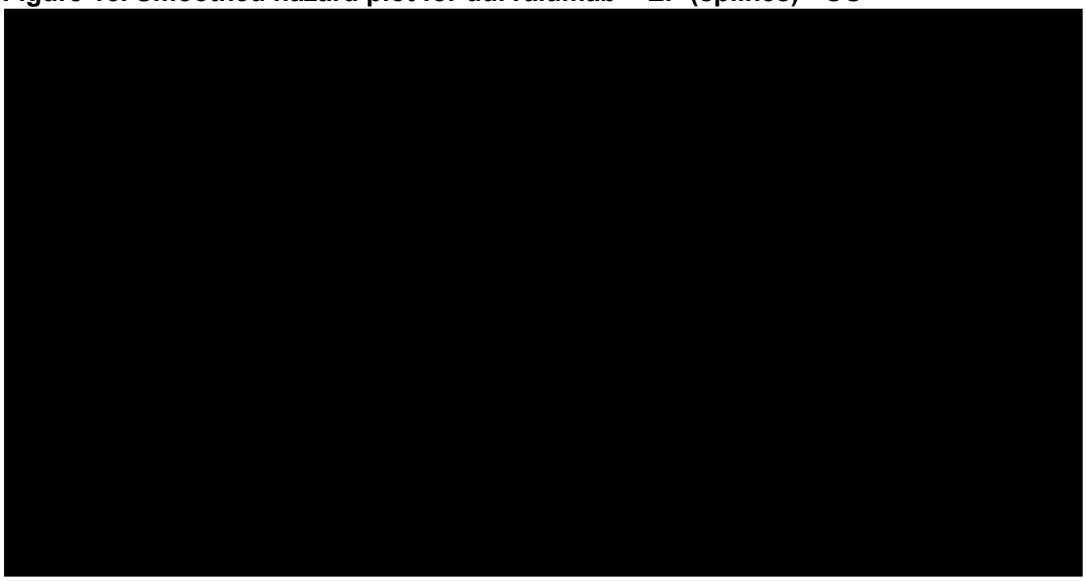


Abbreviations: Durva, Durvalumab; EP, Etoposide and platinum-based chemotherapy; OS, overall survival; S(t), survival function

Assessment of hazard function

Figure 15 represents the smoothed hazard plot for durvalumab + EP, which shows that the hazard changes over the course of the trial (e.g., an initial increase, then decrease). This is often observed in immunotherapies. As specified in NICE DSU TSD 21, complex hazard functions are not well-represented by standard parametric models. Flexible models, such as spline-based models, which accommodate hazard functions with complex shapes, should therefore be considered.[76] As shown in Figure 15, the spline-based models approximate the trend of the hazard function, making them superior to standard parametric models.

Figure 15. Smoothed hazard plot for durvalumab + EP (splines) - OS



Abbreviations: Durva, Durvalumab; EP, Etoposide and platinum-based chemotherapy; OS, overall survival

Statistical goodness of fit (AIC/BIC)

Statistical tests based on AIC and BIC scores (Table 26) were used to identify the best-fitting parametric distribution to extrapolate OS. Spline Normal distributions (1 knot and 3 knots) were not available due to a lack of convergence with the model. The Spline Hazard (3 knots) was the best statistically fitting distribution for the durvalumab + EP arm (in terms of AIC and BIC).

Table 26. Measurement of Akaike Information Criterion and Bayesian Information Criterion of the different distributions used to model OS in the ITT population

	Durvalumab + EP	
Distribution	**AIC**	**BIC**
Exponential	1765.59	1769.18
Weibull	1766.53	1773.71
Gompertz	1764.87	1772.05
Lognormal	1774.27	1781.45
Loglogistic	1748.49	1755.67
Generalised Gamma	1761.80	1772.57
Spline Hazard (1 knot)	1763.90	1774.67
Spline Hazard (2 knots)	1729.88	1744.24
Spline Hazard (3 Knots)	**1723.96**	**1741.91**
Spline Odds (1 Knot)	1745.49	1756.26
Spline Odds (2 Knots)	1735.61	1749.98
Spline Odds (3 Knots)	1726.19	1744.14
Spline Normal (1 Knot)	N/A	N/A

	Durvalumab + EP	
Spline Normal (2 Knots)	1740.57	1754.93
Spline Normal (3 Knots)	N/A	N/A

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, EP, etoposide and platinum-based chemotherapy; N/A, Not Available; OS, overall survival.

Visual fit to KM plot

The top five statistically fitting distributions including Spline Odds (1 knot) and Spline Hazards (1 knot) were visually inspected to determine the best fitting to the underlying data, presented in Figure 16. Although none of the distributions perfectly fit the 1- and 2-year trial data, the Spline Odds (2 knots) model fits the closest at 1 years, while models Spline Odds (3 knots) and Spline Hazard (3 knots) fit the closest at both 2 and 3 years. All other inspected distributions were deemed inappropriate for the base case analyses.

Figure 16. Extrapolation of the OS (durvalumab + EP)

Abbreviations: D, Durvalumab; EP, Etoposide and platinum-based chemotherapy; OS, overall survival

Validation of long-term OS extrapolations

Table 27 presents the survival estimates for durvalumab + EP for each distribution. The four Spline distributions that most closely fit the trial data were presented to UK clinicians in one-to-one interviews for their assessment of 5-year survival predictions. To enhance the analysis, the loglogistic and Spline Odds (1 knot) distributions, which predict lower 5-year survival rates, were also included. Clinicians considered the top four best-fitting distributions to be clinically plausible but observed that their 5-year survival estimates were very similar, making the selection of a single model challenging. When asked to identify the most realistic model, the majority of clinicians opted for the distribution within the top four that predicted the lowest 5-year survival rate. Consequently, the Spline Odds (2 knots) was chosen for durvalumab + EP OS in the base case.[77]

Table 27. Survival rates estimated (OS)

		Durvalumab + EP		
Distribution	**1 year (%)**	**2 years (%)**	**3 years (%)**	**5 years (%)**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]

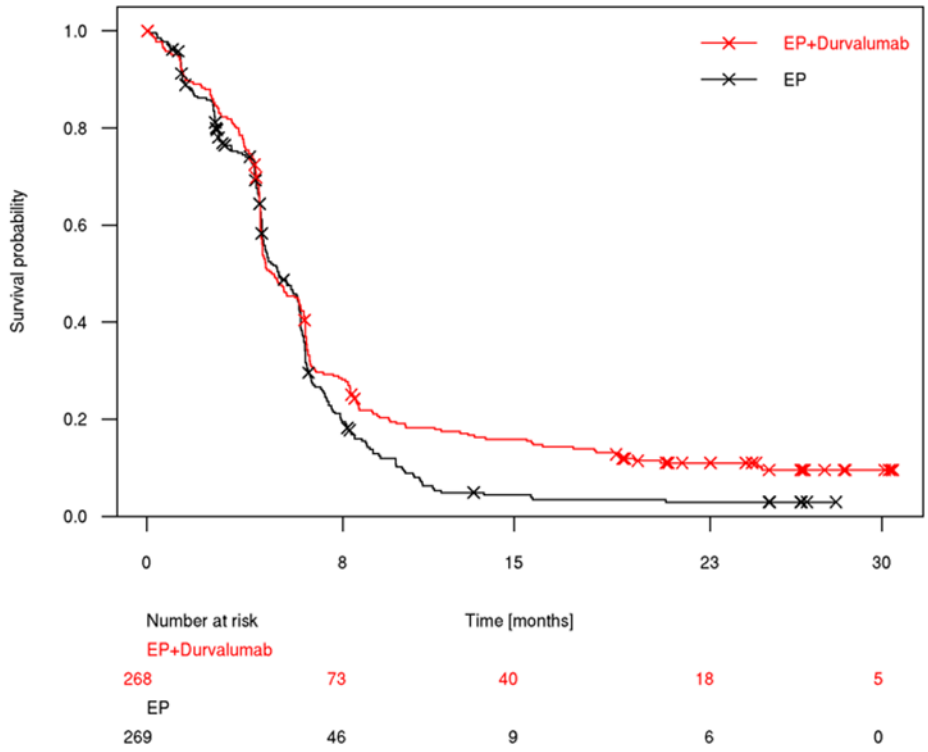
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline Hazard (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]
Spline Hazard (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]
Spline Hazard (3 Knots)	[redacted]	[redacted]	[redacted]	[redacted]
Spline Odds (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]
Spline Odds (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]
Spline Odds (3 Knots)	[redacted]	[redacted]	[redacted]	[redacted]
Spline Normal (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]
Spline Normal (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]
Spline Normal (3 Knots)	[redacted]	[redacted]	[redacted]	[redacted]
CASPIAN KM	**52.8%**	**22.9%**	**17.6%**	**-**

Abbreviations: EP, Etoposide and platinum-based chemotherapy; KM, Kaplan-Meier

Progression-free survival

Figure 17 presents the PFS Kaplan-Meier from the CASPIAN trial, which incorporated 2-year data (DCO 27 January 2020). Similar to OS, an individual model was developed for durvalumab + EP treatment arm.

Figure 17. PFS Kaplan Meier curve of the CASPIAN trial



Abbreviations; 95% CI, 95% Confidence Interval; D, Durvalumab; E, Etoposide and platinum-based chemotherapy; PFS, Progression-free survival; S(t), survival function

Assessment of hazard function

Figure 18 presents the smoothed hazard plot for durvalumab + EP, showing that, similar to OS, the PFS hazard initially increases and then decreases, consistent with immunotherapy patterns. According to NICE DSU TSD 21, complex hazard functions are not well-represented by standard parametric models, necessitating the use of flexible models, such as spline-based models, that can accommodate complex shapes [76]. As shown in Figure 18, the spline-based models approximate the trend of the hazard function, making them superior to standard parametric models.

Figure 18. Smoothed hazard plot for durvalumab + EP (splines) - PFS

Abbreviations: Durva, Durvalumab; EP, Etoposide and platinum-based chemotherapy; PFS, progression-free survival

Statistical goodness of fit (AIC/BIC)

Similar to OS, statistical tests based on AIC and BIC scores (Table 28) were used to identify the best-fitting parametric distribution to extrapolate PFS. Spline Normal distributions (1 knot and 2 knots) were not available due to a lack of convergence with the model. The Spline Odds (2 knots) was the best statistically fitting distribution for the durvalumab + EP arm.

Table 28. Measurement of Akaike Information Criterion and Bayesian Information Criterion of the different distributions used to model PFS

	Durvalumab + EP	
Distribution	**AIC**	**BIC**
Exponential	1489.42	1493.02
Weibull	1488.64	1495.83

	Durvalumab + EP	
Gompertz	1484.01	1491.19
Lognormal	1460.52	1467.70
Loglogistic	1430.75	1437.93
Generalised Gamma	1459.80	1470.57
Spline Odds (1 knot)	1432.57	1443.35
Spline Odds (2 knots)	**1383.56**	**1397.93**
Spline Odds (3 knots)	1385.21	1403.17
Spline Hazard (1 knot)	1447.28	1458.05
Spline Hazard (2 knots)	1384.26	1398.62
Spline Hazard (3 knots)	1383.91	1401.86
Spline Normal (1 Knot)	N/A	N/A
Spline Normal (2 Knots)	N/A	N/A
Spline Normal (3 Knots)	1390.23	1408.19

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

Visual fit to KM plot

The distributions with the top five best statistical fit (including Spline Hazards (2 and 3 knots), Spline Odds (2 and 3 knots) and Spline Normal (3 knots)) were visually inspected to determine the best fitting to the underlying data, presented in Figure 19. Apart from Spline Hazard (3 knots), all inspected distributions fit the trial data well.

Figure 19. Extrapolation of the PFS (durvalumab + EP)

Abbreviations: EP, Etoposide and platinum-based chemotherapy; PFS, progression-free survival

Validation of long-term PFS extrapolations

Table 29 presents the survival estimates for durvalumab + EP for each distribution. The four spline models with the best visual and statistical fit were presented to UK clinicians in one-to-one interviews to gather their opinions on the 5-year data and long-term PFS predictions. For a thorough analysis, the Gompertz and Weibull models were included since they predicted lower 5-year survival rates. The clinical experts agreed that the distributions with the best statistical and visual fit, as reported above, also yielded the most accurate 5-year PFS estimates for patients receiving durvalumab + EP (i.e., 6.1-6.3%).[77] Consequently, among these distributions, the Spline Odds (2 knots) distribution was selected to model PFS in the base case due to its superior statistical fit (based on AIC/BIC criteria).

Table 29. Survival rates estimated (PFS)

	Durvalumab + EP		
Distribution	**1 year (%)**	**2 years (%)**	**5 years (%)**
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
Spline Odds (1 knot)	[redacted]	[redacted]	[redacted]
Spline Odds (2 knots)	[redacted]	[redacted]	[redacted]

	Durvalumab + EP		
Spline Odds (3 knots)	[redacted]	[redacted]	[redacted]
Spline Hazard (1 knot)	[redacted]	[redacted]	[redacted]
Spline Hazard (2 knots)	[redacted]	[redacted]	[redacted]
Spline Hazard (3 knots)	[redacted]	[redacted]	[redacted]
Spline Normal (1 knot)	[redacted]	[redacted]	[redacted]
Spline Normal (2 knots)	[redacted]	[redacted]	[redacted]
Spline Normal (3 knots)	[redacted]	[redacted]	[redacted]
CASPIAN KM	**17.9%**	**11.0%**	**-**

Abbreviations: EP, Etoposide and platinum-based chemotherapy; KM, Kaplan-Meier

Time to treatment discontinuation

The TTD Kaplan-Meier curve of the CASPIAN trial is presented in Figure 16. An individual model was developed for the durvalumab + EP treatment arm.

Figure 20. TTD Kaplan Meier curve of the CASPIAN trial (durvalumab + EP)

Abbreviations: EP, Etoposide and platinum-based chemotherapy

Assessment of hazard function

Figure 21 presents the smoothed hazard plot for durvalumab + EP, which shows that the TTD hazard initially increases and then decreases, in line with OS and PFS hazards and consistent with immunotherapy patterns. According to NICE DSU TSD 21, complex hazard functions are not well-represented by standard parametric models, necessitating the use of flexible models, such as spline-based models, that can accommodate complex shapes [76]. As shown in Figure 21, except for Spline Hazard (1 knot), most of the spline-based models approximate the trend of the hazard function, making them superior to standard parametric models.

Figure 21. Smoothed hazard plot for durvalumab + EP (splines) - TTD

Abbreviations: Durva, Durvalumab; EP, Etoposide and platinum-based chemotherapy; TTD, time to treatment discontinuation

Statistical goodness of fit (AIC/BIC)

Similar to OS and PFS, statistical tests based on the AIC and BIC scores (Table 30) were used to determine the best-fitting parametric distribution to extrapolate TTD. Spline Normal (1 knot and 2 knots) were not available due to convergence issues. The Spline Hazard (2 knots) was the best statistically fitting distribution for the durvalumab + EP arm.

Table 30. Measurement of Akaike Information Criterion and Bayesian Information Criterion of the different distributions used to model time to treatment discontinuation

	Durvalumab + EP	
Distribution	**AIC**	**BIC**
Exponential	1506.42	1510.00
Weibull	1507.61	1514.77
Gompertz	1493.79	1500.95
Lognormal	1535.72	1542.88
Loglogistic	1488.47	1495.63
Generalised Gamma	1505.73	1516.47
Spline Hazard (1 knot)	1508.84	1519.58
Spline Hazard (2 knots)	**1419.48**	**1433.80**
Spline Hazard (3 knots)	1421.81	1439.71
Spline Odds (1 knot)	1466.01	1476.75
Spline Odds (2 knots)	1429.99	1444.30

	Durvalumab + EP	
Spline Odds (3 knots)	1425.91	1443.81
Spline Normal (1 knot)	N/A	N/A
Spline Normal (2 knots)	N/A	N/A
Spline Normal (3 knots)	N/A	N/A

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

Visual fit to KM plot

The top five distributions with the best statistical fit, including the Spline Hazards (1 knot) were visually inspected to identify the best fit to the underlying TTD data (Figure 22). The Spline Hazard (2 knots) and Spline Odds (1 knot) showed the closest fit to the 1-year data, while the Hazard Spline (2 and 3 knots) and the Spline Odds (3 knots) fit the 2-year data best. Consequently, the Spline Hazard (2 knots) demonstrated the best overall fit to the trial data.

Figure 22. Extrapolation of time to treatment discontinuation (durvalumab + EP)

Abbreviations: TTD, Time to Treatment Discontinuation

Validation of long-term TTD extrapolations

Table 31 presents the survival estimates for durvalumab + EP for each distribution. The four Spline distributions with the best visual and statistical fit were presented to UK clinicians in one-to-one interviews for their assessment of 5-year survival predictions.[77] For a thorough analysis, the Gompertz and generalised gamma distributions, which predict lower 5-year survival rates, were also presented. While the clinicians found the top four best-fitting distributions to be clinically plausible, they observed the similarity in 5-year TTD estimates, making it challenging to distinguish a clear preference. There were also mixed opinions on whether patients continue treatment after progression.

Therefore, it was considered both appropriate and conservative to select the distribution among the top four best-fitting models that provided the estimate closest to the 5-year PFS estimate used in the base case (i.e., 6.3%), which was also the distribution with the lowest 5-year TTD (i.e., 6.5%). Therefore, the Spline Odds (2 knots) was selected for the base case analysis.[77]

Table 31. Survival rates estimated (TTD)

	Durvalumab + EP		
Distribution	**1 year (%)**	**2 years (%)**	**5 years (%)**
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
Spline Hazard (1 knot)	[redacted]	[redacted]	[redacted]
Spline Hazard (2 knots)	[redacted]	[redacted]	[redacted]
Spline Hazard (3 knots)	[redacted]	[redacted]	[redacted]
Spline Odds (1 knot)	[redacted]	[redacted]	[redacted]
Spline Odds (2 knots)	[redacted]	[redacted]	[redacted]
Spline Odds (3 knots)	[redacted]	[redacted]	[redacted]
Spline Normal (1 knot)	[redacted]	[redacted]	[redacted]
Spline Normal (2 knots)	[redacted]	[redacted]	[redacted]
Spline Normal (3 knots)	[redacted]	[redacted]	[redacted]
CASPIAN KM	[redacted]	[redacted]	[redacted]

Abbreviations: EP, Etoposide and platinum-based chemotherapy; KM, Kaplan-Meier

Overview of distributions used in the base case analysis

A summary of the base case survival models for each outcome is presented in Table 32.

Table 32. Overview of the distributions used for the base case analysis

	Durvalumab + EP	Rationale
OS	Spline Odds (2 knots)	The most appropriate distribution to model OS based on hazard profile, statistical and visual goodness of fit, and clinical plausibility of 5-year survival
	Scenario: Spline Hazard (3 knots)	Best fitting distribution based on statistical and visual fit
PFS	Spline Odds (2 knots)	The most appropriate distribution to model PFS based on hazard profile, statistical and visual goodness of fit, and clinical plausibility of 5-year survival
	Scenario: Spline Hazards (2 & 3 knots)	Next best-fitting distributions
TTD	Spline Odds (2 knots)	The most appropriate distribution to model TTD and visual goodness of fit, and clinical plausibility of 5-year survival
	Scenario: Spline Hazard (2 knots)	Best fitting distribution based on statistical and visual fit

Abbreviations: EP, etoposide and platinum-based chemotherapy; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

B.4.2.1.4.2 Relative efficacy

As described in Section B.1.1 and B.3.9, atezolizumab + EP is recommended by NICE and is considered the current SoC for first line ES-SCLC. In the absence of a study directly comparing durvalumab + EP and atezolizumab + EP, an ITC has been conducted to inform survival.

The ITC results showed a directional improvement in OS for durvalumab + EP and a marginal directional improvement in PFS for atezolizumab + EP. Therefore, a conservative assumption of equal efficacy for OS and PFS was made in the model. This means that the PFS and OS curves of atezolizumab + EP were modelled by applying a HR of 1 to the corresponding PFS and OS curves of durvalumab + EP. For consistency, the TTD curve of atezolizumab + EP was modelling by applying the PFS HR (i.e., HR=1) to the durvalumab + EP TTD curve. This approach was deemed suitable based on the assumption of equal efficacy in both PFS and OS. It is anticipated that patients in the atezolizumab + EP arm would discontinue treatment at a similar rate to those in the durvalumab + EP arm, as treatment discontinuation is primarily attributed to progression events, assumed to be consistent across both arms.

B.4.2.1.4.3 Adverse events

AEs were excluded from the base-case analysis since similar safety is assumed between durvalumab + EP and atezolizumab + EP. A scenario including costs related to AEs is presented in Section B.4.5.2 .

In this scenario, AEs were applied as a one-off event in the first model cycle. Given previous trends in the modelling of AEs in oncology, only grade 3 or higher treatment-emergent AEs occurring in greater than 2% in either the durvalumab + EP arm in CASPIAN trial or atezolizumab + EP in Impower133 were factored.[52,62]

A summary of treatment-emergent AEs is shown below in Table 33.

Table 33. Summary of treatment-emergent AE probabilities applied in the economic analysis

Adverse event	Durvalumab + EP	Atezolizumab + EP
Neutropenia	24.2%	22.7%
Anaemia	9.1%	14.1%
Thrombocytopenia	5.7%	10.1%
Febrile neutropenia	5.3%	3.0%
Neutrophil count decreased	6.4%	14.1%
Leukopenia	6.4%	5.1%
Hyponatraemia	3.8%	0.0%
Pneumonia	1.9%	2.0%
White blood cell count decreased	1.5%	3.0%
Lipase increased	3.4%	0.0%
Platelet count decreased	1.5%	3.5%
Hypertension	3.0%	0.0%
Amylase increased	2.3%	0.0%
Source	CASPIAN[52]	Impower133[62]

Abbreviations: EP, etoposide and platinum-based chemotherapy; WBC, white blood cell.

B.4.2.1.5 General population mortality

General population mortality is based on tables published by the Office for National Statistics for the UK (England and Wales).[78]

To ensure that extrapolated survival functions do not provide unrealistic long-term OS extrapolations, a cap on the hazard function is applied so that the extrapolated hazard of death never falls below that of the general population (adjusted for the age and sex of the modelled population).

B.4.3 *Cost and healthcare resource use identification, measurement and valuation*

Cost parameters included in the model were drug acquisition and administration (both first-line and subsequent therapies), healthcare resource use (HCRU) associated with disease management by treatment and /or disease status, the management of AEs and terminal care costs.

Where identified costs were not current, these were inflated to the 2023 cost year, using Hospital & Community Health Services Pay & Prices Index or the healthcare index of the Consumer Price Indice.[79]

B.4.3.1 Resource identification, measurement and valuation studies

An SLR was conducted in December 2018, updated in March 2020 and again in May 2024 to identify resource use data from the published literature (see Appendix G for details). In total, 25 studies were identified through the electronic and grey literature searches. The included studies consisted of 12 cost estimation studies, 11 economic evaluations and 2 pre-existing SLRs on costs and resource use in SCLC.

The reported cost studies from the literature were considered to either not be relevant to the decision problem or not reflect current clinical practice. NICE technology appraisals for SCLC and NSCLC were also reviewed to identify resource use data. The findings were in line with those reported in the NICE appraisal for atezolizumab + EP for first-line treatment of adult patients with ES-SCLC (TA638).[3]

B.4.3.1.1 Appropriateness of NHS reference costs/payment by results tariffs

The costs of health care resources attributable to secondary care (i.e. drug administration, AE management, specialist physician visits) were sourced from the latest version of NHS Reference Costs,[80] and primary/community care costs will be sourced from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care.[79]

B.4.3.2 Intervention and comparators' acquisition costs

B.4.3.2.1 Drug acquisition costs

Drug unit costs were sourced from the BNF,[81] and eMIT databases[82] (shown in Table 34). Drug regimens were based on the CASPIAN and IMpower133 trials.

