Single Technology Appraisal

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

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 Accord:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response
   b. Clarification response addendum

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

4. **Expert personal perspectives** from:
   a. Dr Shobhit Baijal – clinical expert, nominated by Accord

5. **External Assessment Report** prepared by Newcastle University
   a. External Assessment Report
   b. EAG addendum pre ACM1

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Serplulimab with carboplatin and etoposide for untreated extensive-stage small cell lung cancer

[ID6346]

Document B

Company evidence submission

February 2025

File name	Version	Contains confidential information	Date
ID6346_Company evidence submission	June 2025 confidentiality update	Yes	27th June 2025

Contents

Abbreviations

ADA	Anti-drug antibody	MAIC	Matching adjusted indirect comparison
AE	Adverse event	MET	Mesenchymal-epithelial transition
AIC	Akaike Information Criterion	MIA	Melanoma inhibitory activity
AUC	Area under the curve	NA	Not applicable
AWMSG	All Wales Medicines Strategy Group	NCCN	National Comprehensive Cancer Network
BIC	Bayesian Information Criterion	NCI	National Cancer Institute
BNF	British National Formulary	NE	Not evaluable
BSA	Body surface area	NHB	Net health benefit
BSC	Best supportive care	NHSCII	NHS cost inflation index
CADTH	Canadian Agency for Drugs and Technologies in Health	NICE	National Institute for Health and Care Excellence
CAV	Cyclophosphamide, doxorubicin and vincristine	NMA	Network meta-analysis
CHMP	Committee for Medicinal Products for Human Use	NR	Not reached
ChT	Chemotherapy	NSCLC	Non-small cell lung cancer
CI	Confidence interval	NYHA	New York Heart Association
CNS	Central nervous system	ORR	Objective response rate
COPD	Chronic obstructive pulmonary disease	OS	Overall survival
CPS	Combined positive score	PAS	Patient access scheme
CR	Complete response	PBAC	Pharmaceutical Benefits Advisory Committee
CRD	Centre for Reviews and Dissemination	PbR	Payment by results
CSR	Clinical study report	PCI	Prophylactic cranial irradiation
CTCAE	Common Terminology Criteria for Adverse Events	PD	Progressed disease
DoR	Duration of response	PF	Progression-free
DSA	Deterministic sensitivity analysis	PFS	Progression-free survival
DSU	Decision Support Unit	PICOS	Population, intervention, comparison, outcomes, study
ECG	Electrocardiogram	PK	Pharmacokinetics
ECOG	Eastern Cooperative Oncology Group	PKS	Pharmacokinetics set
EMA	European Medicines Agency	PPS	Per protocol set
EORTC	European Organization for Research and Treatment of Cancer	PR	Partial response
EOT	End of treatment	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EpC	Etoposide plus carboplatin	PRO	Patient-reported outcome

ESMO	European Society for Medical Oncology	PS	Performance status
ESS	Effective sample size	PSS	Personal social services
ES-SCLC	Extensive-stage small cell lung cancer	PSSRU	Personal Social Services Reporting Unit
FDA	Food and Drugs Administration	QALY	Quality-adjusted life years
HAS	Haute Autorité de Santé	QoL	Quality of life
HCRU	Healthcare resource utilisation	RCT	Randomised controlled trial
HCV	Hepatitis C virus	RDI	Relative dose intensity
HIV	Human immunodeficiency virus	RECIST	Response Evaluation Criteria in Solid Tumors
HR	Hazard ratio	SAE	Serious adverse event
HRG	Healthcare Resource Group	SBU	Statens beredning för medicinsk och social utvärdering
HRQoL	Health-related quality of life	SCLC	Small cell lung cancer
HTA	Health technology assessment	SD	Standard deviation
ICER	Incremental cost-effectiveness ratio	SE	Standard error
ICF	Informed consent form	SLR	Systematic literature review
IDMC	Independent Data Monitoring Committee	SmPC	Summary of product characteristics
ILCCO	International Lung Cancer Consortium	SoC	Standard of care
IPD	Individual patient data	TEAE	Treatment-emergent adverse event
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	TMB	Tumour mutation burden
IRRC	Independent Radiology Review Committee	TNM	Tumour-node-metastasis
ITC	Indirect treatment comparison	TPS	Tumour proportion score
ITT	Intention to treat	TRAE	Treatment-related adverse event
KM	Kaplan-Meier	TRT	Thoracic radiation therapy
KOL	Key opinion leader	TSG	Tumour suppressor gene
LC	Lung cancer	TTD	Time to deterioration
LDH	Lactate dehydrogenase	TTOT	Time-to-off treatment
LIF	Leukaemia inhibitory factor	USD	United States dollar
LSM	Least squares mean	VALSG	Veterans Administration Lung Study Group
LY	Life year	VAS	Visual Analogue Score
LYG	Life year gained	WHO	World Health Organization