For durvalumab, [redacted].

Table 34. Drug acquisition costs

Drug	Vial size/tablet dose	Pack size	Cost per pack	Source

Drug	Vial size/tablet dose	Pack size	Cost per pack	Source
Durvalumab with commercial access agreement	500 mg	1	[redacted]	BNF via NICE[81]
Atezolizumab without commercial access agreement *	1200 mg	1	£3,807.69	BNF via NICE[81]
Carboplatin	50 mg	1	£9.28	eMIT (June 2023)[82]
	150 mg	1	£20.22	eMIT (June 2023)[82]
	450 mg	1	£48.09	eMIT (June 2023)[82]
	600 mg	1	£71.44	eMIT (June 2023)[82]
Cisplatin	10 mg	1	£3.23	eMIT (June 2023)[82]
	50 mg	1	£27.98	eMIT (June 2023)[82]
	100 mg	1	£29.27	eMIT (June 2023)[82]
Etoposide	100 mg	1	£4.57	eMIT (June 2023)[82]
	500 mg	1	£13.40	eMIT (June 2023)[82]

* Price with commercial access agreement discount is confidential and has been redacted from the committee papers in TA638[3]

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool.

B.4.3.2.2 Drug administration costs

Drug administration costs, obtained from the NHS Reference Costs 2021/22 (Table 35),[80] were applied per administration for intravenous (IV) or subcutaneous (SC) drug administration.

In the initial phase, durvalumab and atezolizumab are administered in combination with EP; therefore, the SB14Z cost was applied to 100% of patients receiving either treatment regimen. In the maintenance phase, durvalumab monotherapy is administered IV, therefore the model assumed 100% of patients receiving durvalumab would receive it via IV, utilising the SB12Z cost. For atezolizumab monotherapy, there is variability in the adoption of SC administration based on insights from clinical experts obtained through one-to-one interviews.[2] While some clinicians had transitioned patients to SC, others had not. As a result, the model conservatively estimated that 75% of patients receiving atezolizumab would receive SC, with the N10AF cost applied, while the remaining 25% would receive IV, with the SB12Z cost being applied.

For second-line therapies (cyclophosphamide + doxorubicin + vincristine [CAV] and EP) (Section B.4.3.2.5), the SB13Z and SB14Z costs were applied, respectively.

Where applicable, for subsequent administration costs within the same treatment cycle a standard cost of £326.46 (SB15Z) was applied.

Table 35. Drug administration costs

Treatment Setting	Administration	Cost per administration	Source
Outpatient	Simple Parenteral Chemotherapy at First Attendance	£207.59	NHS Reference Costs 2021/22: SB12Z[80]
	More Complex Parenteral Chemotherapy at First Attendance	£256.95	NHS Reference Costs 2021/22: SB13Z[80]
	Complex Chemotherapy including Prolonged Infusion at First Attendance	£440.71	NHS Reference Costs 2021/22: SB14Z[80]
	Subsequent Elements of a Chemotherapy Cycle	£326.46	NHS Reference Costs 2021/22: SB15Z[80]
	Subcutaneous administration – Specialist Nursing	£119.00	NHS Reference Costs 2021/22: N10AF[80]

Abbreviations: NHS: National Health Service

B.4.3.2.3 Dosing regimens

The treatment regimens for durvalumab + EP and atezolizumab + EP were obtained from CASPIAN and Impower133 trial data, respectively.[52,62] The posology for all included treatments was sourced from key pivotal trials, corresponding Summary of Product Characteristics (SmPC) or label.

In the base case, the duration of treatment for durvalumab + EP is modelled using the TTD curve derived from the CASPIAN trial. However, the model also allows for treatment duration to be modelled directly via the PFS curve. The duration of treatment for atezolizumab + EP is modelled by applying the PFS HR (i.e., HR=1) to the TTD curve of durvalumab + EP (see Section B.4.2.1.4.2 for details).

It was assumed that SC administration of atezolizumab comes at no extra cost to the NHS compared to IV administration of atezolizumab, thus the cost and dose was assumed to be the same for both methods.

Table 36 provides an overview of treatment characteristics and costs for the intervention and comparator.

Table 36. Treatment characteristics and costs for the intervention and comparator technologies

	Durvalumab + EP	Atezolizumab + EP
Pharmaceutical formulation	Solution for infusion	Solution for infusion
(Anticipated) care setting	Hospital	Hospital
Acquisition cost (excluding VAT)	*Durvalumab* List price: £2,466 per 500 mg Commercial access agreement price: [redacted] per 500 mg	*Atezolizumab* List price: £3,807.69 per 1,200 mg Commercial access agreement price: Confidential
Method of administration	Intravenous injection	Intravenous or subcutaneous injection
Dosing frequency	Durvalumab + EP: 1 every 3 weeks Durvalumab monotherapy: 1 every 4 weeks	Atezolizumab + EP: 1 every 3 weeks Atezolizumab monotherapy: 1 every 3 weeks

Abbreviations: EP, Etoposide + Platinum agent (carboplatin or cisplatin); VAT, value added tax

B.4.3.2.4 Drug wastage

Drug acquisition costs were calculated based on the patient's body surface area (BSA), excluding durvalumab and atezolizumab which have fixed doses. All treatments using a weighted dosage dependent on a patient's BSA are subject to wastage and/or vial sharing. Du Bois[d] and Calvert[e] formulae were used for calculating BSA and carboplatin dose respectively. Product wastage was considered in the base case for drugs which are not fixed dose. A scenario analysis with no wastage was explored to capture the impact on the cost savings.

Drug dosing and costs per cycle (with and without wastage) are shown in Table 37. As per both CASPIAN and Impower133 trials, patients were assumed to receive the combination of durvalumab/ atezolizumab + EP for the first 4 weeks (cycles) of the model. Following this initial period, patients were assumed to continue with durvalumab or atezolizumab monotherapy until disease progression or treatment discontinuation.[27,62] The percentage split of patients receiving carboplatin and cisplatin in the treatment regimen of the durvalumab + EP arm was based on the CASPIAN data. Patients in the atezolizumab + EP arm received carboplatin-based chemotherapy only, as per Impower133.[62]

[d] $(W^{0.425}xH^{0.725})x0.007184$

[e] Carboplatin Dose=Target AUC*(GFR+25)

Table 37. Drug dosing and acquisition costs per cycle

Treatment regimen	Drug	Dose per cycle	Relative dose intensity	Cost per cycle (without wastage)	Cost per cycle (with wastage)
Durvalumab + EP	Durvalumab	1431 mg	95.4%	[redacted]	[redacted]
	Carboplatin	434 mg	100.0%	£46.34	£52.47
	Etoposide	183 mg	100.0%	£4.91	£10.36
	Cisplatin	137 mg	100.0%	£40.24	£48.39
	Total weighted cost (cycles 1-4)	-	-	[redacted]	[redacted]
	Total weighted cost (cycles 5+)	-	-	[redacted]	[redacted]
Atezolizumab + EP	Atezolizumab	1139 mg	94.9%	£3,613.50	£3,807.69
	Carboplatin	400 mg	92.3%	£42.77	£56.73
	Etoposide	164 mg	89.4%	£4.39	£9.43
	Total weighted cost (cycles 1-4 only)	-	-	**£3,660.66**	**£3,873.85**
	Total weighted cost (cycles 5+)	-	-	**£3,613.50**	**£3,807.69**

Abbreviations: AUC, area under-the-curve; EP, etoposide + platinum.

B.4.3.2.5 Subsequent treatment

The model estimates the cost of subsequent lines of treatment after disease progression, accounting for costs based on the proportion of patients receiving further therapies, the distribution of treatments used at each line, and the duration of treatment.

Clinical experts estimated that approximately 20-50% of ES-SCLC patients receive second-line treatment following first-line discontinuation. Consequently, a middle-ground figure of 35% was incorporated into the model (Table 38).[2] Experts indicated that for second-line treatment, the majority of patients would receive CAV, while the remaining would be re-challenged with etoposide + carboplatin. Consequently, it was assumed that 70% of patients receive CAV and 30% receive etoposide + carboplatin (Table 39).

Clinical experts also stated that they may consider third-line treatment with topotecan; however, due to limited supply, very few patients would receive third-line treatment.[2] Therefore, the model does not include third-line therapies in the base case analysis (Table 38), though there is an option to include third-line treatment if required.

Given the assumed equal efficacy between durvalumab + EP and atezolizumab + EP, it was considered appropriate to assume the same proportion of patients receiving subsequent therapies and the same distribution of therapies across both arms.

Subsequent treatment costs were applied as one-off costs in the model. Further details are presented in Appendix H.

Table 38. Proportion of patients receiving 2nd line therapy post-1st line discontinuation and 3rd line therapy post 2nd line discontinuation

	Durvalumab + EP, Atezolizumab + EP
Patients receiving 2nd line therapy (post-1st line discontinuation)	35.0%
Patients receiving 3rd line therapy (post-2nd line discontinuation)	0.0%

Abbreviations: EP, Etoposide + Platinum agent (carboplatin or cisplatin)

Table 39. Subsequent treatment derived from CASPIAN trial and used in the model

Regimen	**Durvalumab + EP,** Atezolizumab + EP
	2nd Line
Platinum Doublets	
Etoposide + Carboplatin	30.0%
Other Chemotherapy Regimens	
Cyclophosphamide + Doxorubicin + Vincristine (CAV)	70.0%

Abbreviations: EP, Etoposide + Platinum agent (carboplatin or cisplatin)

For the time spent on each subsequent therapy, data from CASPIAN was used. Parametric models were used to estimate mean durations of subsequent therapy. The best model in terms of BIC and AIC was the Weibull model. Therefore, the Weibull model was used to calculate the mean survival time for each component. In the atezolizumab + EP arm, the same mean duration of subsequent treatment as in the durvalumab + EP arm was assumed.

Table 40. Mean duration of subsequent treatment

Regimen	**Durvalumab + EP, Atezolizumab + EP (duration in months)**
	2nd line
Combination chemotherapy regimens	3.13

Abbreviations: EP, Etoposide + Platinum agent (carboplatin or cisplatin)

B.4.3.2.6 Radiotherapy

In the UK, NICE Guidelines NG122 includes a microcosting of prophylactic cranial radiotherapy (PCI).[37] A similar approach was adopted to calculate the costing of PCI for

the model. The cost of an average course per patient was applied to the proportion of patients receiving it at the time of discontinuation of initial therapy.

Table 41 presents the percentage of patients having PCI from CASPIAN. PCI was only allowed in the CASPIAN control arm, i.e. EP, but not in the intervention arm, i.e., durvalumab + EP. In Impower133, 10.9% of patients in the atezolizumab + EP arm received PCI after 1st line treatment.[62] In a scenario analysis, patients in the durvalumab + EP arm received PCI after 1st line treatment.

Table 41. Proportion of patients receiving PCI

Patients receiving PCI (assumed 10 fractions per patient)	After 1st line treatment	After 2nd line treatment	Source
Durvalumab + EP	0%	0%	CASPIAN CSP[52]
Atezolizumab + EP	10.9%	0%	Horn 2018[62]

Abbreviations: CSR, Clinical Study Report; EP, Etoposide + Platinum agent (carboplatin or cisplatin); PCI, prophylactic cranial irradiation

Table 42 presents the cost calculations for one course (10 fractions) of PCI using NHS Reference costs 2021/22.[80] The cost of a course (10 fractions) of thoracic or other radiotherapy was assumed to be the same cost as a course of PCI, i.e. £3,239.82. Based on CASPIAN data, it was assumed that 25.7% of patients in PPS would receive other radiotherapy in both durvalumab + EP and atezolizumab + EP arms.[52] Thoracic or other radiotherapy costs in post-progression were assigned as one-off costs across both treatment arms.

Table 42. UK: PCI Cost Calculations for one course

Resource	**Unit Cost**	**Source**
PCI Planning & Fitting	£590.91	SC46Z: Preparation for Simple Radiotherapy with Imaging & Dosimetry, with Technical Support (Outpatient)[80]
Radiotherapy Fraction	£113.75	SC22Z: Deliver a Fraction of Treatment on a Megavoltage Machine (Outpatient)[80]
Number of Fractions	10	Standard of Care
Consent Appointments	£187.30	WF01B: Non-Admitted Face-to-Face Attendance, First (Consultant Led 800 - Clinical Oncology)[80]
Appointments During Treatment	£132.10	WF01A: Non-Admitted Face-to-Face Attendance, Follow-up (Consultant Led 800 - Clinical Oncology)[80]
Follow-Up Appointment	£132.10	WF01A: Non-Admitted Face-to-Face Attendance, Follow-up (Consultant Led 800 - Clinical Oncology)[80]
Proportion Accessing Telephone Services	33%	Committee Assumption
Cost per Telephone Appointment	£62.37	WF01C: Non-Admitted Non-Face-to-Face Attendance, Follow-up (Non-Consultant Led 800 - Clinical Oncology)[80]

Resource	Unit Cost	Source
Total cost per patient	***£3,239.82***	
Total cost per fraction	***£323.98***	

Abbreviations: PCI: Prophylactic cranial irradiation

B.4.3.3 Intervention and comparators' healthcare resource use and associated costs

As no relevant sources of HCRU data for SCLC patients were identified, pre and post-progression resource use estimates were identified from a study of NSCLC patients in a UK setting (Brown 2013).[83] This source was used in the economic analyses of several NSCLC appraisals (TA483,[74] TA484,[84] TA531,[85] TA584),[86] as well as in the appraisal for atezolizumab in ES-SCLC (TA638).[3]

Resource use estimates are presented in Table 43 and the associated costs, primarily sourced from NHS reference cost and PSSRU data,[79,80] are reported in Table 44. Terminal care costs were calculated based on the setting: hospital (52.5%), hospice (3.1%) and home (44.4%), based on deaths registered in England & Wales published by the Office of National Statistics.[87]

Resource use was assumed to be equivalent for durvalumab + EP and atezolizumab + EP.

Table 43. Healthcare resource use

Resource	On treatment	Units	Off treatment	Units	Terminal care	Units	Source
Healthcare staff & consultations							
Outpatient consultations	9.61	visits per annum	7.91	visits per annum	0.00	visits in terminal phase	Brown 2013
GP consultations	12.00	visits per annum	0.00	visits per annum	0.00	visits in terminal phase	Brown 2013
GP home visits	0.00	visits per annum	0.50	visits per week	7.00	visits in terminal phase	Brown 2013
Therapist visits	0.00	visits per annum	0.50	visits per week	0.00	visits in terminal phase	Brown 2013
Community nurse visits	8.70	visits per annum	8.70	visits per annum	28.00	hours in terminal phase	Brown 2013
Specialist nurse consultations	12.00	visits per annum	12.00	visits per annum	0.00	visits in terminal phase	Brown 2013
Macmillan nurse	0.00	visits per annum	0.00	visits per annum	50.00	hours in terminal phase	Brown 2013
Inpatient stay	0.00	days per annum	0.00	days per annum	9.66	days in terminal phase	Brown 2013
Scans & monitoring							
Chest radiography	6.79	scans per annum	6.50	scans per annum	0.00	scans in terminal phase	Brown 2013
CT scan: chest	0.62	scans per annum	0.24	scans per annum	0.00	scans in terminal phase	Brown 2013
CT scan: other	0.36	scans per annum	0.42	scans per annum	0.00	scans in terminal phase	Brown 2013
Electrocardiogram	1.04	scans per annum	0.88	scans per annum	0.00	scans in terminal phase	Brown 2013

Abbreviations: GP, general practitioner; CT, computed tomography; PD-L1, programmed death-ligand 1; TMB, tumour mutational burden.
Brown et al, 2013[83]

Table 44. Healthcare resource use costs

Resource	Cost	Unit	Source
Prophylactic cranial irradiation	£3,239.82	per course (10 fractions)	NICE Guideline NG122[66] and NHS Reference Costs 2021/22[80]
Other radiotherapy	£3,239.82	per course (10 fractions)	Assumed equal to PCI
Outpatient visit	£221.48	per visit	NHS Reference Costs 2021/22: WB01A (Consultant Led Non-Admitted Face-to-Face Attendance, Medical Oncology)[80]
Chest radiography	£38.28	per scan	NHS Reference Costs 2021/22: DAPF (Direct Access Plain Film)[80]
CT scan (chest)	£133.99	per scan	NHS Reference Costs 2021/22: RD24Z (Computerised Tomography Scan of Two Areas, with Contract - Outpatient)[80]
CT scan (other)	£139.49	per scan	NHS Reference Costs 2021/22: RD26Z (Computerised Tomography Scan of Three Areas, with Contract - Outpatient)[80]
Electrocardiogram	£221.48	per scan	NHS Reference Costs 2021/22: EY51Z (Electrocardiogram Monitoring or Stress Testing)[80]
Community nurse visit	£82.00	per visit	PSSRU 2023 - Cost per working hour including qualifications (Band 8a)[79]
Clinical nurse specialist	£58.00	per visit	PSSRU 2023 - Cost per working hour including qualifications (Band 6)[79]
Macmillan nurse	£54.69	per visit	Assumed 66.7% of community nurse cost (Brown 2013)[83]
GP consultation	£56.00	per visit	PSSRU 2023 - Cost per patient contact lasting 10 minutes, including direct care staff costs (including qualifications)[79]
GP home visit	£108.91	per visit	PSSRU 2016 and TA638 (Inflated to 2022/23 using HCHS Index)[3,88]
Therapist visit	£63.00	per visit	PSSRU 2023 - Cost per working hour for community-based scientific and professional staff (Band 8)[79]
Inpatient Stay	£5,229.78	per day	NHS Reference Costs 2021/22: DZ17L-R (Respiratory Neoplasms with Interventions with CC Score 0-10+, Non-elective Long Stay - Non-elective Short Stay - Day case)[80]
Terminal care in hospital: Episode	£2,887.12	per patient	NHS Reference Costs 2021/22: DZ17S-T (Respiratory Neoplasms without Interventions with CC Score 8+)[80] – duration of 7.56 days
Terminal care in hospital: Additional days	£1,001.98	per day	NHS Reference Costs 2021/22: DZ17S-T (Respiratory Neoplasms without Interventions with CC Score 8+, Non-elective short stay)[80]
Terminal care in hospice	£6,243.26	per patient	Assumed 25% of hospital terminal care (Brown 2013)[83] – duration of 9.66 days

Abbreviations: GP, general practitioner; CT, computed tomography; HCHS, Hospital & Community Health Services; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PCI, prophylactic cranial irradiation; PSSRU, Personal Social Services Research Unit; TA, technology appraisal

B.4.3.4 Adverse reaction unit costs and resource use

Adverse events costs were only considered in scenario analysis. Costs were applied as a one-time cost and were sourced from the NHS Reference Costs 2021/22 or eMIT December 2023.[80,82]

Table 45. Adverse event costs

Resource	Cost	Source
Amylase increased	£56.48	PSSRU 2023/eMIT December 2023[79,82] (Assumed to be equal to Lipase increased)
Anaemia	£882.80	NHS Reference Costs 2021/22: SA04G-L (Iron Deficiency Anaemia with CC Score 0-14+)[80]
Febrile neutropenia	£5,948.77	Brown 2013 (Inflated to 2022/23 using HCHS index)[79,83]
Hypertension	£200.28	As per TA823, assumed to be equal to Hypokalaemia using NHS Reference Costs (Inflated to 2022/23 using HCHS index)[79,89]
Hyponatraemia	£200.28	As per TA823, assumed to be equal to Hypokalaemia using NHS Reference Costs (Inflated to 2022/23 using HCHS index)[79,89]
Leukopenia	£770.65	Assumed to be equal to Neutropenia
Lipase increased	£56.48	PSSRU 2023/eMIT December 2023[79,82]
Neutropenia	£770.65	NHS Reference Costs 2021/22: WJ11Z (Other Disorders of Immunity) [80]
Neutrophil count decrease	£770.65	Assumed to be equal to Neutropenia
Platelet Count Decrease	£1,088.38	Assumed to be equal to Thrombocytopenia
Pneumonia/pneumonitis	£2,495.77	NHS Reference Costs 2021/22: DZ23J-N (Bronchopneumonia, with CC Score 0-11+)[80]
Thrombocytopenia	£1,088.38	NHS Reference Costs 2021/22: SA12G-K (Thrombocytopenia with CC Score 0-8+)[80]
White blood cell count decrease	£770.65	Assumed to be equal to Neutropenia

Abbreviations: CC score, complication and comorbidity score; eMIT, electronic market information tool; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

B.4.3.5 Clinical expert validation

Clinical expert validation was sought for this cost-comparison analysis. The validation consisted of one-to-one teleconference interviews conducted in June 2024, including 6 UK clinical experts (5 medical oncologists and one clinical oncologist). All 6 experts were based in the UK, and they provided clinical input into the modelling assumptions and inputs, e.g., clinical practice in 1st and 2nd line treatment and beyond in ES-SCLC. Additionally, 3 of these clinicians specifically validated the long-term extrapolations.[2,77]

B.4.3.6 Summary of base-case analysis inputs

Table 46 provides an overview of the base-case inputs used in the cost-comparison analysis.