Tables and figures

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

1.1 Decision problem

Serplulimab (Hetronifly®) in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (Accord Data on File, 2024a). The submission covers the technology's full marketing authorisation for this indication.

The decision problem presented in this document is described in *Table 1*. The clinical and economic analysis are in line with the NICE reference case, with no major deviations from the final scope.

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	Adults with untreated extensive-stage small cell lung cancer	NA
Intervention	Serplulimab with carboplatin and etoposide	Serplulimab with carboplatin and etoposide	NA
Comparator(s)	Platinum-based combination chemotherapy Atezolizumab with carboplatin and etoposide (for people with Eastern Cooperative Oncology Group performance status of 0 or 1) Durvalumab (subject to NICE appraisal)	Platinum-based combination chemotherapy Atezolizumab with carboplatin and etoposide (for people with Eastern Cooperative Oncology Group performance status of 0 or 1)	Durvalumab has not been included in this appraisal as it is not recommended at the time of submission, although a NICE recommendation is expected on 19th February 2025. At the time of the decision problem meeting, Accord were informed that durvalumab was not a relevant comparator.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	NA

***Abbreviations**: NA, not applicable*

1.2 Description of the technology being evaluated

Table 2 presents an overview of the drug being evaluated (serplulimab). Please see Appendix C for the Summary of Product Characteristics and UK public assessment report for serplulimab.

Table 2: Technology being evaluated

UK approved name and brand name	Serplulimab (Hetronifly®)
Mechanism of action	Serplulimab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor, blocking its interaction with ligands PD-L1 and PD-L2 leading to broader immune suppression than therapies that only inhibit PD-L1. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Serplulimab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth. (Accord Data on File, 2024a) The PD-1 receptor occupation of peripheral T-cells and interleukin-2 (IL-2) release ability in vitro were studied in a Phase 1 study involving 29 Chinese patients with advanced solid tumour who were injected with single and multiple doses (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg) of serplulimab. The results showed that serplulimab could stably maintain the saturation state of receptor occupation and sustained functional blockage at the dosage from 0.3 mg/kg to 10 mg/kg at a 2 week interval. (Accord Data on File, 2024a)
Marketing authorisation/CE mark status	• On 19 September 2024, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Hetronifly®, intended for the treatment of extensive-stage small cell lung cancer (ES-SCLC) (European Medicines Agency, 2024d) • EMA marketing authorisation expected 14th February 2025 • MHRA approval expected March 2025
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Serplulimab in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (Accord Data on File, 2024a). For more details, please see Appendix C.
Method of administration and dosage	Serplulimab is for intravenous use. Treatment must be initiated and supervised by a physician experienced in cancer treatment (Accord Data on File, 2024a). The recommended dose of serplulimab is 4.5 mg/kg every 3 weeks until disease progression or unacceptable toxicity. Dose escalation or reduction of serplulimab is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability. (Accord Data on File, 2024a)
Additional tests or investigations	It is not expected that any additional tests or investigations will be required to take place compared to what already occurs in standard practice. ESMO instructions state that a diagnosis should be made based on the World Health Organization (WHO) criteria. These include: • Physical examination

	• Imaging (such as chest X-rays, CT scans, and MRI) • Bronchoscopy to examine the inside of the lung • Taking a biopsy for a histopathology examination that defines the lung cancer subtype • Molecular testing to identify specific genetic mutations or biomarkers Currently, no predictive biomarker is available, and PD-L1 and tumour mutation burden (TMB) testing are not recommended in routine clinical practice. ESMO highlights that for a pathological diagnosis, histology is preferred over cytology (Dingemans et al., 2021).
List price and average cost of a course of treatment	£1,321.83 per vial (proposed price)
Patient access scheme (if applicable)	A patient access scheme (PAS) simple discount of [redacted]) will be available for serplulimab in the form of a simple discount.