Table 46. Summary of variables applied in the economic model

Variable	Value	CI	Reference to section in submission
General model parameters			
Time horizon	15 years	Fixed	B.4.2.1
Discount rate - costs	3.5%	Fixed	B.4.2.1
Baseline patient characteristics			
Age (years)	62.4	95% CI of point estimate assumed	B.4.2.1.1
% male	69.6%	95% CI of point estimate assumed	B.4.2.1.1
Body weight (kg)	73.1	95% CI of point estimate assumed	B.4.2.1.1
Body surface area (metres squared)	1.81	95% CI of point estimate assumed	B.4.2.1.1
Clinical data from CASPIAN trial			
OS	Spline Odds (2 knots) model	N/A	B.4.2.1.4.1
PFS	Spline Odds (2 knots) model	N/A	B.4.2.1.4.1
TTD	Spline Odds (2 knots) model	N/A	B.4.2.1.4.1
Adverse event probabilities (only for scenario analysis)	CASPIAN trial and Impower133 estimates	N/A	B.4.2.1.4.1
Subsequent treatment durations	Weibull model estimates based on CASPIAN trial data	N/A	B.4.2.1.4.1
Drug acquisition costs per pack			
Durvalumab 120 mg	[redacted]*	Fixed	B.4.3.2.1
Durvalumab 500 mg	[redacted]*	Fixed	B.4.3.2.1
Atezolizumab	£3,807.69	Fixed	B.4.3.2.1
Carboplatin 50 mg	£9.28	Fixed	B.4.3.2.1
Carboplatin 150 mg	£20.22	Fixed	B.4.3.2.1
Carboplatin 450 mg	£48.09	Fixed	B.4.3.2.1
Carboplatin 600 mg	£71.44	Fixed	B.4.3.2.1
Cisplatin 10 mg	£3.23	Fixed	B.4.3.2.1
Cisplatin 50 mg	£27.98	Fixed	B.4.3.2.1
Cisplatin 100 mg	£29.27	Fixed	B.4.3.2.1
Etoposide 100 mg	£4.57	Fixed	B.4.3.2.1
Etoposide 500 mg	£13.40	Fixed	B.4.3.2.1
Drug administration costs			
Outpatient - Simple parenteral chemotherapy at first attendance	£207.59	+/-10% variation	B.4.3.2.2
Outpatient - More complex parenteral chemotherapy at first attendance	£256.95	+/-10% variation	B.4.3.2.2
Outpatient - Complex chemotherapy including prolonged infusion at first attendance	£440.71	+/-10% variation	B.4.3.2.2

Variable	Value	CI	Reference to section in submission
Outpatient - Subsequent elements of a chemotherapy cycle	£326.46	+/-10% variation	B.4.3.2.2
Subcutaneous administration - Specialist Nursing, Cancer Related, Adult, Face to face	£119.00	+/-10% variation	B.4.3.2.2
Radiotherapy costs			
PCI planning & fitting	£590.91	+/-10% variation	B.4.3.2.6
Radiotherapy fraction	£113.75	+/-10% variation	B.4.3.2.6
Number of fractions	10	+/-10% variation	B.4.3.2.6
Consent appointments	£187.30	+/-10% variation	B.4.3.2.6
Appointments during treatment	£132.10	+/-10% variation	B.4.3.2.6
Follow-up appointment	£132.10	+/-10% variation	B.4.3.2.6
Cost per telephone appointment	£62.37	+/-10% variation	B.4.3.2.6
Healthcare resource use costs			
Prophylactic cranial irradiation (per course – 10 fractions)	£3,239.82	+/-10% variation	B.4.3.3
Other radiotherapy (per course – 10 fractions)	£3,239.82	+/-10% variation	B.4.3.3
Outpatient visit	£221.48	+/-10% variation	B.4.3.3
Chest radiography	£38.28	+/-10% variation	B.4.3.3
CT scan (chest)	£133.99	+/-10% variation	B.4.3.3
CT scan (other)	£139.49	+/-10% variation	B.4.3.3
Electrocardiogram	£221.48	+/-10% variation	B.4.3.3
Community nurse visit	£82.00	+/-10% variation	B.4.3.3
Clinical nurse specialist	£58.00	+/-10% variation	B.4.3.3
Macmillan nurse	£54.69	+/-10% variation	B.4.3.3
GP consultation	£56.00	+/-10% variation	B.4.3.3
GP home visit	£108.91	+/-10% variation	B.4.3.3
Therapist visit	£63.00	+/-10% variation	B.4.3.3

* Price based on commercial access agreement

Abbreviations: CI, confidence interval; CT, computed tomography; GP, general practitioner; OS, overall survival; PCI, prophylactic cranial irradiation; PFS, progression-free survival; TTD, time to discontinuation

B.4.3.7 Assumptions and limitations

The economic analysis includes multiple strengths:

- The base case analysis is based on a simple, transparent, and well-accepted model structure, extensively used in modelling oncology treatments (PartSA model), including atezolizumab + EP for ES-SCLC (TA638) [3]
- The model is based on mature 3-year OS data from the CASPIAN trial[45]
- The estimates of PFS and TTD are relatively mature and not subject to significant uncertainty
- In the base-case, treatment costs for durvalumab + EP were modelled based on TTD curves, providing a more accurate reflection of real-life clinical practice

- Conservative assumptions were made for PFS and TTD curve selection for durvalumab + EP to avoid potential underestimation of treatment costs
- Clinical experts validated all extrapolations of OS, PFS and TTD curves

Limitations and uncertainties with the analysis include:

- The impact on costs and outcomes of subsequent treatments are subject to uncertainty. For example, second-line treatment costs were modelled based on CASPIAN data, given the lack of available data on subsequent treatment regimens for ES-SCLC patients. However, this uncertainty was reduced by including only second-line treatments indicated by clinical experts.[2]
- HCRU included in the model is largely informed by data on NSCLC due to the lack of data available in ES-SCLC patients

B.4.4 *Base-case results*

The base case results are presented in Table 47. The drug acquisition costs are greater for atezolizumab + EP. Although the administration cost for durvalumab + EP is marginally greater than atezolizumab + EP, the less frequent administrations (every 4 weeks) in the maintenance phase result in the total administration cost being similar to atezolizumab, which follows a 3-week administration cycle in the maintenance phase. The reduced frequency of durvalumab administration also lessens the burden on patients as they require fewer treatment visits. Within HCRU costs, testing, monitoring, other radiotherapy, and terminal care were the same across both treatment arms. However, patients in the atezolizumab + EP arm receive first-line PCI, whereas those in the durvalumab + EP arm do not, resulting in higher (total) HCRU costs for the atezolizumab + EP arm.

Table 47. Base-case results

Regimen	Drug costs (1st line)	Administration costs (1st line)	Subsequent treatments costs	HCRU costs (incl. radiotherapy, monitoring and terminal care)	Total costs	Incremental costs
Durvalumab + EP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab + EP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EP, etoposide and platinum-based chemotherapy; HCRU, healthcare resource use

B.4.5 *Sensitivity and scenario analyses*

B.4.5.1 Univariate sensitivity analysis

One-way (deterministic) sensitivity analysis (DSA) was performed on all major model variables in the base case, to identify key model drivers and examine key areas of uncertainty. The base case inputs for the majority of parameters were varied using published

confidence intervals when available or +/-10% variation. The results of univariate sensitivity analysis are presented for durvalumab + EP versus atezolizumab + EP in Figure 23.

The results of the DSA demonstrate that the model is robust against changes on the model parameters. The parameters that have the greatest impact on the costs are the discount rates for costs and the administration costs for simple parenteral chemotherapy and subcutaneous administration.

Figure 23. Tornado plot (durvalumab + EP vs. atezolizumab + EP)

Abbreviations: 2L, second-line; chemo, chemotherapy; GP, general practitioner; mono, monotherapy, PCI, prophylactic cranial radiotherapy; ToT, time on treatment

B.4.5.2 Scenario analysis

In all scenarios tested, durvalumab + EP consistently demonstrated cost savings compared to atezolizumab + EP, when using the discounted commercial agreement price for durvalumab. Key scenario analyses are summarised in Table 48.

Table 48. Key scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	Inc. costs	Impact on inc. costs (% change)
Base case			[redacted]	-
Alternative OS model – scenario 1	Application of Spline Hazard (3 knots) parametric model to the durvalumab + EP (instead of Spline Odds [2 knots] model)	Testing the impact of using the second-best statistical fit for the durvalumab + EP OS curve	[redacted]	0.0%
Alternative PFS model – scenario 2	Application of Spline Hazard (3 knots) parametric model to the durvalumab + EP (instead of Spline	Testing the impact of using the second-best (according to AIC) statistical fit for the durvalumab + EP PFS curve	[redacted]	0.0%

Scenario and cross reference	Scenario detail	Brief rationale	Inc. costs	Impact on inc. costs (% change)
	Odds [2 knots] model)			
Alternative PFS model – scenario 3	Application of Spline Hazard (2 knots) parametric model to the durvalumab + EP (instead of Spline Odds [2 knots] model)	Testing the impact of using the second-best (according to BIC) statistical fit for the durvalumab + EP PFS curve	[redacted]	0.0%
Alternative TTD model – scenario 4	Application of Spline Hazard (2 knots) parametric model to the durvalumab + EP (instead of Spline Odds [2 knots] model)	Testing the impact of using the second-best (according to BIC) statistical fit for the durvalumab + EP TTD curve	[redacted]	+1.1%
10-year time horizon – scenario 5	Reduced time horizon for economic analysis from 15 years to 10 years	NICE reference case	[redacted]	-9.3%
5-year time horizon – scenario 6	Reduced time horizon for economic analysis from 15 years to 5 years	NICE reference case	[redacted]	-26.0%
Using PFS instead of TTD to model treatment costs across both arms – scenario 7	Using the PFS curve to estimate time on treatment, and subsequently treatment-related costs	Exploring the impact of using PFS data to model treatment discontinuation	[redacted]	-3.7%
Vial sharing – scenario 8	Assume no wastage for vials	Testing the impact of allowing for vial sharing	[redacted]	-12.1%
Inclusion of AEs – scenario 9	Including Grade 3+ treatment-emergent AEs across both arms	Testing the impact of including the treatment-AEs reported in the durvalumab and atezolizumab pivotal trials (i.e., relaxing the assumption about	[redacted]	-0.1%

Scenario and cross reference	Scenario detail	Brief rationale	Inc. costs	Impact on inc. costs (% change)
		safety equivalence) reported in the pivotal trials i.e., CASPIAN, Impower133).[52,62]		
PCI therapy for durvalumab + EP arm after first-line treatment – scenario 10	Assume that 10.9% of patients in the durvalumab + EP arm will receive PCI (in line with Impower133)[61]	Testing the impact of assuming the same proportion of patients across both arms would receive PCI	[redacted]	-1.0%

Abbreviations: EP, etoposide and platinum-based chemotherapy; inc, incremental; KM, Kaplan-Meier; OS, overall survival; PCI, prophylactic cranial irradiation

B.4.6 *Subgroup analysis*

No subgroup analyses were considered.

B.4.7 *Model Validation*

B.4.7.1 Model Quality Check

A health economist formally validated the cost-comparison analysis for internal accuracy. This included quality check of the model navigation, formatting and presentation, inputs, logical tests, technical implementation, and validation of the results. Overall, the results of the validation process provide confidence to the technical and conceptual validity of the model. Validation used a checklist aligned with detailed checklists and errors identified were corrected and integrated into the model.[90] Details of the validation process are presented separately in Appendix I.

B.4.8 *Interpretation and conclusions of economic evidence*

The aim of this analysis was to compare total costs associated with durvalumab + EP versus atezolizumab + EP in the treatment of adult patients with ES-SCLC. In the base case, treatment with durvalumab + EP resulted in cost savings of [redacted] compared to treatment with atezolizumab + EP, when using the [redacted] for durvalumab. All considered scenario analyses results, where alternative model assumptions were assessed, were consistent with the results observed in the base case. Durvalumab + EP would offer an additional treatment option for the heterogeneous ES-SCLC patient population, potentially leading to cost savings for the NHS while providing conservatively similar clinical efficacy and improved safety to atezolizumab + EP.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost comparison appraisal

Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer [ID6404]

Summary of Information for Patients (SIP)

August 2024

File name	Version	Contains confidential information	Date
ID6404 Durvalumab vi. NICE SIP template [noCON]	1.0	No	14/08/2024

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):

Durvalumab (IMFINZI®)

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

The purpose of this submission to the National Institute for Health and Care Excellence (NICE) is to evaluate an additional treatment regimen for people with extensive-stage small-cell lung cancer (ES-SCLC). This additional treatment regimen involves treating people's SCLC with durvalumab in combination with etoposide and platinum-based chemotherapy (EP), then continuing treatment with durvalumab alone. It is anticipated that durvalumab in combination with etoposide and either carboplatin or cisplatin will be used to treat certain adults with ES-SCLC[1].

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.

Durvalumab + EP is indicated for the first-line treatment of adults with ES-SCLC[2]. Marketing authorisation for durvalumab + EP was granted by the EMA via the centralised procedure on 27/08/2020[2].

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:

AstraZeneca UK Limited engages with the following patient advocacy groups in lung cancer, with the aims of strengthening patient insights and responding to requests for information: EGFR Positive UK and Roy Castle Lung Cancer Foundation.
AstraZeneca UK is also a corporate supporter of UK Lung Cancer Coalition, which includes patient advocacy groups.

Funding provided to UK patient groups is published annually on our 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.

Overview of SCLC

Lung cancer is the third most common cancer and the most frequent cause of cancer deaths in the United Kingdom (UK).[3] The main types of lung cancer in the UK are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLC represents an aggressive form of lung cancer, accounting for approximately 10% of all lung cancers in England.[4]

Whereas the cancer is confined to one portion of the lung in limited-stage SCLC (LS-SCLC), the disease has spread to various parts of the lung(s) and possibly metastasised to other body parts in ES-SCLC.[5]

ES-SCLC patients are often burdened with symptoms such as cough, chest pain, shortness of breath, arm/shoulder pain, constant tiredness/fatigue, and appetite loss.

How many people have the condition

Section 1b describes the anticipated eligible population for durvalumab. For this population, it is estimated that 1,329 patients will be eligible and treated with durvalumab and chemotherapy in ES-SCLC based on:

- There are approximately 34,516 patients with lung cancer in England[4]
- 10% of patients with lung cancer are expected to have SCLC[4]
- 55% of patients with SCLC are expected to have ES-SCLC[6]
- 70% of ES-SCLC patients are expected to be drug-treated[4]

Life expectancy

In England, only 2 out of every 10 people are alive 5 years after being diagnosed with lung cancer.[3] This is much lower than other common types of cancer such as breast and prostate in which closer to 9 out of every 10 people are alive 5 years after being diagnosed.[7,8] More specifically, only 5% to 6% of SCLC patients survive 5 years after being diagnosed.[7,8] ES-SCLC patients are expected to stay alive for approximately 12 months with current treatment options.[9]

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?

How is ES-SCLC diagnosed?

In the UK, SCLC is diagnosed using a variety of tests. These might include all or some of the following: chest X-rays, bronchoscopy, computerised tomography (CT), magnetic resonance imaging (MRI), positron-emission tomography CT (PET-CT), ultrasound scans, and lung cancer samples (biopsies).[10]

How is the severity of ES-SCLC determined?

At diagnosis, the severity of a person's cancer is determined by assessing the size of the tumour, whether lymph nodes are affected, and whether cancer has spread to other organs in the body. A stage is given that indicates disease severity that ranges from stage I (least severe, early-stage) to stage IV (most severe, advanced stage). People with ES-SCLC typically have Stage IV disease, where the cancer has spread widely throughout the lung, from one lung to another, to lymph nodes on the other side of the chest, or to other parts of the body.[11]

2c) Current treatment options:

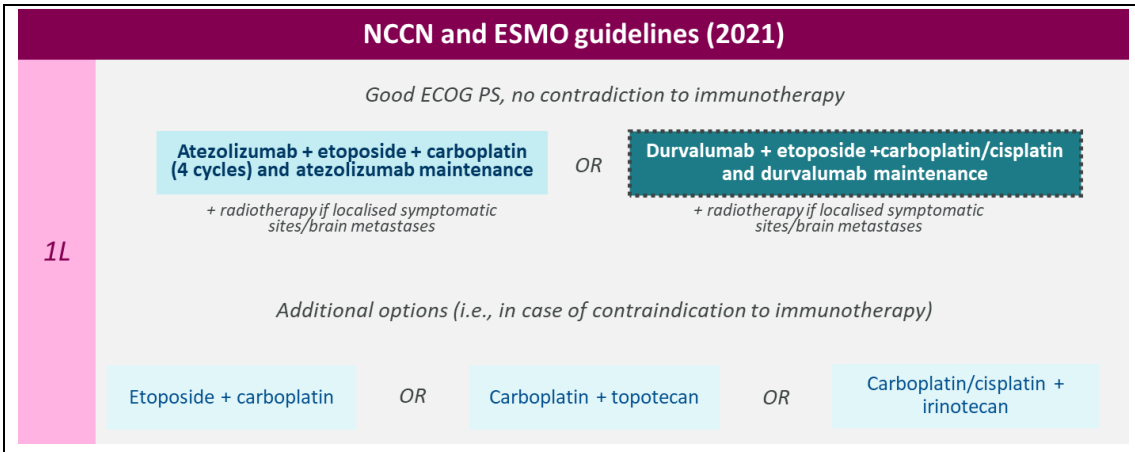
The purpose of this section is to set the scene on how the condition is currently managed:

- 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.

The current treatment pathway for patients with ES-SCLC is shown in **Figure 1.** This treatment pathway is based on the 2021 ESMO and NCCN guidelines and considers NICE's recommendation of atezolizumab and chemotherapy in ES-SCLC.[12,13]

Although durvalumab + EP is recommended in the NCCN and ESMO guidelines, it has not yet been available in the UK.

Figure 1. The current treatment pathway for ES-SCLC, summarised from the 2021 NCCN and ESMO guidelines[12,13]



Atezolizumab plus chemotherapy

Currently, the preferred treatment option for untreated ES-SCLC is atezolizumab in combination with chemotherapy (etoposide and carboplatin), followed by maintenance treatment with atezolizumab alone, for eligible patients. Atezolizumab + EP for ES-SCLC was approved by NICE in July 2020[14]. Like durvalumab, atezolizumab is an immuno-oncology therapy that is designed to recognise a specific target protein in the body to help people's immune system fight their cancer. Although atezolizumab has helped to improve patient outcomes in ES-SCLC, it remains the only therapy recommended by NICE for ES-SCLC since chemotherapy.

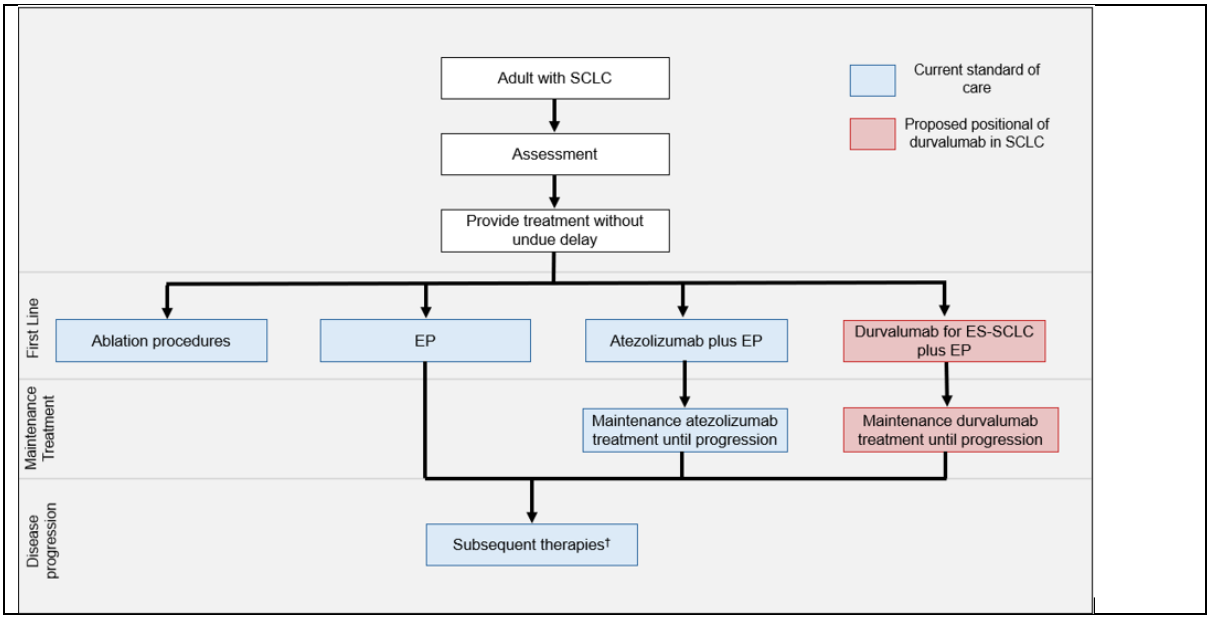
Chemotherapy

In the UK, platinum-based chemotherapy (medications used to treat cancer that contain the element platinum) is recommended for people with a good performance status (World Health Organisation [WHO] 0 or 1), a tumour size between 4cm and 5cm, and when the tumour has not spread to lymph nodes or outside lungs).[10,15] However, chemotherapy is associated with several side effects and a large proportion of eligible people either choose not to have chemotherapy or are not fit enough to tolerate it. Chemotherapy is either provided in combination with atezolizumab as described above or is provided alone for patients who are ineligible to receive immunotherapy. Chemotherapy can also be given to patients who have worsened or not improved following treatment with atezolizumab.

Proposed place of durvalumab in the treatment pathway for ES-SCLC

Given the lack of therapies available, there is a need for additional safe and effective treatment options to improve the outlook and burden for patients with ES-SCLC. **Figure 2** shows the current treatment pathway with the addition of durvalumab. As demonstrated by the results of CASPIAN (see Section 3e) and compared to atezolizumab (by indirect comparison [see Section 3e]), durvalumab + EP may reduce the risk death, and therefore improve the possibility of successful long-term outcome. In addition, the side effects experienced by the people taking durvalumab are usually manageable and are consistent with what is expected for this medicine. Comparisons with atezolizumab have also shown potentially improved side effects for durvalumab. As such, durvalumab + EP as an additional treatment option in the current pathway of care can address the substantial unmet need among people who have ES-SCLC.

Figure 2. Proposed place of durvalumab in the treatment pathway for ES-SCLC



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.

The symptoms associated with ES-SCLC and treatment adversely affect patients' quality of life. Shortness of breath and pain have been highlighted as the primary concerns in studies for ES-SCLC.[16] Interviews with ES-SCLC patients (n=17) revealed that symptoms of SCLC (such as a burning sensation, fatigue, cough, discomfort, shortness of breath) and treatment-related side-effects (such as constipation, diarrhoea, fatigue, hair loss, vomiting) had an impact on many aspects of their life, including daily activities, emotional functioning, physical functioning and social functioning/relationships, as well as having cognitive, financial and school/work-related effects. Whilst shortness of breath and pain were the most frequently reported symptoms, reduced exertion capacity was the most frequently reported physical limitation. Patients receiving treatment for their ES-SCLC further experience symptoms that may impact their quality of life such as fatigue/tiredness, nausea and hair loss.[16]

Several studies have shown that SCLC is associated with a lower quality of life than non-small cell lung cancer (NSCLC), consistent with the more aggressive course of disease. Both a Polish study and a Canadian comparing quality of life in SCLC compared to NSCLC found that scores on physical, role, cognitive and social functioning domains were significantly lower in SCLC.[17-19]

Within SCLC, there is evidence that patients with ES disease have a lower quality of life than those with LS disease.[20] A systematic review that identified 27 studies reporting on health-related quality of life (HRQoL) in patients with SCLC found that the impact on HRQoL across SCLC stages appeared greatest in patients with ES-SCLC who were treatment naïve, and lower in those who

responded to treatment (either LS or ES). Effects were greatest on physical functioning and activities of daily living.

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.

The Patient Information Leaflet for durvalumab is available here:
https://www.medicines.org.uk/emc/files/pil.9495.pdf
Durvalumab is an immuno-oncology therapy that is designed to recognise a specific target protein in the body to help people's immune system fight their cancer.[1]

There is a protein found on the surface of T cells (a type of immune cell), called programmed cell death-1 (PD-1). The PD-1 protein interacts with another protein found on cancer cells or immune cells called programmed cell death ligand-1 (PD-L1). This PD-1 and PD-L1 interaction reduces T cell activity and prevents the body's immune system from attacking the cancer cells. Durvalumab is a drug that binds to the PD-L1 protein and blocks the interaction with PD-1, thereby increasing the activity of T cells and the immune system's ability to attach to and destroy cancer cells.

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.

Durvalumab is given in combination with etoposide and platinum-based chemotherapy (medications used to treat cancer that contain the element platinum).

Conventional chemotherapy medicines directly kill tumour cells or stop them from dividing. However, under specific conditions, chemotherapy medicines may heighten the immune-stimulation effect of immuno-oncology therapies and improve the immune response to tumour cells. Combining these two medicine groups may mean more tumour cells are killed when given at tolerated doses.[51]

The side effects associated with platinum-based chemotherapy agents and etoposide include increased risk of getting an infection, breathlessness, looking pale, bruising, bleeding gums, nose bleeds, feeling or being sick, changes to liver and kidney, and abdominal pain and cramps[21-24]

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?