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

1.3.1 Disease overview

SUMMARY

- Lung cancer is sub-characterised into small cell lung cancer (SCLC) and non-small cell lung cancer. SCLC, the most aggressive form of lung cancer, can be described as either limited-stage (LS-SCLC) or extensive-stage (ES-SCLC) (American Lung Association, 2025d, American Lung Association, 2025c). SCLC is associated with the loss of tumour suppressor genes and abnormal PD-L1 expression on tumour cells (Kirk et al., 2022, Schwendenwein et al., 2021, Saida et al., 2023).
- In localised disease, common symptoms include cough, wheezing, shortness of breath (dyspnoea), and coughing up blood (haemoptysis). However, patients with metastases can experience additional symptoms (Franco et al., 2021, Bebb et al., 2023). Paraneoplastic syndromes are also common in SCLC (Gazdar et al., 2017).
- Comorbidities are common in SCLC, particular in elderly, male, and low socioeconomic status patients. These include chronic obstructive pulmonary disease (COPD), connective tissue disease, tuberculosis, anaemia, congestive heart failure, renal diseases, and peripheral vascular disease (Aarts et al., 2015, Tammemagi et al., 2003).
- SCLC is characterised by an aggressive undifferentiated neoplasia with a high proliferation rate and early metastasis, and a high propensity to spread to the brain (Alvarado-Luna and Morales-Espinosa, 2016, García-Campelo et al., 2023, Li et al., 2021, Quan et al., 2004). The disease is initially sensitive to chemotherapy and radiotherapy but develops early resistance (Bernhardt and Jalal, 2016, Alvarado-Luna and Morales-Espinosa, 2016, Dingemans et al., 2021). Disease prognosis remains poor, with a 5-year overall survival (OS) rate of 5% in the UK (Khakwani et al., 2014).
- Lung cancer is one of the most common cancer types, and is equally present in women and men (Dingemans et al., 2021, House of Commons Library, 2023). SCLC accounts for between 13% and 17% of all lung cancers, and around 70% of SCLC cases are regarded as ES-SCLC at diagnosis (Gazdar et al., 2017, Alvarado-Luna and Morales-Espinosa, 2016, Bernhardt and Jalal, 2016, Roche Pharma AG, 2019, Blackhall et al., 2023). It is estimated that 6,766 ES-SCLC patients will be eligible for serplulimab treatment in the UK in 2025.
- The reported 5-year survival rate for ES-SCLC is 5% in the UK, and the disease is associated with a high burden to HRQoL (Khakwani et al., 2014, Basumallik and Agarwal,

SUMMARY
2023, Koinis et al., 2016). Patients with ES-SCLC experience a substantial impact on multiple physical and social aspects of their life, including the completion of daily activities, hobbies, and work. Disease symptoms have a high impact on physical, social, and emotional aspects. Patients' mental health can also be impacted substantially (Bebb et al., 2023, Feliciano et al., 2020). • ES-SCLC is deemed incurable, and treatment is palliative in nature (Bebb et al., 2023). Platinum-based chemotherapy and etoposide is a long-established first-line treatment associated with a median OS of 9 to 10 months, although it has serious side effects (Dingemans et al., 2021, Montanino et al., 2021, Wlodarczyk et al., 2018, Zhang et al., 2022).