Durvalumab is a medicine that is given through an infusion (drip) that goes into a vein in people's arm or to a large vein in the chest. [1]

For ES-SCLC, durvalumab is administered at a dose of 1500 mg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy (alone).

The medicine is given until the cancer begins to spread again, or until the doctor stops treatment due to intolerable side effects.

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.

The CASPIAN clinical study is currently ongoing.

Table 1. Study – CASPIAN (NCT03043872)

Study	CASPIAN
Study design	Phase III, randomised, open-label, comparative, multicentre study
Status	Active, not recruiting
Locations	209 sites in 23 countries across Europe, Asia, North America, and South America
Population	**Key inclusion criteria** • Adults (aged ≥18 years) with histologically or cytologically documented ES-SCLC, or T3-4. WHO/ECOG PS of 0 or 1 and life-expectancy of >12 weeks • No prior treatment with immunotherapy **Key exclusion criteria** • People with active or documented autoimmune or inflammatory disease • People with uncontrolled intercurrent illness, such as ongoing or active infection, interstitial lung disease, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia or serious chronic gastrointestinal condition • People with a history of another primary malignancy • People with an active infection including tuberculosis, hepatitis B or C, or HIV • People with any history of radiotherapy to the chest prior to systemic therapy or planned consolidation chest radiation therapy (except palliative care outside of the chest)
Number of people in the study	There were 268 patients randomly assigned to the durvalumab + chemotherapy group and 269 patients assigned randomly to the chemotherapy only group

Intervention(s)	Durvalumab + etoposide + carboplatin or cisplatin
Comparator(s)	Chemotherapy only: Etoposide + carboplatin or cisplatin
Estimated study completion date	31 December 2024
References for further information	Please refer to the following source for further details: U.S. National Library of Medicine. Durvalumab ± Tremelimumab in Combination With Platinum Based Chemotherapy in Untreated Extensive-Stage Small Cell Lung Cancer (CASPIAN). ClinicalTrials.gov Identifier: NCT03043872. https://www.clinicaltrials.gov/study/NCT03043872?cond=CASPIAN&rank=2

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.

The evidence for the efficacy of durvalumab for the treatment of ES-SCLC comes from one clinical trial and an indirect treatment comparison.

Evidence from clinical trials

The efficacy and safety of durvalumab in combination with etoposide and platinum chemotherapy (durvalumab +EP) have been studied in the clinical trial CASPIAN. Participants in CASPIAN had ES-SCLC and had not yet received treatment for their cancer. Participants took durvalumab at a dose of 1500 mg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy (alone). Durvalumab was given until the cancer began to spread again (progressed), or until the doctor stops treatment due to intolerable side effects.

Two-hundred sixty-eight adults were randomly assigned to durvalumab + EP and 269 were assigned to EP alone. Neither the participant nor their doctor knew which treatment they were taking. The primary aim of CASPIAN was to see how long participants in the study would remain alive with durvalumab + EP (known as overall survival).

Primary outcome (Document B, section B.3.6.1)

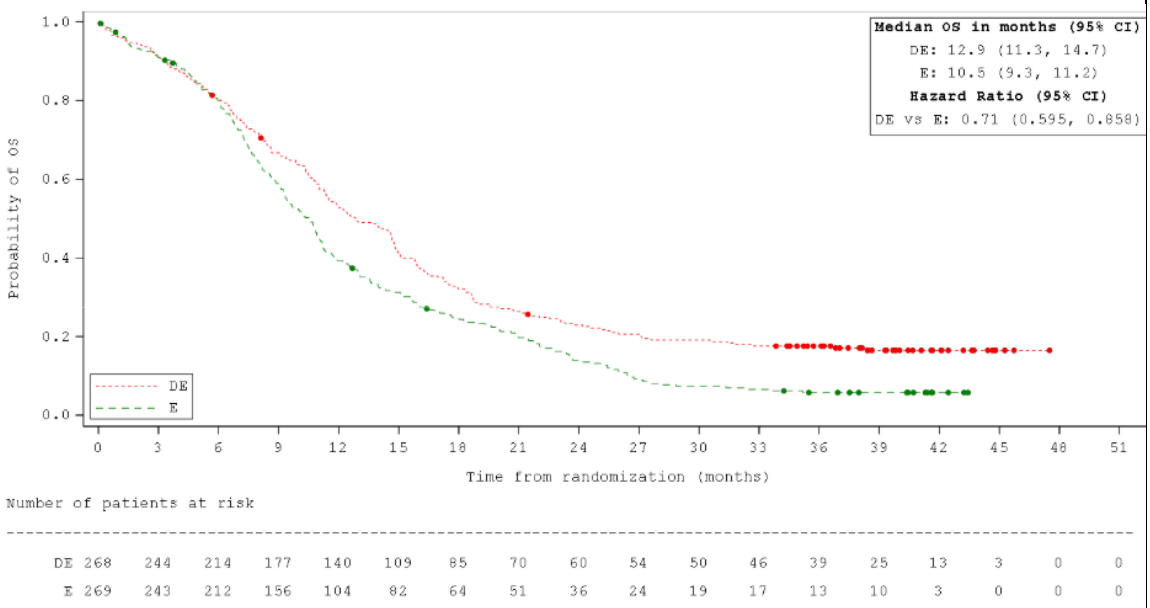
Overall survival in CASPIAN is defined as the time from study randomisation until death.

CASPIAN showed that participants in the durvalumab + EP arm stayed alive for longer compared to participants in the EP alone arm.

- At the data cut off (DCO) of 22 March 2021 (3-year follow-up) the hazard ratio (HR) was 0.71 (95% CI, 0.595, 0.858; p=0.0003), meaning that patients taking durvalumab + EP were 29% less likely to die from their cancer compared to those taking EP alone.

A Kaplan-Meier (KM) plot shows the rate at which an event, in this case, the return of NSCLC or death, occurs over time. A steeper downward slope indicates a higher event rate and therefore a worse prognosis. The KM plot in Figure 3 below shows a clear and sustained separation in favour of durvalumab + EP, showing that a greater number of participants taking durvalumab + EP remained alive for a longer time compared to those who received EP alone as treatment.

Figure 3: Overall survival in CASPIAN; DCO 22 March 2021 (3-year follow-up) (Full Analysis Set)



Abbreviations: CI, confidence interval; D + E/P/DE, durvalumab + etoposide and platinum-based chemotherapy; EP, etoposide plus platinum-based chemotherapy; HR, hazard ratio; (m)OS, (median) overall survival.

Source: CASPIAN CSR 2021[25]

Secondary Outcomes: Progression-free survival (Document B, section B.3.6.3.1)

Progression-free survival (PFS) was a secondary endpoint in the CASPIAN trial. This outcome is also of interest when determining the efficacy of a drug because it demonstrates how long before a patient's cancer starts to spread again after treatment.

Progression-free survival was measured at the DCO 27 January 2020 (2-year follow-up). At this DCO, durvalumab + EP prolonged the time until a patient's cancer started to spread again, resulting in a HR of 0.80; (95% CI: 0.665, 0.959) compared to EP alone.

Evidence from the indirect treatment comparisons

The CASPIAN trial does not directly compare durvalumab with etoposide and platinum chemotherapy (durvalumab +EP) to atezolizumab plus etoposide and platinum chemotherapy (atezolizumab + EP).

Indirect treatment comparisons are a way of comparing treatments that have not been directly compared against each other in a clinical trial and when a common comparator has been used in the respective studies. For example, treatment A is compared with treatment C in Study 1 and treatment B is compared with treatment C in Study 2. Using a common comparator of treatment C and the information from Studies 1 and 2, how well treatment A compares against treatment B can be estimated.

The indirect comparison of durvalumab + EP compared to atezolizumab + EP demonstrated that the two treatments had similar efficacy and safety, and that durvalumab may lower risk of death from ES-SCLC. Details about the methods and results are confidential and presented in Document B, section B.3.9.

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.

In the CASPIAN trial, participants' quality of life was measured using generic and lung cancer-specific questionnaires. These included the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), EORTC QLQ- Lung Cancer 13 (LC13), and the EuroQol 5-dimension questionnaire (EQ-5D).
The impact that durvalumab has on participant HRQoL in CASPIAN is reported in Document B, Section B.3.6.4[25]

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.

Like any medicine, durvalumab can cause side effects, although not everybody gets them. How often and how severe the side effects are can vary from person to person. In the CASPIAN trial, durvalumab was generally well tolerated. The overall frequency of side effects in the CASPIAN trial was comparable between the durvalumab and chemotherapy groups and was consistent with the known safety profile of the individual treatments components. Neutropenia, anaemia, nausea and alopecia were the most commonly experienced side effects by patients in either treatment group. Side effects affecting the immune system were experienced by 53 patients (20.0%) in the durvalumab treatment group and 7 patients (2.6%) in the chemotherapy group.

89.8% of patients in the durvalumab group completed their treatment regimen (i.e., received all planned rounds of durvalumab and chemotherapy).

Table 2. Most common AEs reported in ≥15% of patients in CASPIAN

Side effect	Durvalumab + chemotherapy N=265	Chemotherapy only N=266
Neutropenia	111 (41.9)	124 (46.6)
Anaemia	102 (38.5)	125 (47)
Nausea	89 (33.6)	89 (33.5)
Alopecia	84 (31.7)	91 (34.2)

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
-

The key benefits of durvalumab for people with ES-SCLC, their families, and caregivers include:

- The indirect comparison of durvalumab + EP compared to atezolizumab + EP demonstrated that the two treatments had similar efficacy and safety, with durvalumab showing a numerical improvement in data in terms of side effects and lowering risk of death from ES-SCLC. Details about the methods and results are confidential and presented in Document B, section B.3.9.
- The side effects of durvalumab are expected to be manageable and consistent with side effects that have been seen for this treatment when used to treat other types of cancer, and are unlikely to result in the person having to stop their treatment
- Durvalumab is the only treatment which has 3 years' worth of data in ES-SCLC, providing confidence and a peace of mind to patients regarding its impact

Although this is not studied in the CASPIAN trial, it is anticipated that the quality of life of the families and caregivers of people who are treated with durvalumab is likely to be maintained as their loved ones stay tumour-free for longer, thereby avoiding the physical and emotional burden of caring for someone with an aggressive and debilitating cancer

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

- Durvalumab is currently available for intraveneous administration only[1]
- In general, the treatment of ES-SCLC with durvalumab does not have known disadvantages compared with existing therapies

3i) 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.

A cost-comparison model was used to estimate the costs related to using durvalumab + EP versus atezolizumab + EP for ES-SCLC patients. This approach assumes similar efficacy between the two treatment options and considers whether a treatment is cost-saving from a UK healthcare perspective. Differences in HRQoL, therefore, are not modelled in this method.

The model structure is a three-state area under the curve model, also known as a partitioned survival model. This type of model uses three distinct and mutually exclusive health states (PFS, post-progression survival [PPS], and death) to estimate treatment costs relating to durvalumab + EP and atezolizumab +EP. Overall survival and PFS curves are utilised to determine the proportion of patients in each health state. All patients start from the PFS health state. If the cancer begins to spread again and worsen, they can subsequently move into the PPS health state and eventually to the death state. Death is considered the final health state, accounting for model patients who die either from ES-SCLC or from natural causes. Some patients may move directly from the PFS state to the death state. Once a patient progresses, they cannot go back to the PFS health state.

The cost-comparison model was informed by estimates of OS, PFS and subsequent treatment data from the CASPIAN trial. Duration of treatment for durvalumab + EP and atezolizumab + EP was based on TTD data, with duration of subsequent treatment based on patient level estimates by treatment class.

The model incorporated the 3-year data (DCO 22 March 2021). At this DCO, 221 (82%) deaths had occurred in the durvalumab + EP arm. Given that the available clinical trial data covered survival in the first few years, the model used mathematical functions to predict how the disease course develops in the long-term. This process involved performing parametric survival modelling of OS, PFS, and TTD. The data used to predict long-term treatment impact in the model were validated by experienced oncologists who treat ES-SCLC. Additionally, different mathematical functions were used and tested as scenarios for a comprehensive analysis.

The model accounts for costs related to treatments and use of healthcare services. For costs related to healthcare services, the model assumes that these are independent of the treatment being received. Patients in general use health services more frequently at more advanced stages of the disease, therefore the model estimates a greater cost in these states. Healthcare resource use was assumed to be equivalent for durvalumab + EP and atezolizumab + EP.

The impact on costs and outcomes of subsequent treatments (i.e., treatments that follow durvalumab) are subject to some uncertainty. For example, second-line treatment costs were modelled based on data from the CASPIAN study, given the lack of available data on subsequent treatments for ES-SCLC patients. However, this uncertainty was reduced by including only second-line treatments indicated by experienced oncologists. Additionally, given the lack of data available in ES-SCLC, data related to healthcare service use and costs used in the model were largely informed by data on non-small-cell lung cancer (NSCLC).

Durvalumab + EP is cost-saving compared to atezolizumab + EP from a UK healthcare perspective when including the confidential commercial access agreement for durvalumab, meaning that

costs related to treatment are less than those related to atezolizumab +EP. In all scenarios tested, durvalumab + EP consistently demonstrated cost savings compared to atezolizumab + EP.

The objective of treating patients with durvalumab + EP is to prolong the period of time a patient spends without their cancer getting worse and subsequently extend life. Based on the evidence available and the company's economic analysis, durvalumab + EP will be examined by NICE in this appraisal. The committee's decision will be based on the available data for durvalumab + EP in ES-SCLC.

3j) 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)

The current UK treatment pathway does not have many options for ES-SCLC patients and the prognosis for these patients remains poor. With the exception of chemotherapy, atezolizumab + EP remains the only treatment option for patients.

Durvalumab + EP offers an additional immunotherapy treatment option for patients. The indirect comparison of durvalumab + EP compared to atezolizumab + EP demonstrated that the two treatments had similar efficacy and safety, with durvalumab showing a numerical improvement in data in terms of side effects and lowering risk of death from ES-SCLC.

Durvalumab is the only treatment which has 3 years' worth of data in ES-SCLC, providing confidence and a peace of mind to patients regarding its impact.

3k) 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

No equalities issues anticipated.

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.

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

Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe.

Biopsy: A process in which a very small part of tissue in the body is removed to look for signs of disease.

Clinical trial/clinical study: A type of research study that tests how well new medical treatments work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study. When it is called "phase III clinical trial" it tests the safety and how well a new treatment works compared with a standard treatment. For example which group of people have better survival rates or fewer side effects. In most cases, treatments move into phase III clinical trials only after they meet the goals of phase I and phase II clinical trials. Phase 3 clinical trials may include hundreds of people.

CT scan / computerized axial tomography scan: A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3-D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly. A computerized axial tomography scan may be used to help diagnose disease, plan treatment, or find out how well treatment is working. Also called CAT scan, computed tomography scan, computerized tomography, and CT scan.

EORTC QLQ- LC-13: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13.

EMA: European Medicines Agency: The regulatory body that evaluates, approves, and supervises medicines throughout the European Union.

EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire – Cance Module.

EQ-5D: EuroQol 5-dimension questionnaire.

ES-SCLC : Extensive-stage small-cell lung cancer

Follow-up duration: The stated length of time a person's health was monitored over time after treatment.

Health-related quality of life: The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out activities of daily living.

HTA: Health Technology Assessment (bodies): Bodies that make recommendations regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.
Immuno-oncology therapy/Immunotherapy: A type of cancer therapy using substances made by the body or in a laboratory to boost the immune system and help the body find and destroy cancer cells.

Lymph nodes: the lymph nodes are small glands that are part of the body's lymphatic system that carry immune cells that help fight infections or cancer cells. Cancer cells can either start in lymph nodes or spread to the nodes from elsewhere in the body, e.g., the lungs.

MRI: A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue. MRI makes better images of organs and soft tissue than other scanning techniques, such as computed tomography (CT) or x-ray. MRI is especially useful for imaging the brain, the spine, the soft tissue of joints, and the inside of bones. Also called magnetic resonance imaging, NMRI, and nuclear magnetic resonance imaging.

OS: Overall survival, how long people with a disease live.

Platinum-based chemotherapy: Medications used to treat cancer that contain the element platinum. This includes medicines like carboplatin, cisplatin etc.

Stage: A description of how severe a disease is.

Targeted therapy: A type of cancer treatment that targets specific proteins that control how cancer cells grow, divide, and spread. These treatments are designed to fix specific unhealthy areas in the body, such as cells with a specific mutation, for example, an EGFR mutation, while limiting damage to healthy parts of the body.

Treatment cycle: A cycle is the time between one round of treatment until the start of the next.

X-ray imaging: A procedure that uses a type of high-energy radiation called x-rays to take pictures of areas inside the body. X-rays pass through the body onto film or a computer, where the pictures are made. The tissues and organs usually appear in various shades of black and white

because different tissues allow different amounts of the x-ray beams to pass through them. X-ray imaging is used to help diagnose disease and plan treatment. Also called radiography.

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:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer [ID6404]

Clarification questions

August 2024

File name	Version	Contains confidential information	Date
ID6404 Durvalumab company response to clarification questions	**V1.0**	**Yes**	**12 September 2024**

Section A: Clarification on effectiveness data

Please note that all data requested for durvalumab are for the CASPIAN trial durvalumab+etoposide and platinum-based chemotherapy (EP) arm only.

Efficacy data

A1. Priority question. The company has carried out an overall survival (OS) indirect treatment comparison (ITC) using 3-year follow-up data from the CASPIAN trial and 2-year follow-up data from the IMpower133 trial. Please carry out an OS ITC using 2 year follow-up data from both trials:

i. **assuming equivalence for etoposide+carboplatin and etoposide+cisplatin**

ii. **without the assumption of equivalence for etoposide+carboplatin and etoposide+cisplatin**

The ITC base case analysis assuming equivalence of etoposide+carboplatin (ET+CAR) and etoposide+cisplatin (ET+CIS), as described in Document B, was run using the 2-year follow-up data from both trials. Results of the ITC for OS endpoint with the assumption of equivalence using the 2-year follow-up data from both trials are presented in Table 1.

Table 1: Results of the ITC for OS with the assumption of equivalence

Study	Treatment 1	Treatment 2	Within-trial HR (95% CI) Trt 1 versus Trt 2	ITC (between trial) HR (95% CI) durvalumab + EP versus atezolizumab + EP
CASPIAN	durvalumab + EP	EP	0.75 (0.63, 0.91)	[redacted] ([redacted], [redacted])
IMpower133	atezolizumab + EP	EP	0.76 (0.60, 0.95)	

Data from CASPIAN were derived from the IPD corresponding to the OS final analysis data-cut (database lock date: 03 March 2020)

Abbreviations: CI, confidence interval; EP, etoposide + platinum-based chemotherapy; HR, hazard ratio; ITC, indirect treatment comparison; PFS, progression-free survival; Trt, treatment

*Analysis based on the assumption of equivalence between cisplatin and carboplatin

Source: CASPIAN CSR 2020 [1]; Reck et al, 2019[2]

Under the assumption of equivalence, results from ITC demonstrated that there was no significant difference between durvalumab and atezolizumab for OS (hazard ratio [HR]: [redacted] [[redacted], [redacted]]).

Results of the ITC for OS without the assumption of equivalence using the 2-year follow-up data from both trials are presented in Table 2.

Table 2: Results of the ITC for OS without the assumption of equivalence

Study	Treatment 1	Treatment 2	Within-trial HR (95% CI) Trt 1 versus Trt 2	ITC (between trial) HR (95% CI) durvalumab + CIS versus atezolizumab + CAR	ITC (between trial) HR (95% CI) durvalumab + CAR versus atezolizumab + CAR
CASPIAN	durvalumab + CIS	ET+CAR	[redacted][a] ([redacted], [redacted])	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])
CASPIAN	durvalumab + CAR	ET+CAR	0.79 (0.63, 0.98)		
IMpower133	atezolizumab + CAR	ET+CAR	0.76 (0.60, 0.95)		

Data from CASPIAN were derived from the IPD corresponding to the OS final analysis data-cut (database lock date: 03 March 2020)

Abbreviations: AT, atezolizumab; CAR, carboplatin; CI, confidence interval; CIS, cisplatin; DUR, durvalumab; ET, etoposide; HR, hazard ratio; IPD, individual patient data; ITC, indirect treatment comparison; OS, overall survival; Trt, treatment

[a] HR estimated with the digitalization of KM curves

Source: CASPIAN CSR 2020 [1]; Reck et al, 2019[2]

Results from the ITC without the assumption of equivalence indicated that there was no significant difference between both durvalumab + ET + CIS and durvalumab + ET + CAR vs. atezolizumab + ET + CAR for OS (HR: [redacted], HR: [redacted], respectively). The HR for durvalumab + ET + CIS vs. atezolizumab + ET + CAR showed a reduced risk of death for durvalumab + ET + CIS, however, the effect was not statistically significant.

A2. Priority question. Please provide the following charts using 2-year follow-up data:

The company's frequentist Bucher ITC provides the most robust comparative analysis to determine the efficacy of durvalumab + EP versus atezolizumab + EP, accounting for the inclusion of covariates and potential biases and confounding factors. This approach provides a more rigorous and reliable assessment by incorporating available evidence and reducing the impact of individual study limitations, which is not conducted in a naïve analysis. The 2-year ITC results provided in response to A1 further support the findings of similar efficacy concluded in the company base case.

Considering the populations in the CASPIAN and IMpower133 studies are comparable, data from the trials were digitised and plotted to show a naïve comparisons of survival outcomes. The analyses presented below demonstrate consistency between the OS curves for atezolizumab + EP and durvalumab + EP. Additionally, the PFS analysis demonstrates a directional improvement in favour of durvalumab + EP. The ITC remains the most robust method for establishing comparative efficacy, but the resulting plots from the naïve comparison further support the findings of the ITC and the assumption of equivalent efficacy required for the cost-comparison analysis.

i. CASPIAN trial and IMpower133 trial PFS K-M intervention arm data. Please undertake a log-rank test to test for survival differences between patients treated with durvalumab or atezolizumab

Figure 1: CASPIAN and IMpower133 PFS Kaplan-Meier data, intervention arms

2-year PFS data from K-M curve in the CASPIAN study publication and 1-year PFS data from K-M curve in the IMpower133 study publication were digitised and plotted to provide a naïve comparison between the intervention arms.

Abbreviations: PFS, progression-free survival; EP, etoposide + platinum-based chemotherapy
Source: CASPIAN CSR 2020; Horn *et al*., (2018)

ii. CASPIAN trial and IMpower133 trial OS K-M intervention arm data. Please undertake a log-rank test to test for survival differences between patients treated with durvalumab or atezolizumab.

Figure 2: CASPIAN and IMpower133 OS Kaplan-Meier data, intervention arms

2-year OS data from K-M curves in the CASPIAN and IMpower133 study publication were digitised and plotted to provide a naïve comparison between the intervention arms.

Abbreviations: PFS, progression-free survival; EP, etoposide + platinum-based chemotherapy
Source: CASPIAN CSR 2020; Reck *et al*., (2019)

iii. CASPIAN trial and IMpower133 trial PFS K-M comparator arm data. Please undertake a log-rank test to test for survival differences between patients in the comparator arms.

Figure 3: CASPIAN and IMpower133 PFS Kaplan-Meier data, comparator arms

2-year PFS data from K-M curve in the CASPIAN study publication and 1-year PFS data from K-M curve in the IMpower133 study publication were digitised and plotted to provide a naïve comparison between the comparator arms.