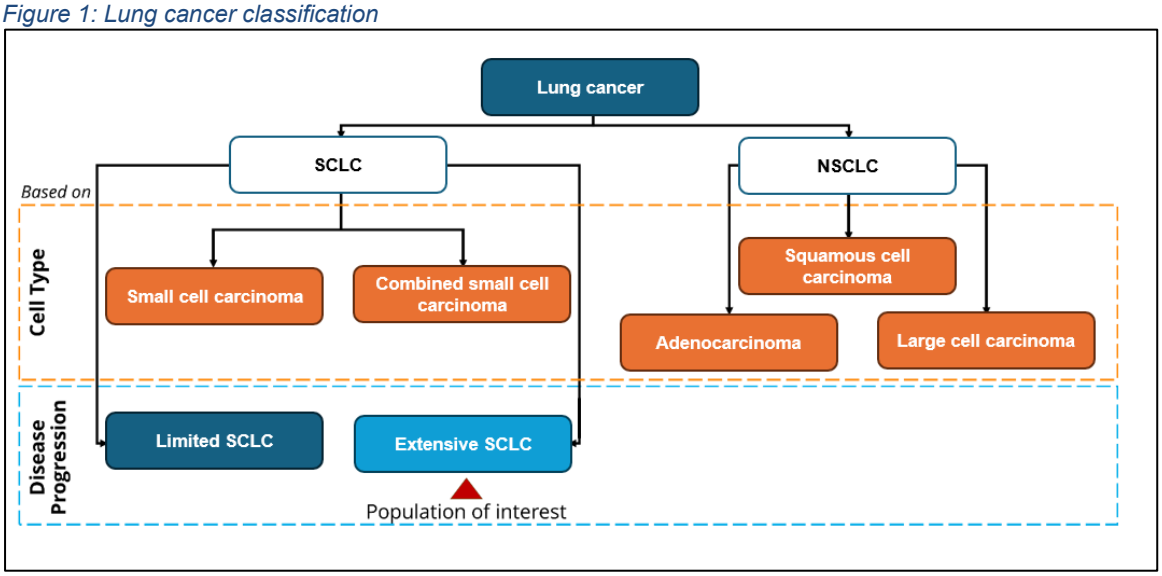
Abbreviations: *COPD, chronic obstructive pulmonary disease; CT, computed tomography; ESMO, European Society for Medical Oncology; ES-SCLC, extensive-stage small cell lung cancer; HRQoL, health-related quality of life; LS-SCLC, limited-stage small cell lung cancer; PD-L1, programmed death-ligand 1; SCLC, small cell lung cancer; TNM, tumour, node, metastasis; VALSG, Veterans Administration Lung Cancer Study Group*

1.3.2 Pathophysiology

Lung cancer (LC) is one of the most common types of cancer globally and a leading cause of cancer-related deaths both worldwide and England, accounting for the highest mortality rates of any cancer among both men and women (World Health Organization, 2025a, World Health Organization, 2025b, NHS Digital, 2024). It occurs when cancer cells grow uncontrollably and cluster together to form a tumour affecting the healthy lung tissue around them (American Lung Association, 2025a). It can be histologically sub-characterised into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (American Cancer Society, American Lung Association, 2025d), as shown in Figure 1.

SCLC is the most aggressive form of lung cancer (Dingemans et al., 2021). SCLC can be described as limited-stage (LS-SCLC) or extensive-stage (ES-SCLC) disease: limited disease is when the cancer has not spread beyond one lung and nearby lymph nodes, and extensive disease is when the cancer has spread beyond one lung and nearby lymph nodes (Kalemkerian, 2012), meaning there is no single area that can be treated with radiotherapy (Gomez-Randulfe et al., 2024).