Abbreviations: PFS, progression-free survival; EP, etoposide + platinum-based chemotherapy
Source: Goldman *et al*., (2021); Horn *et al*., (2018)

iv. CASPIAN trial and IMpower133 trial OS K-M comparator arm data. Please undertake a log-rank test to test for survival differences between patients in the comparator arms.

Figure 4: CASPIAN and IMpower133 OS Kaplan-Meier data, comparator arms

2-year OS data from K-M curves in the CASPIAN and IMpower133 study publication were digitised and plotted to provide a naïve comparison between the comparator arms.

Abbreviations: PFS, progression-free survival; EP, etoposide + platinum-based chemotherapy
Source: Goldman *et al*., (2021); Reck *et al*., (2019)

A3. Priority question. Given that restricted mean survival time (RMST) analysis does not require the proportional hazards assumption to hold, please conduct PFS and OS RMST analyses for the comparison of durvalumab versus atezolizumab (2-year follow-up data).

In the absence of published 2-year PFS Kaplan-Meier graph for atezolizumab, the 1-year data cut from IMPower-133 primary publication was used in the PFS RMST analysis.[3] The 2-year follow-up IMpower133 data were available for OS.[2] Two-year follow up data were used for CASPIAN PFS and OS outcomes.[1]

Table 3: Data inputs for PFS RMST NMA - pooling CIS and CAR (t* = 17 months)

Study	Treatment 1	Treatment 2	RMST mean difference (months)	SE (RMST mean difference)
CASPIAN	durvalumab + EP	EP	[redacted]	[redacted]
IMpower133	atezolizumab + EP	EP	[redacted]	[redacted]

Data from CASPIAN were derived from the IPD corresponding to the FA OS data-cut

Abbreviations: PFS, progression-free survival; RMST, restricted mean survival time; NMA, network meta-analysis; SE, standard error; EP, etoposide + platinum-based chemotherapy; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; Trt, treatment

*Analysis based on the assumption of equivalence between cisplatin and carboplatin

Source: CASPIAN CSR 2020 [1]; Horn et al, 2018[3]

Table 4: Data inputs for OS RMST NMA - pooling CIS and CAR (t* = 28 months)

Study	Treatment 1	Treatment 2	RMST mean difference (months)	SE (RMST mean difference)
CASPIAN	durvalumab + EP	EP	[redacted]	[redacted]
IMpower133	atezolizumab + EP	EP	[redacted]	[redacted]

Data from CASPIAN were derived from the IPD corresponding to the 2-year data-cut

Abbreviations: PFS, progression-free survival; NMA, network meta-analysis; EP, etoposide + platinum-based chemotherapy; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; Trt, treatment

*Analysis based on the assumption of equivalence between cisplatin and carboplatin

Source: CASPIAN CSR 2020[1]; Reck et al, 2019[2]

A4. Please clarify why objective response rate (ORR) indirect treatment comparisons (ITCs) were not conducted.

Overall survival was considered the most important outcome for considering efficacy in extensive-stage small cell lung cancer (ES-SCLC) as it entirely captured the survival benefit of the treatment and long-term follow-up data were available for both the CASPIAN and IMpower133 trials. The PFS and safety outcomes were also analysed as supplementary outcomes of interest to establish comparative efficacy and safety.

The ORR outcome was not considered in the ITCs as it was not deemed as a significant outcome for establishing comparative efficacy, particularly in light of the cost-comparison assessment. Although ORR is a relevant endpoint in clinical trials for ES-SCLC, it does not capture long-term efficacy.

Safety data

A5. ITCs for Grade 3/4 treatment-related adverse events (AEs), serious treatment-related AEs and individual treatment-related Grade 3/4 AEs (febrile neutropenia, thrombocytopenia, leukopenia, anaemia, neutropenia, decreased neutrophil count) are presented in the company submission (CS) (Appendix D.3.4.3).

i. Please provide the rationale for focusing on the AEs in these ITCs.

Although overall survival was considered to be the most important outcome for assessing the difference in survival benefits between durvalumab + EP and atezolizumab + EP, we included the above safety outcomes within the analyses to establish comparative safety for completeness. Grade 3/4 AEs can be considered severe and/or life threatening and are frequently of particular interest in NICE technology appraisals.

ii. Please clarify why were ITCs were not conducted for:

- AEs of special interest (AESIs)
- immune mediated AEs (imAEs)
- AEs leading to treatment withdrawal
- treatment-related AEs leading to treatment withdrawal
- AESIs leading to treatment withdrawal
- imAEs leading to treatment withdrawal
- AEs resulting in death
- treatment-related AEs resulting in death

The above AEs were not included in the ITCs as the preference was to use absolute grade 3/4 AE incidence data from the trial publications.

A6. Please recreate CS, Table 22 for CASPIAN trial Grade 3/4 AEs.

Please refer to pages 1867 to 1877 of the CASPIAN CSR appendix (now provided) for details on adverse events of any common terminology criteria for adverse events (CTCAE) grade 3 or 4 by system organ and preferred term.[4]

A7. Please provide the number and type(s) of CASPIAN trial durvalumab arm AESIs and imAEs that led to treatment discontinuation.

Table 5: AESIs and imAEs leading to treatment discontinuation

	Durvalumab + EP (N=265)	
AE leading to discontinuation of study treatment	**AESI, n (%)**	**imAE, n (%)**
Any AE	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Diarrhoea/colitis	[redacted]	[redacted]
Hepatic event	-	[redacted]

Abbreviations: AESI,adverse event of special interest; imAEs, immune-mediated adverse events; EP, etoposide + platinum-based chemotherapy; AE, adverse event

Source: CASPIAN CSR Appendix 2019[4]

The CASPIAN trial

A8. Please confirm how many (n, %) patients in the durvalumab arm went on to receive maintenance durvalumab treatment after completing their cycles of chemotherapy.

[redacted] patients ([redacted]%) from the durvalumab + EP arm of the CASPIAN trial completed 5 or more cycles of durvalumab (i.e., including initial treatment period). Additionally, [redacted] patients ([redacted]%) completed their cycles of chemotherapy from the durvalumab + EP arm.[1]

A9. Please confirm if there were any patients who received maintenance durvalumab treatment who did not receive at least four cycles of chemotherapy and present the number (n, %) and if available, a summary of the reasons for not completing at least four cycles.

As stated within above answer to question A8, [redacted] patients ([redacted]%) completed their cycles of chemotherapy from the durvalumab + EP arm.[1] The median number of chemotherapy cycles received by patients in the durvalumab + EP arm was 4 (4-4). The reasons for patients discontinuing chemotherapy are summarised below:

- Withdrawal by subjects: [redacted] patients ([redacted]%)
- Adverse events: [redacted] patients ([redacted]%)
- Disease progression: [redacted] patients ([redacted]%)
- Deviation of study-specific withdrawal criteria: [redacted] patients ([redacted]%)
- Other: [redacted] patients ([redacted]%)

Section B: Clarification on cost effectiveness data

None

Section C: Textual clarification and additional points

C1. Please provide a list abbreviations used in the CS.

ACD	Appraisal consultation document
AE	Adverse event
AESI	Adverse event of special interest
AFT	Accelerated failure time
AIC	Akaike Information Criterion
AIS	Adenocarcinoma in situ
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
AT	Atezolizumab
AUC	Area under the curve
AZ	AstraZeneca
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSA	Body surface area
CAR	Carboplatin

CAV	Cyclophosphamide, doxorubicin and vincristine
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMA	Cost-minimisation analysis
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRD	Centre for reviews and dissemination
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CUA	Cost-utility analysis
D	Durvalumab
DCO	Data cut-off
DCR	Disease control rate
DFS	Disease-free survival
DIC	Deviance information criterion
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAP	Early access programme
EMA	European medicines agency
EP	Etoposide and platinum-based chemotherapy
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EP	Etoposide and platinum-based chemotherapy
EQ-5D	5-dimension EuroQol questionnaire
ERG	Evidence review group

ES	Extensive-stage
ESMO	European Society of Medical Oncology
ET	Etoposide
EU	European Union
GCSF	Granulocyte-colony stimulating factor
GHS	Global health status
H	Hypothesis
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
IO	Immuno-oncology
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KOL	Key opinion leader
LS	Limited-stage
LY	Life year
LYG	Life years gained
M	Metastasis
mAb	Monoclonal antibody
MMRM	Mixed model with repeated measures
MRI	Magnetic resonance imaging
N	Lymph node
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit

NR	Not reported
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PartSA	Partitioned survival analysis/model
PAS	Patient access scheme
PbR	Payment by results
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PD-1	Programmed death protein 1
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
PH	Proportional hazards
PICOS	Population, Intervention, Comparator, Outcome, and Study type
PK	Pharmacokinetic(s)
PO	Taken orally
PPS	Post-progression survival
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
Q3W	Once every three weeks
Q4W	Once every four weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RT	Radiotherapy
RWE	Real-world evidence
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SCC	Small-cell carcinoma

SCIC	Squamous cell carcinoma in situ
SCLC	Small-cell lung cancer
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
T	Tumour
TA	Technology appraisal
TFI	Treatment-free interval
TNM	Tumor size, lymph nodes affected, metastases
TRT	Thoracic radiotherapy
TSD	Technical support document
TTD	Time to discontinuation
TTF	Time to treatment failure
TTO	Time trade-off
TTP	Time to progression
UK	United Kingdom
VA	Veterans' Administration
WHO	World Health Organization

References

1. AstraZeneca. A phase III, randomized, multicenter, open-label, comparative study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for the first-line treatment in patients with extensive disease small-cell lung cancer (SCLC) (CASPIAN) - Clinical Study Report Final Anaylsis, 2020.
2. Reck M, Liu SV, Mansfield AS, et al. IMpower133: Updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo)+ carboplatin+ etoposide in extensive-stage SCLC (ES-SCLC). Annals of Oncology 2019;30:v710-v711.
3. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. New England Journal of Medicine 2018;379:2220-2229.
4. AstraZeneca. A phase III, randomized, multicenter, open-label, comparative study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for the first-line treatment in patients with extensive disease small-cell lung cancer (SCLC) (CASPIAN) - Appendices, 2019.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer (review of TA662) [ID6404]

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.

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	**RCLCF has received the following funding :** - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project; £15,000 grant for Information Services) - BMS (£30,000 for 1 year funding of GLCC project) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1820 Advisory board Honorarium) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- Gilead (£30,000 for 1 year funding of GLCC project) - Sanofi (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project) - Novocure (£30,000 for 1 year funding of GLCC project) - Roche (£30,000 for 1 year funding of GLCC project) - Regeneron (£30,000 for 1 year funding of GLCC project) - Merck (£30,000 for 1 year funding of GLCC project - AstraZeneca (£30,000 for 1 year funding of GLCC project; £19,500 for GLCC Project Translation; £500 for Meeting Speaker Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project) - Takeda (£30,000 for 1 year funding of GLCC project) - Janssen (£24,000 grant funding for Ask The Nurse Service)
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?	The National Lung Cancer Audit 2024 (for patients diagnosed in 2022), reported around 10% of lung cancer being of small cell pathological sub type. SCLC is widely accepted to be around 10 to 15% of lung cancer cases. A diagnosis of extensive SCLC is devastating. Small cell is a particularly aggressive type of cancer, patients often being very symptomatic at presentation. This is a rapidly progressive disease and as such, patients should be assessed quickly and systemic anticancer treatment started quickly. SCLC is very responsive to initial chemotherapy/immunotherapy. However, despite the sometimes dramatic response, many patients relapse and die within six months of diagnosis. The overall 5 year survival for SCLC (limited and extensive stage disease) is only about 5%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. 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?	Outcomes of current treatment remain poor in extensive stage SCLC. There have been relative few developments in the treatment of this type of lung cancer in decades. As such, there is a huge need for therapies with better outcomes than currently available. (note - Atezolizumab with carboplatin and etoposide in extensive stage SCLC was recommended by NICE [TA638] in 2020. We understand that there are no direct comparisons of Atezolizumab and Durvalumab in this combination and indication)
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 note the results of the CASPIAN trial, in patients with previously untreated extensive stage SCLC, in which those who received etoposide and platinum based chemotherapy with the addition of Durvalumab, was associated with a significantly longer overall survival, as compared with those patients who received chemotherapy alone.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with Durvalumab treatment.

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 is an aggressive disease, with very few advances in treatment over decades. • The outcome from current standard treatment, for this patient group, is woefully poor. There is massive unmet need.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer (review of TA662) [ID6404]

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.

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 13 pages.

About you

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? **Yes** 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 registration fees and sponsorship**
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes Sponsorship BTOG 2024 platinum £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.)	To improve overall survival, to improve progression-free survival
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.)	The technology is unlikely to improve objective response rate. However, a clinically significant improvement in relative progression free survival by 20% or relative overall survival by 30% would be considered meaningful in an aggressive condition with little improvement in treatment over 30 years.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes; extensive stage small cell lung cancer remains an aggressive cancer with real world median survival less than 12 months. Whilst atezolizumab is already NICE approved for extensive stage SCLC, durvalumab would add another treatment option for cisplatin-treated patients, albeit with similar efficacy to atezolizumab.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Extensive stage small cell lung cancer patients that meet the NHS England/ Blueteq criteria for atezolizumab (TA638) are generally treated with carboplatin-etoposide-atezolizumab first line. Patients with poorer performance status are treated with chemotherapy alone with schedule modifications to minimize toxicities.
9a. Are any clinical guidelines used in the	As per NICE guidelines and ESMO guidelines

treatment of the condition, and if so, which?	
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, this is a well-defined pathway with little meaningful variation between centres and between experts.
9c. What impact would the technology have on the current pathway of care?	Durvalumab access would be another option instead of atezolizumab (TA638). As per the CASPIAN trial of durvalumab, access would allow the ability to combine with cisplatin or carboplatin rather than limiting to carboplatin only as per atezolizumab.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Durvalumab is not currently used for SCLC in current care
10a. How does healthcare resource use differ between the technology and current care?	Durvalumab would be used in place of atezolizumab (TA638)
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment or education as durvalumab is already used in oncology practice routinely.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The OS benefit for durvalumab from the CASPIAN trial was very similar to that observed for atezolizumab form the IMP133 trial.
11a. Do you expect the technology to increase length of life more than current care?	Durvalumab will increase survival over chemotherapy alone as per the CASPIAN trial. However, as the benefit for OS observed was similar to that observed with chemotherapy-atezolizumab (TA638), it is unlikely to improve survival over current practice (chemotherapy-atezolizumab).
11b. Do you expect the technology to increase health-related quality of life more than current care?	No, for the same reasons as 11a
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

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	Durvalumab will allow a 4 weekly IV dosing. Currently atezolizumab is administered 3 or 4 weekly IV or 3 weekly S/C. Durvalumab will also allow treatment with cisplatin or carboplatin rather than carboplatin alone as is currently the case with atezolizumab.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will be given until loss of clinical benefit, or unacceptable toxicities with regular imaging assessments as per routine care.
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?	Durvalumab is not innovative given that atezolizumab is already NICE approved and available for the same indication. However, durvalumab was innovative in improving overall survival over chemotherapy alone at the time the CASPIAN trial reported
16a. Is the technology a 'step-change' in the management of the condition?	No, as per #16

16b. Does the use of the technology address any particular unmet need of the patient population?	No, as per #13
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?	Yes, immune checkpoint inhibitors can be associated with significant immune-related toxicities. However, these are already observed for atezolizumab which is already NICE approved. Hence, no additional toxicities would be observed over that experienced with atezolizumab

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?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival and progression-free survival. Yes, these were measured.
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	No

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA638?	No
21. How do data on real-world experience compare with the trial data?	Several groups have reported real world experience of durvalumab in extensive stage small cell lung cancer. As these are not trials populations they inevitable have inferior survival (prognosis) compared to trials populations who have fewer co-morbidities.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Durvalumab when added to platinum-etoposide chemotherapy improves overall survival over chemotherapy alone in extensive stage SCLC • Durvalumab would be used in the same place as atezolizumab currently is, per NICE TA638 • The efficacy associated with durvaluamb-chemotherapy is very similar to that observed for atezolizaumb-chemotherapy • Durvalumab trial data allows the potential to treat with cisplatin or carboplatin not just carboplatin (which is the case for atezolizumab) •

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EAG cost-comparison report

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small cell lung cancer (Review of TA662) [ID6404]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 168879

Completed 3 October 2024
Updated 22 October 2024

CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small cell lung cancer (Review of TA662) [ID6404]

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Date completed: 3 October 2024; updated 22 October 2024 following company factual accuracy check

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 168879

Acknowledgements: The authors would like to thank Lynn Campbell, Medical Oncologist, Belfast City Hospital, Belfast who provided feedback on a draft version of the report.

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

Declared competing interests of the authors: None.

Declared competing interests of peer reviewers: Lynn Campbell has received reimbursement from Roche for attending the All Ireland Lung Cancer Conference (2022), reimbursement from Takeda for attending the World Conference on Lung Cancer (2022) and reimbursement from MSD for attending the European Society for Medical Oncology Congress (2023).

This report should be referenced as follows: Fleeman N, Bryning S, Beale S, Boland A, Dundar Y, Marsden A, Green J. Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small cell lung cancer (Review of TA662) [ID6404]: A Cost-comparison Technology Appraisal. LRiG, University of Liverpool, 2024

Contributions of authors:

Nigel Fleeman	Project lead, critical appraisal of the clinical and statistical evidence and supervised the final report
Samuel Bryning	Critical appraisal of the economic model and economic evidence
Sophie Beale	Critical appraisal of the clinical, statistical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical, statistical and economic evidence, editorial input
Yenal Dundar	Conduct of searches for the EAG and critical appraisal of the company systematic review
Ashley Marsden	Critical appraisal of the company submission
John Green	Clinical advice and critical appraisal of the clinical evidence

TABLE OF CONTENTS

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AUC	area under the curve
BSA	body surface area
CNS	central nervous system
CS	company submission
DUR+ET+CAR	durvalumab+etoposide+carboplatin
DUR+ET+CIS	durvalumab+etoposide+cisplatin
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EP	etoposide plus platinum-based chemotherapy
ES-SCLC	extensive-stage small cell lung cancer
ET+CAR	etoposide+carboplatin
ET+CIS	etoposide+cisplatin
HRQoL	health-related quality of life
imAE	immune-modulated adverse event
IPD	individual patient data
ITC	indirect treatment comparison
IO	immunotherapy
ITT	intention to treat
IV	intravenous
K-M	Kaplan-Meier
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
ORR	objective response rate
OS	overall survival
PCI	prophylactic cranial irradiation
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand
PFS	progression-free survival
PH	proportional hazards
RCT	randomised controlled trial
RDI	relative dose intensity
SC	subcutaneous
SCLC	small cell lung cancer
STA	Single Technology Appraisal
TA	Technology Appraisal

1 EXECUTIVE SUMMARY

The National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) of durvalumab in combination with etoposide and platinum-based chemotherapy (EP) for untreated extensive stage small cell lung cancer (ES-SCLC) (TA662) was terminated in 2020; NICE was unable to make a recommendation because the company's evidence submission was withdrawn. In 2024, the company asked NICE to review TA662 using cost-comparison methods, with atezolizumab+EP (TA638) as the comparator. Following review and consultation with stakeholders, NICE determined that durvalumab+EP for untreated ES-SCLC should be appraised via the cost-comparison process and that atezolizumab+EP was the appropriate comparator.

1.1 Decision problem

In line with the final scope issued by NICE, for patients with ES-SCLC, the company has provided evidence to compare the clinical effectiveness of durvalumab+EP versus atezolizumab+EP. The External Assessment Group (EAG) agrees with the company and NICE that the appropriate comparator to durvalumab+EP is atezolizumab+EP.

Durvalumab and atezolizumab belong to the same class of drugs. The frequency that durvalumab+EP and atezolizumab+EP are administered is the same during the induction phase (in combination with EP every 3 weeks for 4 cycles); however, during the maintenance phase, durvalumab monotherapy is delivered every 4 weeks and atezolizumab monotherapy is typically delivered every 3 weeks. Durvalumab can only be administered via intravenous (IV) infusion, whilst atezolizumab can be administered by IV infusion or subcutaneous (SC) injection. The two treatments can also differ in terms of platinum-based chemotherapy used during the induction phase of treatment; durvalumab can be administered in combination with carboplatin or cisplatin whilst atezolizumab can only be administered in combination with carboplatin. The company and EAG agree that carboplatin and cisplatin can be considered similarly efficacious; however, clinical advice to the EAG is that, in the NHS, carboplatin is preferred to cisplatin as it is considered to have a better safety profile.

1.2 Clinical effectiveness evidence

There is no direct evidence to compare the clinical effectiveness of durvalumab+EP versus atezolizumab+EP; the company, therefore, carried out indirect treatment comparisons (ITCs). The company and EAG agree that CASPIAN trial (durvalumab+EP) and IMpower133 trial (atezolizumab+EP) patient and trial characteristics are comparable. However, the EAG considers that within-trial overall survival (OS) and progression-free survival (PFS)

proportional hazards (PH) assumptions are violated, which may mean that ITC results are unreliable.

Company base case and sensitivity analysis unadjusted ITC OS and PFS results for the comparison of durvalumab+EP versus atezolizumab+EP showed that there were no statistically significant differences in efficacy. However, confidence intervals were wide; further, there is ongoing debate around whether confidence intervals that include 1 should be used to support claims of similar health benefits. Results from 3/24 company safety ITCs were statistically significant; all three of these results suggested that patients treated with durvalumab+EP experienced fewer adverse events (AEs) than patients treated with atezolizumab+EP.

The EAG asked the company (clarification questions A2 and A3) to provide statistical evidence to demonstrate the similarity of survival outcomes for patients treated with durvalumab+EP and atezolizumab+EP. The company provided Kaplan-Meier data but did not carry out the requested across trial log-rank tests and restricted mean survival time analyses.

The EAG considers that, based on the available clinical effectiveness evidence, it is appropriate to carry out a cost-comparison analysis (durvalumab+EP versus atezolizumab+EP).

1.3 Economic evidence

The company developed a cost-comparison model in Microsoft® Excel. With the exception of treatment cycle numbering (see Section 5.2), the EAG is satisfied that the company model algorithms are accurate and that the parameter values used in the model match the values presented in the company submission (CS) and in the original sources. The EAG considers that the company model is robust and generates reliable cost-comparison analysis results for the comparison of durvalumab+EP versus atezolizumab+EP. EAG revisions only had a small effect on company base case results.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) of durvalumab in combination with etoposide and platinum-based chemotherapy (EP) for untreated extensive stage small cell lung cancer (ES-SCLC) (TA662[1]) was terminated in 2020; NICE was unable to make a recommendation because the company's evidence submission was withdrawn. In 2024, the company asked NICE to review TA662[1] using cost-comparison methods, with atezolizumab+EP (TA638[2]) as the comparator.[3] Following review and consultation with stakeholders, NICE determined that durvalumab+EP for untreated ES-SCLC should be appraised via the cost-comparison process and that atezolizumab+EP was the appropriate comparator.[3]

The External Assessment Group (EAG) critique of the company submission (CS) is presented in this report. All references to the CS are to the company's Document B, which is the company's full evidence submission. Additional evidence was provided by the company in response to the clarification letter.