Figure 1: Lung cancer classification

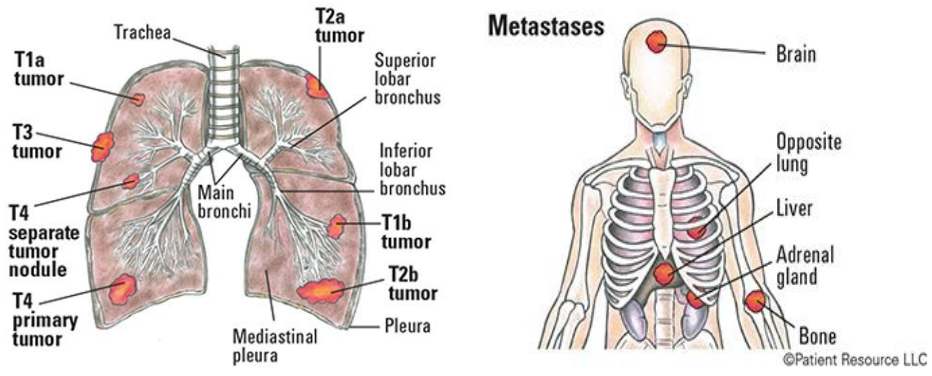


***Abbreviations**: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer*
***Source**: Adapted from (American Cancer Society, American Lung Association, 2025d)*

ES-SCLC is defined as the presence of metastatic disease outside the hemi-thorax at first diagnosis, representing roughly 70% of SCLC cases (Montanino et al., 2021, Taniguchi et al., 2020). Common metastasis sites are the brain, liver, adrenal gland, and bone, as shown in Figure 2 (Society for Immunotherapy of Cancer, Roche Pharma AG, 2019). Tumour spread is often asymptomatic until the disease develops into a more advanced stage (Blackhall et al., 2023).

ESMO Clinical Practice Guidelines for SCLC recommend the use of the tumour-node-metastasis (TNM) system to classify SCLC due to its high prognostic value (Dingemans et al., 2021, Shepherd et al., 2007). However, most clinical trials retain a binary distinction between LS-SCLC and ES-SCLC, a classification which originated in the late 1950s with the Veterans' Administration Lung Study Group (VALSG). Currently, the two staging methods co-exist.

Figure 2: Anatomy of the lung and possible metastases locations



***Abbreviations**: T, tumour*
***Source**: (Society for Immunotherapy of Cancer)*

Tumour suppressor genes (TSGs) are frequently involved in maintaining homeostasis. The loss of these genes causes cellular plasticity, driving numerous cancers, including SCLC (Kirk et al., 2022). Most patients have key TSGs inactivated, such as retinoblastoma 1 (RB1) and tumour protein p53 (TP53), but attempts to target these alterations remain unsuccessful. SCLC tumours are typically characterised by genomic instability (RB1 and TP53) manifested in aneuploidy and multiple intra-chromosomal and inter-chromosomal rearrangements. The high TMB associated with SCLC is largely attributed to tobacco exposure (Gazdar et al., 2017, Taniguchi et al., 2020). Rapid tumour growth, increased vascularity, and a high metastatic potential are other characteristic factors linked to SCLC (Gazdar et al., 2017).

Programmed cell death protein 1 (PD-1) plays a vital role in inhibiting immune response and promoting self-tolerance through modulating T-cell activity, activating apoptosis of antigen-specific T-cells and inhibiting apoptosis of regulatory T-cells. Programmed cell death-ligand 1 (PD-L1) is a trans-membrane protein that is a co-inhibitory factor of the immune response and can combine with PD-1 to reduce the proliferation of PD-1 positive cells (Yanyan et al., 2020). Programmed cell death-ligand 2 (PD-L2) is another ligand of PD-1; studies demonstrated that PD-L2 is highly expressed in human cancers and that its expression has been proven to play an important role in cancer growth and cell proliferation (Wang et al., 2023). A considerable portion of SCLC patients exhibit abnormal PD-L1 and PD-L2 expression on tumour cells (Schwendenwein et al., 2021, Kursunel et al., 2022). Therefore, the PD-1/PD-L1 and PD-L2 signalling pathway is a major therapeutic target for immunotherapies that use immune checkpoint inhibitors (Schwendenwein et al., 2021, Saida et al., 2023).

1.3.3 Symptomatology

SCLC predominantly develops in patients aged 60 to 70 years old and is strongly associated with a history of smoking. It is often asymptomatic in early stages (Blackhall et al., 2023). Symptoms present typically with a short duration, on average at 3 months, and frequently with a metastasis (Bernhardt and Jalal, 2016). Roughly

70% of SCLC patients present with ES-SCLC at diagnosis, typically with symptoms (Blackhall et al., 2023).