2.2 Background

SCLC is an aggressive form of lung cancer and is associated with a poor prognosis; symptoms include cough, chest pain, dyspnoea, arm/shoulder pain, fatigue and appetite loss (CS, Table 6). There are two categories of SCLC: limited-stage (LS) and extensive stage (ES) (CS, Table 4). SCLC is less common than non-small cell lung cancer (NSCLC), is almost universally related to smoking and has a worse 5-year survival than NSCLC (CS, Table 3). Recommendations for the management of SCLC differ from those for the management of NSCLC.

2.3 Clinical pathway

European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines[4,5] recommend immunotherapy (IO) for treating ES-SCLC. The recommended treatment with IO (atezolizumab or durvalumab) is four cycles of induction treatment in combination with EP (the NCCN guidelines[5] permit up to six cycles of induction treatment if deemed necessary) followed by IO monotherapy as maintenance treatment until disease progression or unacceptable toxicity. Recommended treatment for patients ineligible for IO is four to six cycles of EP. Currently, the only NICE recommended IO for ES-SCLC is atezolizumab+EP for patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1.[2] In this appraisal, durvalumab+EP is being considered as an alternative to atezolizumab+EP for ES-SCLC for patients with ECOG PS 0 to 1.

3 EAG CRITIQUE OF THE COMPANY DECISION PROBLEM

The decision problem addressed by the company in the CS matches the final scope[3] issued by NICE (Table 1). See Section 3.1 to Section 3.5 for EAG comments on the evidence base, population, intervention, comparators, outcomes, economic analysis and subgroups.

Table 1 The final scope issued by NICE and the company decision problem

Element	Final scope[3] issued by NICE and addressed by the company
Population	Adults with untreated ES-SCLC
Intervention	Durvalumab+EP
Comparator(s)	Atezolizumab+EP
Outcomes	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life
Economic analysis	Cost comparison
Subgroups	No subgroups were specified in the final scope[3] issued by NICE

EP=etoposide+platinum-based chemotherapy; ES=extensive stage; SCLC=small cell lung cancer; NICE=National Institute for Health and Care Excellence

3.1 Sources of clinical effectiveness evidence

The two main sources of the clinical effectiveness data presented in the CS are the CASPIAN trial[6] (durvalumab+EP) and the IMpower133 trial[7] (atezolizumab+EP).

CASPIAN trial

The CASPIAN trial is a phase III, open-label, international, multicentre, randomised controlled trial (RCT) that enrolled previously untreated adults with ES-SCLC (Eastern Cooperative Oncology Group performance status [ECOG PS] 0 to 1 who were allowed to have treated or asymptomatic brain/central nervous system [CNS] metastases). The trial has three arms, two of which provide data that are relevant to this appraisal: durvalumab+EP (n=268) and EP (n=269). The primary outcome is overall survival (OS) (median OS follow-up: 39.4 months).

IMpower133 trial

The IMpower133 trial is a phase I/III, double-blind, placebo-controlled, international, multicentre, RCT that enrolled previously untreated adults with ES-SCLC (ECOG PS 0 to 1 and no evidence of untreated active brain/CNS metastases). The trial has two arms: atezolizumab+EP (n=201) and placebo+EP (n=202). There are two primary outcomes, progression-free survival (PFS) and OS (median OS follow-up: 22.9 months).

3.2 Population

Clinical advice to the EAG is that the patients enrolled in the CASPIAN and IMpower133 trials have the characteristics of patients with untreated ES-SCLC who would be considered eligible for treatment with an IO in NHS clinical practice.

3.3 Intervention

The intervention is durvalumab+EP (carboplatin or cisplatin). Durvalumab is a high-affinity, human, recombinant immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that selectively binds to programmed cell death-ligand 1 (PD-L1) and blocks the interaction of PD-L1 with programmed cell death-1 (PD-1) and cluster of differentiation 80 (CD80) receptors. By inhibition of the immune responses in the tumour micro-environment, treatment with durvalumab leads to prolonged T-cell activation and anti-tumour activity (CS, Table 2).

The durvalumab+EP induction phase (4 x 21 day treatment cycles) treatment protocol is as follows:

- durvalumab: 1500mg, IV, administered Day 1 of each cycle
- carboplatin: area under curve (AUC) 5-6 mg/ml/min, IV or cisplatin 75–80mg/m² on Day 1 of each cycle
- etoposide: 80–100mg/m^2 of body surface area (BSA), IV, Days 1 through Day 3 of each cycle

The induction phase is followed by maintenance therapy: durvalumab 1500mg, IV, every 4 weeks until loss of clinical benefit or unmanageable toxicity.

In 2020, durvalumab+EP was licensed by the European Medicines Agency (EMA)[8] as a first-line treatment option for adults with ES-SCLC; the EMA licence was issued prior to the Medicines Healthcare products Regulatory Agency (MHRA) carrying out licensing for new medicines (January 2021).

3.4 Comparators

The comparator is atezolizumab+EP (carboplatin) which was recommended by NICE[2] as an option for untreated ES-SCLC in adults with ECOG PS 0 or 1 in July 2020 (based on evidence largely derived from the IMpower133 trial). Clinical advice to the EAG is that NHS patients who would be considered for treatment with durvalumab+EP have the same characteristics as NHS patients currently considered for treatment with atezolizumab+EP.

Atezolizumab is a monoclonal antibody designed to target PD-1. It blocks the PD-L1 protein, preventing it from binding to PD-1 and B7-1, allowing T-cells to attack cancer cells.

In the IMpower133 trial, the atezolizumab+EP induction phase (4 x 21 day treatment cycles) treatment protocol is as follows:

- atezolizumab: 1200mg, IV, administered Day 1 of each cycle
- carboplatin: AUC 5mg/ml/min, IV, Day 1 of each cycle
- etoposide: 100mg/m^2 of BSA, IV, Days 1 through Day 3 of each cycle

The induction phase is followed by maintenance therapy: atezolizumab 1200mg, IV, every 3 weeks until loss of clinical benefit or unmanageable toxicity.

The only platinum chemotherapy that is used in combination with atezolizumab during the induction phase is carboplatin.[2] Most clinicians consider that the efficacy of carboplatin is similar to the efficacy of cisplatin; this assumption is supported by OS, PFS and objective response rate (ORR) meta-analysis results published in 2012[9] and by US cohort study OS results published in 2022.[10] Clinical advice to the EAG is that, in NHS clinical practice, the preferred platinum-based chemotherapy tends to be carboplatin as it is considered less toxic than cisplatin. Published results[9] show that carboplatin and cisplatin have different toxicity profiles; haematological adverse events (AEs) (e.g., myelosuppression including neutropenia, anaemia, and thrombocytopenia) were more common for patients treated with carboplatin, whilst nausea/vomiting, neurotoxicity and renal toxicity were more common for patients treated with cisplatin. The different toxicity profiles may affect clinician and patient treatment choices.

Additional treatment regimens for atezolizumab+EP are described in the Summary of Product Characteristics (SmPC) for atezolizumab.[11] These include IV atezolizumab (840mg) every 2 weeks or IV atezolizumab (1680mg) every 4 weeks. A subcutaneous (SC) injection of atezolizumab (1875mg every 3 weeks) was also approved in 2023.[12] Compared with IV atezolizumab, SC atezolizumab is less invasive and has lower service delivery costs (e.g., clinic costs, health professional time). According to the NICE medicines optimisation briefing,[13] it is anticipated that most people starting atezolizumab treatment will have the SC injection. However, people who are receiving IV chemotherapy in combination with atezolizumab may remain on the IV infusion.[14]

In the CS, all clinical effectivenessresults for durvalumab+EP versus atezolizumab+EP have been generated using data from patients who received IV atezolizumab (as in the IMpower133 trial); no comparative results have been generated using SC atezolizumab. However, results from the phase III IMscin001 trial (SC atezolizumab versus IV atezolizumab for patients with NSCLC)[15] show that efficacy, safety and immunogenicity SC outcomes were similar to, and consistent with, IV outcomes.[15]

3.5 Outcomes

Evidence for all the outcomes specified in the final scope issued by NICE[3] is presented in the CS. Comparative durvalumab+EP versus atezolizumab+EP effectiveness (OS and PFS) and some adverse events (AE) evidence was generated using indirect treatment comparisons (ITCs), whilst a naïve treatment comparison was conducted by the EAG to generate comparative health-related quality of life (HRQoL) data. Additional ITC evidence for OS and naïve comparisons of OS and PFS was presented by the company in response to clarification questions A2 and A3.

Details about the company ITCs and naïve comparisons, the EAG's critique of the company ITCs and naïve comparisons and the EAG's own naïve comparisons are presented in Section 4 and/or Appendix 2 (Section 10.2).

3.6 Economic analysis

The EAG agrees with the company and NICE that it is appropriate to carry out a cost-comparison analysis comparing durvalumab+EP versus atezolizumab+EP. The EAG's consideration of the economic evidence provided by the company is presented in Section 6.

4 CLINICAL EFFECTIVENESS EVIDENCE

4.1 Critique of the methods of review(s)

The EAG considers that the company's systematic literature review (SLR) was conducted to a good standard (Table 2); searches carried out by the EAG did not identify any additional relevant studies.

Table 2 Company SLR: EAG appraisal of the review methods

Review process	EAG response	EAG comment
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes CS, Appendix D.1 and CS, Appendix D.1.2	The study question was specified using the PICOS framework
Were appropriate sources searched?	Yes CS, Appendix D.1.1	Electronic searches of Embase, MEDLINE, The Cochrane Library, and hand searches of registries and conference proceedings were carried out
Was the timespan of the searches appropriate?	Yes CS, Appendix D.1.1	Date of most recent search: 17 May 2024
Were appropriate search terms used?	Yes CS, Appendix D.1.3	Search strings included keywords, medical subject headings and free text words
Were the eligibility criteria appropriate to the decision problem?	Yes CS, Appendix D.1.2	Eligibility criteria were wide (and therefore sufficient) to find studies relevant to the decision problem addressed by the company; only RCTs were included
Was study selection applied by two or more reviewers independently?	Yes CS, Appendix D.1.4	All title/abstract and full-text publications were reviewed by a second independent reviewer, with discrepancies resolved via discussion
Was data extracted by two or more reviewers independently?	Unclear	Not reported
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes CS, Appendix D.1.7	Conducted in accordance with the CRD recommended tool[16]
Was the quality assessment conducted by two or more reviewers independently?	Unclear	Not reported
Were attempts to synthesise evidence appropriate?	Yes CS, Section B.3.9 CS, Appendix D.3	ITCs (see Section 4.3 of this EAG report)

CRD=Centre for Reviews and Dissemination; CS=company submission; EAG=External Assessment Group; ITC=indirect treatment comparison; PICOS=Population, Intervention, Comparator, Outcome, and Study type; RCT=randomised controlled trial; SLR=systematic literature review

4.2 Included studies

The company identified two RCTs: one durvalumab+EP trial (CASPIAN trial) and one atezolizumab+EP trial (IMpower133 trial). Key trial sources and publications are listed in Table 3.

Table 3 Included studies: key trial references and data extracted from these sources

Trial Treatment	Key reference	Outcomes relevant to the decision problem presented and data cut-off date
CASPIAN Durvalumab+EP	CASPIAN trial CSR 2019: primary analysis[17]	Outcome data from this data-cut (April 2019) did not inform clinical effectiveness in the CS but AE data were used to inform treatment-emergent AE probabilities applied in the company's economic analysis
	Paz-Ares 2019[18]	Outcome data (April 2019) are the same as reported in CSR primary analysis[17]
	Goldman 2020[19]	HRQoL (April 2019)*
	CASPIAN trial CSR 2020: final analysis[20]	PFS, HRQoL, AEs (March 2020)
	Goldman 2021[21]	PFS, HRQoL, AEs (March 2020) as reported in CSR: final analysis[20]
	CASPIAN trial CSR 2021 addendum[22]	Updated OS (March 2021)
	Paz-Ares 2022[23]	Updated OS (March 2021) as reported in CSR 2021 addendum[22]
IMpower133 Atezolizumab+EP	Horn 2018[24]	OS, PFS and AEs (April 2018): final analysis for PFS
	TA638[2] including committee papers[25]	OS, PFS, AEs and HRQoL (April 2018): primary analysis
	Reck 2019[26]	Updated OS (January 2019) reported as conference abstract
	Mansfield 2020[27]*	HRQoL (April 2018) as reported in Califano 2018[28]
	Liu 2021[29]	Updated OS (January 2019) as reported in Reck 2019[26] plus updated AE data

* Results from this paper were not reported by the company, only baseline data in CS, Section B.1.3.2.1 (Symptom burden); results from this paper have been cited by EAG (Appendix 2, Section 10.2.6)
AE=adverse event; CS=company submission; CSR=clinical study report; EAG=External Assessment Group; EP=etoposide+platinum-based chemotherapy; HRQoL=health-related quality of life; OS=overall survival; PFS=progression-free survival; SAE=serious adverse events

4.2.1 CASPIAN and IMpower133 trial characteristics

Key CASPIAN and IMpower133 trial characteristics are presented in CS, Appendix 1 (Section 10.1). Both trials enrolled patients with ES-SCLC. The main differences between the CASPIAN and IMpower133 trials are:

- the CASPIAN trial was open-label and the IMpower133 trial was double-blind (open-label trials may be subject to bias)
- stratification factors differed; however, the baseline patient characteristics that could be compared were broadly similar (Section 4.2.3)
- CASPIAN trial patients could have been treated with carboplatin or cisplatin, although most patients were treated with carboplatin (75% were randomised to carboplatin and 78% received cisplatin during the trial[18]). In the IMpower133 trial, all patients were treated with carboplatin (Section 4.2.3)
- prophylactic cranial irradiation (PCI) was not permitted in the CASPIAN trial Intervention arms but was permitted in the IMpower133 trial (the clinical impact of this difference is not known); NICE has recommended (NG122[30]) that PCI should be considered for patients with ES-SCLC who have had a partial or complete response to chemotherapy within the thorax and at distant sites (and also following response to first-line treatment if they have PS 0-2)
- CASPIAN trial median OS follow-up was longer (39.4 months) than IMpower133 trial median OS follow-up (22.9 months); however, data were available after approximately 1-year and 2-years of follow-up from both trials

4.2.2 CASPIAN and IMpower133 trial eligibility criteria

A comparison of the CASPIAN and IMpower133 trial eligibility criteria is presented in the CS (CS, Appendix D.3.1.2.4, Table 14 and Table 15). Complete eligibility criteria for both trials have been published (Paz-Ares 2019[18] [CASPIAN trial], Horn 2018[24] [IMpower133] and the European Medicines Agency [EMA] Assessment Reports for durvalumab+EP for ES-SCLC[31] and atezolizumab+EP for ES-SCLC[11]). Clinical advice to the EAG agrees with the company that CASPIAN trial and IMpower133 trial eligibility criteria were broadly similar.

4.2.3 CASPIAN and IMpower133 trial patient characteristics

A comparison of baseline CASPIAN and IMpower133 trial patient characteristics is provided in the CS (CS, Appendix D.3.1.2.5, Table 16). Where comparable data are available, baseline characteristics appear similar (Table 4). Clinical advice to the EAG agrees with the company that CASPIAN trial and IMpower133 trial patient baseline characteristics were broadly similar.

Table 4 CASPIAN and IMpower133 trials: baseline characteristics

Baseline characteristic	CASPIAN trial		IMpower133 trial	
	Durvalumab+ EP (n=268)	EP (n=269)	Atezolizumab+ EP (n=201)	Placebo+ EP (n=202)
Median age (range), years	62 (28 to 82)	63 (35 to 82)	64 (28 to 90)	64 (26 to 87)
Age group				
<65 years	167 (62.3%)	157 (58.4%)	111 (55.2%)	106 (52.5%)
≥65 years	101 (37.7%)	112 (41.6%)	90 (44.8%)	96 (47.5%)
Male	190 (70.9%)	184 (68.4%)	129 (64.2%)	132 (65.3%)
WHO/ECOG PS				
0	99 (36.9%)	90 (33.5%)	73 (36.3%)	67 (33.2%)
1	169 (63.1%)	179 (66.5%)	128 (63.7%)	135 (66.8%)
Smoking status				
Non-smoker	22 (8.2%)	15 (5.6%)	9 (4.5%)	3 (1.5%)
Ex-smoker	126 (47.0%)	128 (47.6%)	118 (58.7%)	124 (61.4%)
Current smoker	120 (44.8%)	126 (46.8%)	74 (36.8%)	75 (37.1%)
Disease-related characteristics				
AJCC stage IV disease	240 (89.6%)	245 (91.1%)	Not reported	Not reported
Brain metastases	28 (10.4%)	27 (10.0%)	17 (8.5%)	18 (8.9%)
Liver metastases	108 (40.3%)	104 (38.7%)	77 (38.3%)	72 (35.6%)
Platinum chemotherapy (induction phase)*				
Carboplatin	201 (75.0%)	201 (74.7%)	201 (100%)	202 (100%)
Cisplatin	67 (25.0%)	68 (25.5%)	0	0

* It is reported in Paz-Ares 2019[18] (Table 2) that patients were allowed to switch between cisplatin and carboplatin at the investigator's discretion and hence slightly more patients received carboplatin (208 [78.5%] in intervention arm and 208 [77.3%] in comparator arm) and slightly fewer received cisplatin (65 [24.3%] in intervention arm and 67 [24.9%] in comparator arm) than as randomised

AJCC=American Joint Committee on Cancer; CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; EP=etoposide+platinum-based chemotherapy; NICE=National Institute for Health and Care Excellence; WHO =World Health Organization

Source (CASPIAN): Paz-Ares 2019;[23] CS, Section B.3.3.2 (Table 12, Table 13); CS, Appendix D.3.1.2.5 (Table 16)

Source (IMpower133): TA638[2] NICE Committee papers (Roche CS, Table 9)

4.2.4 CASPIAN and IMpower133 trial quality assessment

The company conducted quality assessments of the CASPIAN and IMpower133 trials using criteria recommended in the NICE Guide to the Methods of Technology Appraisal;[32] these methods are consistent with the methods recommended by the Centre for Reviews and Dissemination (CRD).[16] The EAG agrees with the company's assessments (Table 5) and considers that both trials are of good quality (i.e., well-designed and well-conducted).

Table 5 CASPIAN and IMpower133 trials: quality assessment

Quality assessment item	CASPIAN trial	IMpower133 trial
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	n/a	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No*	Yes
Were there any unexpected imbalances in dropouts between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis?	Yes	Yes

* The company highlights that although the CASPIAN trial was open-label and trial investigators and patients were not blinded to treatment allocation, the company study team was blinded to aggregate treatment information
CS=company submission; n/a=not applicable
Source CS, Table 15; CS, Appendix D.1.7 (Figure 4)

4.2.5 CASPIAN and IMpower133 trial results

CASPIAN and IMpower133 trial OS, PFS, ORR, HRQoL and safety results are summarised in Appendix 2 (Section 10.2). For all intention to treat (ITT) efficacy outcomes, except ORR for patients treated with atezolizumab+EP, point-estimates favoured the Interventions (durvalumab+EP or atezolizumab+EP) versus EP. For HRQoL, patients in the Intervention arms experienced a numerically reduced burden for most symptoms over time. Longer median time to treatment deterioration was observed for patients in the Intervention arms compared with those in the EP arms for treatment-related or lung-cancer related symptoms.

4.3 Indirect treatment comparisons

The company carried out OS, PFS and AE ITCs to compare the relative clinical effectiveness of durvalumab+EP versus atezolizumab+EP (CS, Section B.3.9). Results for the analyses of the following treatment-related Grade 3/4 AEs are presented in CS, Appendix D.3.4.3: febrile neutropenia, thrombocytopenia, leukopenia, anaemia, neutropenia and decreased neutrophil count. The ITCs were carried out using a frequentist Bucher approach.[33] The EAG considers that the methods used by the company to conduct (unadjusted) ITCs were appropriate; the EAG's only concern is that the within-trial (CASPIAN trial and IMpower133 trial) PFS and OS proportional hazard (PH) assumptions do not hold (see Section 4.3.5).

4.3.1 Treatment effect modifiers and/or prognostic factors

The company's ad-hoc literature review did not identify any treatment effect modifiers and/or prognostic factors for patients with ES-SCLC (CS, Appendix D.3.1). The company assessed whether CASPIAN trial patient baseline characteristics were treatment effect modifiers and/or prognostic factors for OS and PFS by examining individual CASPIAN trial individual patient

data (IPD). A list of the baseline characteristics examined, and whether the company considered the characteristic to be a potential treatment effect modifier and/or prognostic factor, is provided in Table 6.

Table 6 CASPIAN trial: potential treatment effect modifiers and/or prognostic factors*

Characteristic	Potential treatment effect modifiers and/or prognostic factor	
	Overall survival	Progression-free survival
Gender	**Yes**	**Yes**
Age	No	No
Performance status	**Yes**	**Yes**
Smoking status	No	No
Brain metastases	No	**Yes**
Disease stage	No	No
Race	No	**Yes**
Liver metastases	**Yes**	**Yes**
LDH level	**Yes**	No

* Characteristics were considered potential treatment effect modifiers and/or prognostic factors if the Cox model interaction term was <0.05
LDH=lactate dehydrogenase
Source: CS, Appendix D.3.1.1 (Table 8, Table 9)

The company considered that, as CASPIAN trial and IMpower133 trial baseline patient characteristics were similar, it was appropriate to carry out unadjusted ITCs; the company highlights that data were not available to compare race or lactate dehydrogenase (see also Table 4).

Clinical advice to the EAG is that the potential treatment effect modifiers and/or prognostic factors identified by the company are important; however, the EAG considers that as these are evenly distributed between the CASPIAN and IMpower133 trials, the approach taken by the company was appropriate.

4.3.2 Comparability of CASPIAN and IMpower133 trial and patient characteristics

The company's trial and patient characteristic comparability assessments are reported in CS, Appendix D.3.1.2. The company considered that the characteristics of patients enrolled in the CASPIAN and IMpower133 trials were broadly comparable. The EAG agrees with this conclusion (see Sections 4.2.1 to 4.2.3).

4.3.3 Comparability of CASPIAN and IMpower133 trial EP arms

The CASPIAN and IMpower133 trials are linked via EP arms; however, the CASPIAN trial and IMpower133 trial EP arms differ:

- CASPIAN trial: placebo was not included as part of the EP arm, and patients were permitted treatment with carboplatin or cisplatin

- IMpower133 trial: the EP arm included placebo, and patients were only permitted treatment with carboplatin

The company tested the assumption of equivalence of the EP arms by:

1. sourcing evidence from an ad-hoc literature review
2. using CASPIAN trial IPD (Cox PH regression models) to compare the effectiveness (OS and PFS) of treatment with carboplatin versus cisplatin

Following these two assessments, the company concluded that efficacy was similar but that carboplatin and cisplatin had different safety profiles (CS, Appendix D.3.1.2.7 [p70]). The company carried out unadjusted ITC sensitivity analyses using results from the following CASPIAN trial subgroup analyses (rather than the ITT analysis) for OS and PFS:

- durvalumab+etoposide+carboplatin (DUR+ET+CAR) versus etoposide+carboplatin (ET+CAR)
- DUR+ET+CAR versus etoposide+cisplatin (ET+CIS)
- durvalumab+etoposide+cisplatin (DUR+ET+CIS) versus ET+CAR
- DUR+ET+CIS versus ET+CIS

Sensitivity analysis results were then presented by the company for:

- DUR+ET+CAR versus atezolizumab+EP
- DUR+ET+CIS versus atezolizumab+EP

The EAG considers that the approach taken by the company was appropriate.

4.3.4 Indirect treatment comparison inputs

The data inputs used in the company ITCs is summarised in Table 7.