The symptoms of SCLC vary depending on the tumour's location and size. In cases of localised disease, common symptoms include cough, wheezing, shortness of breath (dyspnoea), and coughing up blood (haemoptysis). However, approximately two-thirds of SCLC patients are diagnosed with metastases, affecting organs such as the contralateral lung, brain, liver, adrenal glands, bones, or bone marrow; one study of ES-SCLC patients found that >95% presented with metastases (Franco et al., 2021). These metastases can lead to additional symptoms, including neurological issues, nerve pain, fatigue, loss of appetite (anorexia), and weight loss (Bebb et al., 2023).

Patients with ES-SCLC may additionally present with abdominal pain, bone pain, nausea, vomiting, anorexia, weight loss, or focal neurologic deficits. Patients with regional extension may experience vocal hoarseness, chest or throat pain, dysphagia, or superior vena cava syndrome in cases of centrally located tumours (Bernhardt and Jalal, 2016).

Paraneoplastic syndromes are more common in SCLC than in any other type of cancer. These are distant manifestations of the tumour, such as endocrine or immunological implications, and do not originate directly at the primary tumour site. Paraneoplastic syndromes associated with SCLC fall into endocrine or neuronal classes. Endocrine symptoms often result from the abnormal production of hormones by neuroendocrine cells, leading to conditions such as inappropriate antidiuretic hormone production and adrenocorticotropic hormone (ACTH)-associated Cushing’s syndrome. Among immune-mediated neurological syndromes, the Lambert-Eaton myasthenic syndrome is the most frequent, and is characterised by muscle weakness (Gazdar et al., 2017).

It is common for SCLC patients to present with comorbidities. There is a positive correlation between the presence of comorbidities, and increasing age, being male, or having a low socioeconomic status (Aarts et al., 2015). COPD and connective tissue disease are the most common comorbidities, but tuberculosis, anaemia,

congestive heart failure, renal diseases, and peripheral vascular disease, can also arise (Tammemagi et al., 2003).

1.3.4 Risk factors

The primary cause of SCLC is tobacco use: 95% of patients have a positive smoking history (Bernhardt and Jalal, 2016, Alvarado-Luna and Morales-Espinosa, 2016). Among never smokers, second-hand smoke exposure significantly increases the risk of developing lung cancer, particularly SCLC (OR: 3.09; 95% CI: 1.62, 5.89) (Kim et al., 2014). Exposure to dangerous chemicals such as radon, asbestos, halogenated ethers, uranium, arsenic, and chromium, is also a risk factor (American Lung Association, 2025b, Bernhardt and Jalal, 2016). As such, workers in the chemical manufacturing industry are considered to be a high-risk patient group (Alvarado-Luna and Morales-Espinosa, 2016). Genetic factors may play a role in lung cancer development, with higher risks observed when lung cancer family history is registered (American Lung Association, 2025b).

1.3.5 Disease progression and prognosis

SCLC is characterised by an aggressive undifferentiated neoplasia with a high proliferation rate and early metastasis (Alvarado-Luna and Morales-Espinosa, 2016). It has a high propensity to spread to the brain: approximately 10% to 20% of patients present with brain metastases at the initial diagnosis, and eventually up to 40% to 50% will develop a brain metastasis during the course of their disease (García-Campelo et al., 2023, Li et al., 2021, Quan et al., 2004). Although the disease is initially sensitive to chemotherapy and radiotherapy (RT), it develops early resistance, showing early progression and a lack of sensitivity to further pharmacological treatment (Bernhardt and Jalal, 2016, Alvarado-Luna and Morales-Espinosa, 2016, Dingemans et al., 2021).