Table 7 Data inputs in the company ITCs presented in the CS

Trial	Overall survival	Progression-free survival	Adverse events
CASPIAN trial	HR 3-year follow-up	HR 2-year follow-up	OR 2-year follow-up
IMpower133 trial	HR 2-year follow-up	HR 1-year follow-up*	OR 1-year follow-up

* 2-year follow-up point-estimate is identical, see Appendix 2, Section 10.2.3 (Table 19)
CS=company submission; HR=hazard ratio; ITC=indirect treatment comparison; OR=odds ratio

As the company OS ITC was populated with CASPIAN trial 3-year follow-up data and IMpower133 trial 2-year follow-up data, the EAG asked the company to also carry out an OS ITC using 2-year follow-up data from the CASPIAN and IMpower133 trials (clarification question A1).

4.3.5 Validity of the OS and PFS proportional hazards assumptions

As described in CS, Appendix D.3.1.2.6, the validity of the PH assumption was investigated using CASPIAN trial IPD and IMpower133 trial reconstructed IPD (derived from digitising

Kaplan-Meier [K-M] data) based on:

- the cumulative hazard plot and Schoenfeld residual plot (visual assessment)
- the global Schoenfeld residuals test (statistical assessment, $p<0.05$ suggesting the PH assumption is violated)

The company concluded that the within-trial PH assumptions did not hold for the CASPIAN and IMpower133 trial survival data (OS and PFS) (CS, Appendix D.3.1.2.6). The EAG considers that as within-trial OS and PFS PH assumptions were violated, ITC results may be unreliable.

4.3.6 OS and PFS ITC results

Company OS and PFS results are presented in Table 8. Base case and sensitivity analysis OS and PFS results showed that, in all cases, efficacy did not differ statistically significantly between durvalumab+EP and atezolizumab+EP. However, confidence intervals are wide; further, there is ongoing debate around whether confidence intervals that include 1 should be used to support claims of similar health benefits.

Table 8 Company OS and PFS ITC results

Outcome HR (95% CI)	**Base case (assumption of equivalence)**	**Sensitivity analysis (without assumption of equivalence)**	
	DUR+EP vs ATEZ+EP	**DUR+ET+CAR vs ATEZ+ET+CAR**	**DUR+ET+CIS vs ATEZ+ET+CAR**
Overall survival	[redacted]	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]	[redacted]

ATEZ=atezolizumab; CAR=carboplatin; CI=confidence interval; CIS=cisplatin; CS=company submission; DUR=durvalumab; EP=etoposide+platinum-based chemotherapy; ET=etoposide; HR=hazard ratio
Source: CS, Section 3.9.2 (Table 16); CS, Section 3.9.3 (Table 17); CS, Appendix D.3.4.1.2, (Table 20); CS, Appendix D.3.4.2.2, (Table 22)

While non-statistically significant results do not provide evidence of similarity, the null hypothesis (which the analyses aim to disprove) is that there is no difference between durvalumab+EP and atezolizumab+EP. However, the test for statistical significance relies on the PH assumption holding between the within trial arms (durvalumab+EP versus EP and atezolizumab+EP versus placebo+EP). The company have found this not to be the case for OS and PFS, which makes interpreting these ITC results problematic.

4.3.7 Safety ITC results

Company's safety results are present in Table 9. Results from 3/24 comparisons were statistically significant (bold text); all three of these results suggested that patients treated with durvalumab+EP experienced fewer AEs than patients treated with atezolizumab+EP.

Table 9 Company safety ITC results

Outcome OR (95% CI)	Base case	Sensitivity analyses	
	DUR+EP vs ATEZ+EP	DUR+ET+CAR vs ATEZ+ET+CAR	DUR+ET+CIS vs ATEZ+ET+CAR
TR-SAEs	[redacted]	[redacted]	[redacted]
TR-Grade 3/4 AEs			
All	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Decreased neutrophil count	[redacted]	[redacted]	[redacted]

Results denoted in bold are statistically significantly different, favouring durvalumab
AE=adverse event; ATEZ=atezolizumab; CAR=carboplatin; CI=confidence interval; CIS=cisplatin; CS=company submission; DUR=durvalumab; EP=etoposide+platinum-based chemotherapy; ET=etoposide; OR=odds ratio; SAE=serious adverse event; TR=treatment-related
Source: CS, Section 3.9.4 (Table 18); CS, Appendix D.3.4.3 (Table 23 to Table 26)

4.4 Additional clinical effectiveness evidence

4.4.1 OS ITC: 2-year follow-up data

The company presented OS ITC results generated using CASPIAN trial 2-year follow-up data in response to clarification question A1. These results were similar to company base case OS results, i.e., the difference between durvalumab+EP and atezolizumab+EP was not statistically significant; again, confidence intervals are wide (Table 10).

Table 10 Company OS ITC results (2-year follow-up)

Outcome HR (95% CI)	Base case (assumption of equivalence)	Sensitivity analysis (without assumption of equivalence)	
	DUR+EP vs ATEZ+EP	DUR+ET+CAR vs ATEZ+ET+CAR	DUR+ET+CIS vs ATEZ+ET+CAR
Overall survival	[redacted]	[redacted]	[redacted]

ATEZ=atezolizumab; CAR=carboplatin; CI=confidence interval; CIS=cisplatin; DUR=durvalumab; EP=etoposide +platinum-based chemotherapy; ET=etoposide; HR=hazard ratio
Source: company response to clarification question A1 (Table 1, Table 2)

4.4.2 K-M charts using 2-years follow-up data

In response to clarification question A2, the company provided OS and PFS K-M data comparing data from the CASPIAN and IMpower133 trial Intervention arms and CASPIAN and IMpower133 trial comparator arms. The EAG considers that the OS and PFS K-M data provided by the company support the view that durvalumab+EP and atezolizumab+EP are similar (and the two EP arms are similar).

The EAG also asked the company to carry out between trial log-rank tests to provide statistical evidence of the similarity of survival outcomes from both trials; the company did not provide this information.

4.4.3 Restricted mean survival time analysis

As the company within-trial PH assessments did not hold, the EAG asked the company to carry out OS and PFS restricted mean survival time (RMST) analyses for the comparison of durvalumab+EP versus atezolizumab+EP (2-year follow-up data) (clarification question A3). The company only provided within-trial RMST differences for these analyses and did not provide statistical test results for the comparison of durvalumab+EP versus atezolizumab+EP. Examination of the within-trial RMST differences add weight to the company's argument that durvalumab+EP and atezolizumab+EP are clinically similar; in both trials, the within-trial RMST difference was approximately [redacted] for OS and [redacted] for PFS.

4.5 Published network meta-analysis results

The EAG has identified eight published network meta-analyses (NMAs)[34-41] that compared the efficacy and safety of durvalumab+EP and atezolizumab+EP. These NMAs[34-41] considered data from between four and ten RCTs (as additional treatments were included in these NMAs) which included between 1547[34] and 5544[35] patients, in total. An EAG summary of published ITC results is presented in Table 11. Published OS, PFS and Grade 3/4 AE ITC results are in line with company ITC results.

Table 11 EAG summary of published network meta-analysis results

Outcome	Number of NMAs	Summary published ITC results: durvalumab+EP versus atezolizumab+EP
OS	8[a]	No statistically significant difference found from any NMA[34-41]
PFS	8[a]	No statistically significant difference found from any NMA[34-41]
ORR	5	Four NMAs[34,35,40,41] found ORR was statistically significantly superior for patients treated with durvalumab+EP; one NMA[38] found no statistically significant difference
Grade ≥3 AEs	8[b]	No statistically significant difference found from any NMA[34-41]
imAEs	2	Results from one NMA[39] showed that patients treated with durvalumab+EP experienced statistically significantly more any Grade imAEs (but no difference in Grade 3/4 imAEs)[c] Results from one NMA[34] found no statistically significant difference in any Grade imAEs

[a] One NMA[40] utilised the fractional polynomial model to evaluate the adjusted HRs for OS and PFS, an approach that does not required the proportional hazards assumption to hold
[b] Seven studies[34-38,40,41] reported AEs of any causality, one study reported treatment-related AEs[39]
[c] The EAG considers it to be surprising that the difference in any Grade imAEs was found to be statistically significantly in favour of atezolizumab+EP versus durvalumab+EP when the trial publications show fewer imAEs reported by patients with durvalumab+EP than atezolizumab+EP (see Appendix 2, Section 10.2.7, Table 21)
AE=adverse event; EAG=External Assessment Group; EP=etoposide+platinum-based chemotherapy; imAE=immune-modulated adverse event; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

4.6 Summary statement

A comparison of durvalumab+EP and atezolizumab+EP is presented in Table 12.

Table 12 Comparison of durvalumab+EP and atezolizumab+EP

Metric	Durvalumab+EP	Atezolizumab+EP
Company	AstraZeneca	Roche
Brand name	Imfinzi	Tecentriq
Drug class	Monoclonal antibody, immune checkpoint inhibitor	Monoclonal antibody, immune checkpoint inhibitor
Mechanism of action	PD-L1 blocking antibody. Blocks PD-L1 interaction with both PD-1 and CD80 on T cells	PD-L1 blocking antibody. Inhibits binding of PD-L1 to both PD-1 and CD80
Given with (as induction treatment)	EP: Etoposide+carboplatin or etoposide+cisplatin	EP: Etoposide+carboplatin
Maintenance treatment	Monotherapy treatment every 4 weeks	Monotherapy treatment every 3 weeks
Administrative route	Intravenous infusion	Intravenous infusion or subcutaneous injection
Frequency of administration in main trials	Durvalumab+EP every 3 weeks for 4 cycles, followed by durvalumab every 4 weeks as monotherapy	Atezolizumab+EP every 3 weeks for 4 cycles, followed by atezolizumab every 3 weeks as monotherapy
Contraindications	Severe hypersensitivity to durvalumab or any of its components	Severe hypersensitivity to atezolizumab or any of its components
Results		
Within-trial: OS	Results from all within-trial analyses show that the Intervention is statistically significantly superior to the EP comparator	
Within-trial: PFS		
Unadjusted ITC: PFS	Results from all unadjusted ITCs show that there are no statistically significant differences between durvalumab+EP and atezolizumab+EP	
Unadjusted ITC: OS		
K-M charts	Visual inspection of the four K-M charts provided by the company in response to clarification question A2, support the view that Intervention and EP comparator data from the CASPIAN and IMpower133 trials are similar	
AEs	Results from 3/24 company AE ITCs are statistically significant; all three of these results suggested that patients treated with durvalumab+EP experienced fewer AEs than patients treated with atezolizumab+EP	
HRQoL	Over time, the burden of most symptoms experienced by patients in the durvalumab+EP and atezolizumab+EP arms of the CASPIAN trial and IMpower133 trial decreased	

AE=adverse event; CD80=cluster of differentiation 80; EP=etoposide+platinum-based chemotherapy; HRQoL=health-related quality of life; ITC=indirect treatment comparison; K-M=Kaplan-Meier; OS=overall survival; PD-L1=programmed cell death-ligand1; PD-1=programmed cell death-1; PFS=progression-free survival

The EAG agrees with the company and NICE that the appropriate comparator to durvalumab+EP is atezolizumab+EP. The EAG also considers that, based on the available clinical effectiveness evidence, it is appropriate to carry out a cost-comparison analysis (durvalumab+EP versus atezolizumab+EP).

5 EAG CRITIQUE OF COMPANY COST COMPARISON EVIDENCE

5.1 Company approach to cost comparison analysis

The company submitted an economic model, developed in Microsoft® Excel, to generate cost effectiveness results for durvalumab+EP versus atezolizumab+EP for patients with untreated ES-SCLC. The EAG agrees with the company and NICE that it is appropriate to carry out a cost-comparison analysis of durvalumab+EP versus atezolizumab+EP (see Section 3 and Section 4).

With the exception of treatment cycle numbering (see Section 5.2), the EAG is satisfied that the company model algorithms are accurate and that the parameter values used in the model match the values presented in the CS and in the original sources.

The EAG considers that the time horizon used in the company model (15 years) is appropriate as only a small proportion of patients ([redacted]%) are estimated to remain on treatment beyond this time point. The company generated cost-comparison analysis results using a partitioned survival model and assumed that there were no differences in OS, PFS, treatment duration, subsequent treatments or the incidence of AEs. In the model, it was assumed that 75% of patients were treated with SC atezolizumab and 25% of patients were treated with IV atezolizumab; clinical advice to the EAG is that this assumption was appropriate. As efficacy and safety outcomes for patients treated with durvalumab+EP and patients treated with atezolizumab+EP appear to be similar, the company modelling assumptions are appropriate.

The key drivers of the company's cost-comparison analysis results are the costs of purchasing durvalumab and atezolizumab (and, to a lesser extent, drug administration and radiotherapy costs).

5.2 EAG correction and revisions

The EAG has identified and corrected one minor error: company model Markov traces treatment cycle numbering. The EAG made three revisions to the company model (see Section 5.2.1 to Section 5.2.3).

5.2.1 Platinum chemotherapy costs

In the company model, it is assumed that [redacted]% of patients treated with durvalumab+EP receive carboplatin and [redacted]% receive cisplatin (this is in line with CASPIAN trial data) and all patients treated with atezolizumab+EP receive carboplatin-based chemotherapy (this is in line with the IMpower133 trial data). Clinical advice to the company and the EAG is that, in NHS clinical practice, there appears to be no substantial efficacy differences between these two platinum

agents; however, there is a strong clinical preference to use carboplatin as cisplatin is considered more toxic than carboplatin. To more accurately reflect expected NHS costs, the EAG has revised the model so that all patients treated with durvalumab+EP are treated with carboplatin.

5.2.2 Relative dose intensity

The company applied relative dose intensity (RDI) multipliers to durvalumab and atezolizumab; this approach implicitly models the potential reduction in costs due to missed doses (Table 13). The durvalumab and atezolizumab RDI multipliers are similar (95.4% and 94.9%, respectively); this suggests that missed doses are similar.

Durvalumab and atezolizumab are modelled using fixed doses (1500mg and 1200mg, respectively). The company has, incorrectly, used the RDI multipliers to calculate average doses (in mg) of durvalumab and atezolizumab (1431mg and 1139mg, respectively) and then calculated the whole number of vials needed to provide these average doses. This has reduced the cost of durvalumab and made no change to the cost of atezolizumab. The EAG has therefore applied the correct approach, i.e., applied the RDI multipliers to the costs of the fixed doses.

Table 13 Durvalumab and atezolizumab drug acquisition costs

Drug	Fixed dose	RDI	Cost per administration	
			Company base case: RDI applied to doses (mg)	EAG base case: RDI applied to fix dose
Durvalumab (120mg and 500mg)	1500mg	95.4% (1431mg)	1431mg: [redacted] (2x500mg+4x120mg vials)	[redacted] (95.4% of 3x500mg)
Atezolizumab (840mg and 1200mg)	1200mg*	94.9% (1139mg)	1139mg: £3,808 (1x1200mg vial)	£3,614 (94.9% of 1x1200mg)

* IV and SC unit costs are the same
EAG=External Assessment Group; IV=intravenous; RDI=relative dose intensity; SC=subcutaneous
Source: Company model

5.2.3 Radiotherapy costs

In the company base case analysis, the cost of PCI was only applied to patients treated with atezolizumab+EP; PCI was not permitted in the durvalumab+EP arm of the CASPIAN trial. Clinical advice to the EAG is that, in NHS clinical practice, it is likely that similar proportions of patients treated with durvalumab and atezolizumab would receive PCI. The EAG has therefore presented results from a company scenario analysis (CS, Table 48) in which the same proportion of patients treated with durvalumab+EP and atezolizumab+EP receive PCI (10.9%).

Based on CASPIAN trial data, the company included the cost of other radiotherapy (10 fractions); this other radiotherapy cost (£3,293.82) was applied as a one-off cost after progression to 25.7% of all patients. Clinical advice to the EAG is that radiotherapy offered to patients after progression is typically palliative, with the intent of relieving symptoms, and consists of one fraction or a course of five fractions. Since the same proportions of patients treated with durvalumab+EP and atezolizumab+EP receive post-progression radiotherapy, there is no impact on cost-comparison analysis results from changing the cost of radiotherapy and therefore no change has been made to costs to reflect this lower level of radiotherapy usage.

6 COMPANY AND EAG COST-COMPARISON ANALYSIS RESULTS

The EAG has made the following revisions to the company base case cost comparison analysis:

- all patients treated with durvalumab+EP receive carboplatin (R1)
- correctly applied RDI multipliers (R2)
- PCI cost also applied to 10.9% of patients treated with durvalumab+EP (R3)

Details of the EAG corrections and revisions to the company model are presented in Appendix 3 (Section 10.3). EAG cost-comparison analysis results (durvalumab confidential commercial agreement price) are presented in Table 15. Cost-comparison results using the confidential commercial agreement price for durvalumab, the confidential commercial agreement price for atezolizumab and electronic Market Information Tool (eMIT) prices for all other drugs are provided in a confidential appendix. The sources of the prices used in the confidential appendix are presented in Table 14.

Table 14 Pricing sources used in confidential appendix

Treatment	Price source/type of commercial arrangement
Durvalumab	Confidential commercial agreement
Atezolizumab	Confidential commercial agreement
Carboplatin	eMIT price
Cisplatin	eMIT price
Etoposide	eMIT price
Cyclophosphamide	eMIT price
Doxorubicin	eMIT price
Vincristine	eMIT price

eMIT=electronic Market Information Tool.
Source: Price-tracker (September 2024)

6.1 EAG cost-comparison analysis conclusions

The EAG considers that the company cost-comparison model generates robust cost effectiveness results. EAG revisions only had a small effect on company base case results.

Table 15 Company base case and EAG cost comparison results (durvalumab confidential commercial agreement price)

Scenario/EAG revision	Durvalumab+EP				Atezolizumab+EP				Incremental costs[c]	Change from (A2) base case
	Drug costs (1st line)[a]	HCRU[b]	Subsequent treatment	Total costs	Drug costs[a] (1st line)	HCRU[b]	Subsequent treatment	Total costs		
A1. Company base case	[redacted]	**£18,921**	**£862**	[redacted]	**£90,528**	**£19,260**	**£862**	**£110,651**	[redacted]	-
A2. Corrected company base case	[redacted]	**£18,921**	**£862**	[redacted]	**£90,410**	**£19,260**	**£862**	**£110,532**	[redacted]	-
R1) All patients treated with durvalumab+EP receive carboplatin	[redacted]	£18,921	£862	[redacted]	£90,410	£19,260	£862	£110,532	[redacted]	[redacted]
R2) Correctly apply RDI multipliers	[redacted]	£18,921	£862	[redacted]	£86,157	£19,260	£862	£106,279	[redacted]	[redacted]
R3) PCI cost also applied to durvalumab+EP arm	[redacted]	£19,260	£862	[redacted]	£90,410	£19,260	£862	£110,532	[redacted][d]	[redacted]
B. EAG preferred scenario (R1-R3)	[redacted]	**£19,260**	**£862**	[redacted]	**£86,157**	**£19,260**	**£862**	**£106,279**	[redacted]	[redacted]

[a] Includes administration costs
[b] Includes radiotherapy, monitoring and terminal care costs
[c] All costs are discounted
[d] Incremental cost differs from company scenario analysis due to corrections implemented in company model
EAG=External Assessment Group; EP=etoposide+platinum-based chemotherapy; HCRU=healthcare resource use; PCI=prophylactic cranial irradiation

7 EQUALITIES AND INNOVATION

The company has not reported any equality issues and clinical advice to the EAG is that there are no obvious equality issues.

The evidence suggests that durvalumab+EP and atezolizumab+EP are similar treatments (in terms of mechanism of action, efficacy and safety). Atezolizumab was recommended by NICE as a treatment option for patients with untreated ES-SCLC in 2020[2] and, therefore, durvalumab+EP cannot be considered an innovative treatment.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

8.1 Clinical effectiveness evidence

The company has provided evidence from two good quality RCTs (CASPIAN trial: durvalumab+EP versus EP; IMpower133 trial: atezolizumab+EP versus EP). Durvalumab+EP and atezolizumab+EP have similar mechanisms of action.

Clinical advice to the EAG is that it is appropriate to compare CASPIAN and IMpower133 trial data and the patients enrolled in these trials have characteristics that are similar to the characteristics of NHS patients who are treated with atezolizumab+EP (and who could, if recommended by NICE, be treated with durvalumab+EP).

There is no direct evidence to compare the clinical effectiveness of durvalumab+EP versus atezolizumab+EP and therefore the company has carried out unadjusted OS, PFS and AE ITCs. For survival outcome comparisons, the within-trial PH assumptions do not hold and therefore the efficacy ITC results may be unreliable. However, the company has provided other evidence to support the similarity of durvalumab+EP and atezolizumab+EP and all company efficacy ITC results are in line with published NMA results.

8.2 Cost effectiveness evidence

The EAG considers that company cost-comparison methods were largely appropriate and model results are robust. The EAG correction and revisions were minor and only had a small effect on the size of the company base case results.

8.3 Overall conclusion

The EAG considers that the available clinical effectiveness evidence is sufficiently robust to suggest that durvalumab+EP can be considered similar to atezolizumab+EP. EAG revisions to the company model only had a small effect on the size of the company base case results.

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10 APPENDICES

10.1 Appendix 1: CASPIAN and IMPower133 trial characteristics

CASPIAN and IMpower133 trial characteristics are summarised in Table 16.

Table 16 CASPIAN and IMpower133 trials: key characteristics

Characteristic	CASPIAN trial	IMpower133 trial
Study design	Phase III, open-label, international, multicentre RCT	Phase I/III, double-blind, placebo-controlled, international, multicentre RCT
Location	209 sites across 23 countries in Europe (but not in the UK), Asia, North and South America	106 sites across 21 countries in Europe (including 10 patients from the UK), Asia, North and Central America and Australia
Recruitment	27 March 2017 to 29 May 2018	6 June 2016 to 31 May 2017
Patients	Previously untreated adults with histologically or cytologically documented ES-SCLC, T3 or T4 and WHO PS 0 or 1 with body weight >30kg and life expectancy >12 weeks Patients with brain metastases at baseline needed to be asymptomatic, or treated and stable off steroids and anticonvulsants for at least 1 month prior to study treatment	Previously untreated adults with histologically or cytologically confirmed ES-SCLC as defined according to the Veterans Administration Lung Study Group staging system, measurable ES-SCLC according to RECIST v1.1, and ECOG PS 0 or 1 Patients with treated asymptomatic CNS metastases were eligible provided specific criteria were met[b]
Trial arms	Durvalumab+EP (n=268) Durvalumab+tremelimumab+EP (n=268)[a] EP (n=269)	Atezolizumab+EP (n=201) Placebo+EP (n=202)
Stratification factors	Planned platinum chemotherapy (carboplatin or cisplatin)	Sex and ECOG PS (0 or 1) and presence of brain metastases (yes or no
Immunotherapy schedule (intravenous)	Induction: up to 4 cycles of durvalumab+EP 1500mg every 3 weeks Maintenance: durvalumab 1500mg every 4 weeks	Induction: up to 4 cycles of atezolizumab+EP 1200mg every 3 weeks Maintenance: atezolizumab 1200mg every 3 weeks Patients in the EP arm also received placebo every 3 weeks in both induction and maintenance trial phases
EP schedule (intravenous)	Up to 4 (or 6 in EP arm) 21-day cycles of: • carboplatin AUC 5–6mg/mL per min or cisplatin 75–80mg/m² on day 1 of each cycle • etoposide 80–100mg/m² on days 1–3 of each cycle	Up to 4 21-day cycles of: • carboplatin AUC 5mg/mL per min on day 1 of each cycle • etoposide 100mg/m² on days 1–3 of each cycle
Radiotherapy	During the maintenance phase and post-discontinuation of study drug, PCI was only permitted in the EP arm	During the maintenance phase, palliative PCI was permitted but thoracic radiation therapy was not

Characteristic	CASPIAN trial	IMpower133 trial
	Post-discontinuation of study drug, thoracic radiation was permitted for patients who had been randomised to any trial arm	permitted Use of radiotherapy post-discontinuation of study drug was not limited
Median follow-up times for outcomes, months	**OS: 25.1 and 39.4[c]** PFS: 25.1[c] ORR: 25.1[c] AEs: 25.1[c] HRQoL: 25.1[c]	**OS: 13.9 and 22.9[d]** **PFS: 13.9 and 22.9[d]** ORR: 13.9[e] AEs: 13.9 and 22.9[d] HRQoL: 13.9[e]

Primary outcomes denoted in bold. The IMpower133 trial had co-primary outcomes. The final OS has not been published for the IMpower133 trial. However, the updated OS analysis was conducted after 302 deaths had occurred, the final analysis was planned after 306 deaths had occurred

[a] Patients in this treatment arm are not relevant to this appraisal

[b] Patients with a history of treated asymptomatic CNS metastases were eligible, provided they meet all the following criteria:

- Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)
- No ongoing requirement for corticosteroids as therapy for CNS disease
- No evidence of interim progression between the completion of CNS-directed therapy and randomization
- Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomisation, if all other criteria are met

[c] CASPIAN trial data have also been reported after a median follow-up of 14.2 months but these data did not inform the CS; the company did not report OS results after a median 25.1 months follow-up, however the EAG have reported these data in Section 10.2.2 and also requested analyses using OS data from this data-cut during the clarification process

[d] Company only used data from 13.9 months follow-up in ITCs presented in the CS (but highlighted that OS and PFS data after 22.9 months was very similar); EAG presented OS, PFS and some AE data from 22.9 months follow-up in in Section 10.2

[e] The company did not report results for ORR or HRQoL for the IMpower133 trial; data presented by EAG in Section 10.2

AUC=area under the curve; CNS=central nervous system; CS=company submission; CSR=clinical study report; ECOG PS=Eastern Cooperative Oncology Group performance status; EAG=External Assessment Group EP=etoposide+platinum-based chemotherapy; ES-SCLC=extensive-stage small cell lung cancer; ITC=indirect treatment comparison; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; RECIST=Response Evaluation Criteria in Solid Tumors; PCI=prophylactic cranial irradiation; WHO PS=World Health Organization performance status

Source (CASPIAN): CASPIAN trial CSR 2019;[17] Paz-Ares 2019;[18] Goldman 2020;[19] CASPIAN CSR 2020;[20] Goldman 2021;[21] CASPIAN CSR addendum[22]

Source (IMpower133): Horn 2018;[24] TA638[2] including committee papers;[25] Reck 2019;[26] Mansfield 2020;[27] Liu 2021[29]

10.2 Appendix 2: CASPIAN and IMPower133 trial results

10.2.1 Drug exposure

Exposure to study drugs in the CASPIAN and IMpower133 trials is reported in Table 17.

Table 17 CASPIAN and IMpower133 trial: patient drug exposure

Trial	Treatment	Cycles Median (range)
CASPIAN trial 3 year follow-up	Durvalumab+EP	Durvalumab: 7 (1 to 52) Platinum (carboplatin or cisplatin): 4 (1 to 6)
	EP	Carboplatin: 6 (1 to 6) Cisplatin: 6 (1 to 7)
IMpower133 trial 2 year follow-up	Atezolizumb+EP	Atezolizumab: 7 (1 to 39) Carboplatin: 4 (1 to 6)
	EP	Carboplatin: 4 (1 to 5)

CS=company submission; EMA=European Medicines Agency; EP=etoposide+platinum-based chemotherapy
Source (CASPIAN): CS, Section B.3.10.1; Durvalumab EMA Assessment Report[23] (Table 46)
Source (IMpower133): Committee Papers for TA638[2] (Roche CS, p44); Atezolizumab EMA Assessment Report[11] (Table 39, Table 40); Liu 2021[29]

10.2.2 Overall survival

CASPIAN trial and IMpower133 trial OS results at the latest data-cuts and over a similar follow-up period are summarised in Table 18.

Table 18 CASPIAN and IMpower133 trials: overall survival results

Outcome	CASPIAN		IMpower133	
	Durvalumab+EP (n=268)	EP (n=269)	Atezolizumab+EP (n=201)	Placebo+EP (n=202)
Overall survival after approximately 2 years				
Number of deaths	441 (82.1%)		302 (74.9%)	
Median, months[a]	12.9	10.5[b]	12.3	10.3
HR	0.75 (0.63 to 0.91)		0.76 (0.60 to 0.95)	
Overall survival after approximately 3 years				
Number of deaths	[redacted]		-	
Median, months[a]	12.9	10.5[b]	-	-
HR	0.71 (0.60 to 0.86)		-	

[a] Median overall surviva results for the CASPIAN trial are incorrectly presented for the IMpower133 trial and vice versa in CS, Appendix D.3.1.2.2 (Table 12)
[b] Median overall survival reported for all patients in comparator arm, i.e., treated with carboplatin or cisplatin
CI=confidence interval; CS=company submission; HR=hazard ratio
Source (both trials): CS, Section B.3.3.1 (Table 10); CS, Section 3.9.2 (Table 16); CS, Appendix D.3.1.2.2 (Table 12); CS, Appendix D.3.4.1.1 (Table 19)
Source (CASPIAN): Goldman 2021;[21] Paz-Ares 2022[23]
Source (IMpower133): Liu 2021[29]

10.2.3 Progression-free survival

CASPIAN trial and IMpower133 trial PFS results at the latest data-cuts and over a similar follow-up period are summarised in Table 19.

Table 19 CASPIAN and IMpower133 trials: progression-free survival results

Outcome	CASPIAN		IMpower133	
	Durvalumab+EP (n=268)	EP (n=269)	Atezolizumab+EP (n=201)	Placebo+EP (n=202)
Progression-free survival after approximately 1-year				
Median, months[a]	5.1	5.4[b]	5.2	4.3
HR	0.78 (0.65 to 0.94)		0.77 (0.62 to 0.96)	
Progression-free survival after approximately 2-years				
Median, months[a]	5.1	5.4[b]	5.2	4.3
HR	0.80 (0.67 to 0.96)		0.77 (0.63 to 0.95)	

[a] Median progression-free survival results for the CASPIAN trial are incorrectly presented for the IMpower133 trial and vice versa in CS, Appendix D.3.1.2.2 (Table 12)
[b] Median progression-free survival reported for all patients in comparator arm, i.e., treated with carboplatin or cisplatin
CI=confidence interval; CS=company submission; HR=hazard ratio
Source (both trials): CS, Section 3.9.3 (Table 17); CS, Appendix D.3.1.2.2 (Table 12); CS, Appendix D.3.4.2.1 (Table 21)
Source (CASPIAN): Paz-Ares 2019;[18] Goldman 2021[21]
Source (IMpower133): Horn 2018;[24] Liu 2021[29]

10.2.4 Key CASPIAN trial subgroup results (different EP formulations)

Subgroup results for durvalumab+EP versus ET+CAR or ET+CIS

CASPIAN trial subgroup results for durvalumab+EP versus ET+CAR or ET+CIS are summarised in Table 20.

Table 20 CASPIAN trial: OS and PFS for durvalumab+EP versus ET+CAR or ET+CIS

Outcome	Durvalumab+EP vs ET+CAR	Durvalumab+EP vs ET+CIS
HR (95% CI) after approximately 2-years		
Overall survival	0.79 (0.63 to 0.98)	0.67 (0·46 to 0.97)
Progression-free survival	[redacted]	[redacted]
HR (95% CI) after approximately 3-years		
Overall survival	0.74 (0.60 to 0.91)	0.65 (0.45 to 0.94)
Progression-free survival	-	-

CAR=carboplatin; CI=confidence interval; CIS=cisplatin; CSR=clinical study report; DUR=durvalumab; EP=etoposide+platinum-based chemotherapy; ET=etoposide; HR=hazard ratio
Source: CASPIAN 2020 CSR[20] (Table 14.2.2.15); Goldman 2021;[21] Paz-Ares 2022[23]

Subgroup results for DUR+ET+CAR or DUR+ET+CIS versus ET+CAR

CASPIAN trial subgroup results for DUR+ET+CAR or DUR+ET+CIS versus ET+CAR are summarised in Table 21.

Table 21 CASPIAN trial: OS and PFS for DUR+ET+CAR or DUR+ET+CIS versus ET+CAR

Outcome	DUR+ET+CAR vs ET+CAR	DUR+ET+CIS vs ET+CAR
HR (95% CI) after approximately 2-years		
Overall survival	[redacted]	[redacted]*
Progression-free survival	[redacted]	[redacted]*
HR (95% CI) after approximately 3-years		
Overall survival	[redacted]	[redacted]*
Progression-free survival	-	-

* HR estimated with the digitalization of KM curves
CAR=carboplatin; CI=confidence interval; CIS=cisplatin; CS=company submission; DUR=durvalumab; ET=etoposide; HR=hazard ratio
Source: CS, Appendix D.3.4.1.2 (Table 20); CS, Appendix D.3.4.2.2 (Table 22); company response to clarification question A1 (Table 2)

10.2.5 Objective response rate

CASPIAN trial and IMpower133 trial ORR results at the latest data-cuts for which data were published are summarised in Table 22.

Table 22 CASPIAN and IMpower133 trials: objective response rate*

Objective response rate	CASPIAN trial (2 year follow-up)		IMpower133 trial (1 year follow-up)	
	Durvalumab+EP (n=268)	EP (n=269)	Atezolizumab+EP (n=201)	Placebo+EP (n=202)
Confirmed* %	67.9	58.0	60.2	64.4
OR (95% CI)	1.53 (1.078 to 2.185)		Not reported	

* Confirmed objective response rate was a post-hoc analysis in the CASPIAN trial, unconfirmed objective response rate was a protocol-defined outcome for this trial
CI=confidence interval; CS=company submission; EP=etoposide+platinum-based chemotherapy; OR=odds ratio
Source (CASPIAN): CS, Section B.3.6.3.2 (Figure 9a)
Source (IMpower133): Horn 2018[24]

10.2.6 Health-related quality of life

Patient reported outcome (PRO) data were collected as part of the CASPIAN and IMpower133 trials using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core module (EORTC QLQ-C30) and the EORTC Quality of Life Questionnaire, Lung module (EORTC QLQ-LC13). The company only presented results from the CASPIAN trial. The differences in how PROs were reported and the difference in follow-up at which results were reported in the CS for the CASPIAN trial (2-years) versus the IMpower133 trial publications (1-year) make comparisons between treatment arms across

trials difficult. However, the following general observations can be made when comparing 1-year follow-up data from both trials:

- patients in both the durvalumab+EP and EP arms of the CASPIAN trial experienced a numerically reduced burden for most symptoms over time,; similar results were found between atezolizumab+EP and EP for the same symptoms in the IMpower133 trial (alopecia notably worsened over the first 30-33 weeks in both arms of the IMpower133 trial; this outcome was excluded from the published CASPIAN trial analysis by Goldman 2020[19])
- longer median time to treatment deterioration was observed for patients in the durvalumab+EP arm compared with those in the EP arm for global health status/QoL and all functioning scales, as well as for all QLQ-C30 and QLQ-LC13 symptom scales; similar results were found between atezolizumab+EP and EP for treatment-related or lung-cancer related symptoms in the IMpower133 trial (TTD for global health status/QoL and functional scales were not reported in this trial)

10.2.7 Safety results

The overall safety profiles of the CASPIAN trial durvalumab+EP and EP arms were comparable and consistent with the known safety profiles of individual treatment components. Similar safety conclusions were reported in the Roche CS (TA638[2] Committee papers) for the comparison of atezolizumab+EP versus placebo+EP. The following three tables (Table 23 to Table 25) provide a summary of key CASPIAN and IMpower133 trial AE data, including immune-mediated AE (imAE) data. The company also presented information on the types of adverse events of special interest (AESIs) reported in the CASPIAN trial in CS, Section B.3.10.2 (Table 22).

The EAG considers that, where it was possible to carry out a naïve comparison of AEs experienced by patients treated with durvalumab+EP and patients treated with atezolizumab+EP, AEs were largely comparable and often seemed to favour treatment with durvalumab+EP. However, the EAG considers that results from naïve comparisons of AESI and imAE data are difficult to interpret due to differences in how these AEs were defined in the trials (see Table 26).

Table 23 CASPIAN and IMpower133 trials: summary of adverse events (2 year follow-up)

Adverse event %	CASPIAN trial		IMpower133 trial	
	Durvalumab+EP (n=265)	EP (n=266)	Atezolizumab+EP (n=198)	Placebo+EP (n=196)
All any-cause AEs	98.1	97.0	100.0	96.4
TR-AEs	89.4	89.8	94.9	92.3
All Grade 3/4 AEs	[redacted][a]	[redacted][a]	67.7	63.3
TR-Grade 3/4 AEs	45.7	51.9	57.1	56.1
Any SAE	32.1[b]	36.5	37.4	34.7
TR-SAEs	13.2	18.8	22.7[c]	18.9[c]
Any AESI	[redacted]	[redacted]	41.4	24.5
Any Grade 3/4 AESI	11.3	5.6	8.1	2.6
Any imAE	20.0	2.6	39.9[c]	24.5[c]
Any Grade 3/4 imAE	4.9	0.4	Not reported	Not reported
AEs leading to treatment discontinuation				
TR-AEs	6.0	4.9	Not reported	Not reported
Any-cause AE	10.2	9.4	12.1	3.1
AESIs	[redacted][d]	[redacted]	4.0	1.0
imAEs	[redacted][e]	[redacted]	4.0	1.0
TR-deaths	2.3	0.8	1.5	1.5

[a] In Goldman 2021,[21] data reported to be 59.6% in durvalumab+EP arm versus 59.4% in EP arm
[b] After 3-years follow-up, SAEs increased to 32.5% in durvalumab+EP arm
[c] Data from 1-year follow-up reported as data not available from 2-years follow-up
[d] Date reported to be [redacted]% in company response to clarification question A7
[e] Date reported to be [redacted]% in company response to clarification question A7
AE=adverse event; AESI=AE of special interest; CS=company submission; CSR=clinical study report; imAE=Immune mediated; SAE=serious AE; TR=treatment-related
Source (CASPIAN): CS, Section B.3.10.2 (Table 19); CASPIAN CSR 2020,[20] Section 12.2.3 (Table 46); Goldman 2021[21] including supplementary appendix
Source (IMpower133): Committee Papers for TA638[2] (Roche CS, Table 15); Liu 2021[29]

Table 24 CASPIAN and IMpower133 trials: summary of imAEs (1 year follow-up)*

imAE %	CASPIAN trial		IMpower133 trial	
	Durvalumab+EP (n=265)	EP (n=266)	Atezolizumab+EP (n=198)	Placebo+EP (n=196)
Hypothyroid events	9.1	0.8	Not reported	Not reported
Hypothyroidism	Not reported	Not reported	12.6	0.5
Hyperthyroid events	5.3	0	Not reported	Not reported
Hyperthyroidism	Not reported	Not reported	5.6	2.6
Pneumonitis	2.6	0.8	2.0	2.6
Hepatitis	Not reported	Not reported	7.1	4.6
Hepatic events	2.6	0	Not reported	Not reported
Dermatitis/rash	1.5	0.8	18.7	10.2
Diarrhoea/colitis	1.5	0.4	1.5	0
Thyroiditis	1.5	0	Not reported	Not reported
Type 1 diabetes	1.5	0	0.5	0
Adrenal insufficiency	0.4	0	0	1.0
Pancreatic events	0.4	0	Not reported	Not reported
Pancreatitis	Not reported	Not reported	0.5	1.0
Nephritis	Not reported	Not reported	0.5	0.5
Hypophysitis	Not reported	Not reported	0.5	0,5
Rhabdomyolysis	Not reported	Not reported	1.0	0
Vasculitis	Not reported	Not reported	0	0.5
Arthritis	0.8	0	Not reported	Not reported
Severe cutaneous reaction	Not reported	Not reported	1.0	0
Infusion-related reactions	[redacted]	[redacted]	5.5	2.6

* It is apparent from the CASPIAN final analysis CSR 2020 (2-years follow-up) that additional patients experienced the following imAEs: [redacted] after 2-years follow-up; see CASPIAN final analysis CSR 2020, Table 14.3.6.5

CS=company submission; CSR=clinical study report; imAE=Immune mediated adverse event

Source (CASPIAN): Paz-Ares 2019[18] (Table S8)

Source (IMpower133): Horn 2018[24] (Table S10)

Table 25 CASPIAN and IMpower133 trials: summary of Grade 3/4 imAEs (1 year follow-up)*

imAE %	CASPIAN		IMpower133	
	Durvalumab+EP (n=265)	EP (n=266)	Atezolizumab+EP (n=198)	Placebo+EP (n=196)
Hypothyroid events	0	0	Not reported	Not reported
Hypothyroidism	Not reported	Not reported	0	0
Hyperthyroid events	0	0	Not reported	Not reported
Hyperthyroidism	Not reported	Not reported	0	0
Pneumonitis	0.8	0.4	0.5	1.0
Hepatitis	Not reported	Not reported	1.5	0
Hepatic events	1.9	0	Not reported	Not reported
Dermatitis/rash	0.0	0	2.0	0
Diarrhoea/colitis	0.4	0	1.0	0
Thyroiditis	0.0	0	Not reported	Not reported
Type 1 diabetes	1.5	0	0	0
Adrenal insufficiency	0.0	0	0	0
Pancreatic events	0.4	0	Not reported	Not reported
Pancreatitis	Not reported	Not reported	0.5	1.0
Nephritis	Not reported	Not reported	0.5	0
Hypophysitis	Not reported	Not reported	0.5	0
Rhabdomyolysis	Not reported	Not reported	0.5	0
Vasculitis	Not reported	Not reported	0	0
Arthritis	0	0	Not reported	Not reported
Severe cutaneous reaction	Not reported	Not reported	0	0
Infusion-related reactions	[redacted]	[redacted]	2.0	1.0

It is apparent from the CASPIAN final analysis CSR 2020 (2-years follow-up) that additional patients experienced the following Grade 3/4 imAEs: [redacted] after 2-years follow-up; see CASPIAN final analysis CSR 2020, Table 14.3.6.5
CS=company submission; CSR=clinical study report; imAE=Immune mediated adverse event
Source (CASPIAN): CASPIAN CSR 2019;[12] Paz-Ares 2019[18] (Table S8)
Source (IMpower133): Horn 2018[24] (Table S10)

Table 26 CASPIAN and IMpower133 trials: Definition of AESIs and imAEs

AE type	CASPIAN	IMpower133
AESI	AEs that include, but are not limited to, events with a potential inflammatory or immune mediated mechanism as a result of the mechanism of action of durvalumab that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy	Immune-related AEs defined based on the mechanism of action of atezolizumab, organized by medical concepts
imAE	AE associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is no clear alternate aetiology and required treatment with systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy	Immune-related AEs that were consistent with an immune-mediated mechanism of action of atezolizumab and required treatment with systemic corticosteroids

AE= adverse event; AESI=AE of special interest; imAE=Immune mediated AE
Source (CASPIAN): Paz-Ares 2019[18] (Table S8); CASPIAN CSR 2020 (p183)
Source (IMpower133): Mansfield 2020;[27] Liu 2021[29]

10.3 Appendix 3: EAG revisions to the company model

EAG revisions	Implementation instructions
Correction to treatment cycle numbering in Markov traces	**Insert sheet 'EAG Revisions'** Set value in cell C4 = "C1" Set value in cell D4 = 1 In Sheet 'D +EP' Copy range G27:G1575 Paste values to range H27:H1575 Set value in cell I27=MOD(SEQUENCE(4*(ROUNDUP(C$1575,0)*52-12)/4,,0),4)+1 Copy formula in cell I27 and paste to range I27:I1575 Set value in cell G27=IF('EAG Revision'!D$4=1,I27,H27) Copy formula in cell G27 and paste to range G27:G1575 In Sheet 'Atez + Chemo' Copy range G27:G1575 Paste values to range H27:H1575 Set value in cell I27=MOD(SEQUENCE(3*(ROUNDUP(C$1575,0)*52-12)/3,,0),3)+1 Copy formula in cell I27 and paste to range I27:I1575 Set value in cell G27=IF('EAG Revision'!D$4=1,I27,H27) Copy formula in cell G27 and paste to range G27:G1575
R1) 100% carboplatin in durvalumab+EP arm	In Sheet 'EAG Revisions' Set value in cell C5 = "R1" Set value in cell D5 =1 In Sheet 'Dosing & Adminstration' Set value in cell E14 =IF('EAG Revision'!D5=1,1,201/268) Set value in cell E15 =IF('EAG Revision'!D5=1,0,67/268)
R2) Apply RDI to durvalumab and atezolizumab fixed dose costs	In Sheet 'EAG Revisions' Set value in cell C6 = "R2" Set value in cell D6 =1 In Sheet 'Dosing & Adminstration' Set value in cell D103 =IF('EAG Revision'!D6=1,"Total Vial Sharing", vial_sharing_yn) Set value in cell D109 =IF('EAG Revision'!D6=1,"Total Vial Sharing", vial_sharing_yn)
R3) PCI applied to durvalumab+EP arm	In Sheet 'EAG Revisions' Set value in cell C7 = "R3" Set value in cell D7 = 1 In Sheet 'HCRU' Set value in cell D68 =IF('EAG Revision'!D7=1,D69,0%)

EP=etoposide+platinum-based chemotherapy; PCI=prophylactic cranial irradiation therapy; RDI=relative dose intensity

Cost Comparison Appraisal: Durvalumab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer [ID6404]

EAG report – factual accuracy check and confidential information check: EAG response

Issue 1 Page 11, dosage

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The following sentence on Page 11 is incorrect: "The induction phase is followed by maintenance therapy: durvalumab 1500mg, IV, every 3 weeks until loss of clinical benefit or unmanageable toxicity."	Maintenance therapy with durvalumab is administered every 4 weeks, not every 3 weeks.	Maintenance therapy with durvalumab is administered every 4 weeks, not every 3 weeks. It is important to distinguish this difference from atezolizumab, which is administered every 3 weeks in the maintenance phase.	Typographical error in the original EAG report. The EAG agrees with the company's proposed amendment. Text amended.

Issue 2 Page 10, brain metastases

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The following sentence on Page 10 is inaccurate: The CASPIAN trial is a phase III, open-label, international, multicentre, randomised	Patients in the CASPIAN study were allowed to have treated **or** asymptomatic brain metastases	As per the inclusion criteria in the CASPIAN study, patients were allowed to have treated **or** asymptomatic brain metastases. It is important to	Typographical error in the original EAG report. The EAG agrees with the company's proposed

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
controlled trial (RCT) that enrolled previously untreated adults with ES-SCLC (Eastern Cooperative Oncology Group performance status [ECOG PS] 0 to 1 and no evidence of untreated active brain/central nervous system [CNS] metastases).		distinguish this difference from the IMpower-133 study.	amendment. Text amended.