This is due to the concurrent resistance mechanisms formed by extensive TMB in SCLC and the coexisting subpopulations of cells within a tumour with heterogeneous gene expressions (Schwendenwein et al., 2021). This heterogeneity includes both highly chemo-sensitive and chemo-resistant clones, which often emerge after first-line chemotherapy and lead to rapid tumour repopulation (Alvarado-Luna and Morales-Espinosa, 2016, Bernhardt and Jalal, 2016). As such, disease prognosis

remains poor: in the UK, SCLC has a 5-year OS of 5%, making it the most lethal lung cancer subtype (Khakwani et al., 2014). Survival rates are worse in ES-SCLC patients than in LS-SCLC patients (Blackhall et al., 2023). Additionally, SCLC 5-year survival rates have been found to be lower in England than in other European and North American countries (Khakwani et al., 2014).

Making the distinction between LS-SCLC and ES-SCLC is important to estimate prognosis based on cancer extension, and to determine treatment (American Cancer Society). Poor survival in a chemo-sensitive population is attributed to rapid drug resistance development and failure of treatment at second line and later (Coutinho et al., 2019). Quitting smoking has been related to a reduction in the incidence of the disease and in the risk of mortality (Alvarado-Luna and Morales-Espinosa, 2016).

1.3.6 Epidemiology

Lung cancer is one of the most common cancer types, both worldwide and in the UK, and it accounts for the highest mortality rate of any cancer among both men and women (House of Commons Library, 2023, World Health Organization, 2025a, International Agency for Research on Cancer, 2025, NHS Digital, 2024). Even though lung cancer is equally present in women and men, there has been an increase in female cases in the last few decades: in England, between 1995 and 2019, lung cancer incidence fell by 33% among men but increased by 32% among women (Dingemans et al., 2021, House of Commons Library, 2023). SCLC accounts for between 13% and 17% of all lung cancers (Gazdar et al., 2017, Alvarado-Luna and Morales-Espinosa, 2016, Bernhardt and Jalal, 2016, Roche Pharma AG, 2019, Blackhall et al., 2023), although its incidence has been decreasing in men in recent decades, perhaps due to effective smoking cessation programmes (including in the UK) (Alvarado-Luna and Morales-Espinosa, 2016, Gazdar et al., 2017, Bernhardt and Jalal, 2016).

SCLC has orphan disease designation in the EU (Dingemans et al., 2021) and an application for Orphan designation in was made to the MHRA in September 2024. Approximately 70% of SCLC cases are regarded as extensive disease at diagnosis (Montanino et al., 2021, Taniguchi et al., 2020).

In the UK, it is estimated that 1,618 ES-SCLC patients will be eligible for serplulimab treatment in 2025, rising to 1,684 in 2029. Full details of the patient population calculation can be found in the Budget Impact Analysis appendix.

1.3.7 Disease burden

1.3.7.1 Clinical burden

Due to the rapid proliferation rate of SCLC, the majority of patients present with symptoms within 8 to 12 weeks prior to diagnosis, typically persisting for less than 3 months. The clinical manifestations are heterogeneous, depending on the location and size of the primary tumour. Bebb et al. conducted a noninterventional mixed method study among adult SCLC patients and their caregivers regarding the patient-perceived symptom burden (Bebb et al., 2023). The most impactful symptoms were found to be shortness of breath, fatigue, coughing, chest pain, and nausea/vomiting. SCLC had a high personal and psychological burden among caregivers, whose duties consumed much of their time, similar to the observed symptoms and impact of SCLC as reported by patients (Bebb et al., 2023).

The prognosis for patients with SCLC is poor, with a reported 5-year survival rate in the UK of approximately 5%, and is associated with a high burden to the health-related quality of life (HRQoL) of patients (Basumallik and Agarwal, 2023, Koinis et al., 2016, Khakwani et al., 2014). SCLC has a considerable disease burden, with a significant impact on survival and deterioration of HRQoL because of a late diagnosis and rapid disease progression (Bennett et al., 2017).

For patients with metastases, symptom profile may vary from person to person as it depends on the degree of tumour spread and the organ affected. These symptoms can include neurological issues, nerve pain, fatigue, loss of appetite (anorexia), and weight loss (Bebb et al., 2023).

Approximately 70% of patients with SCLC are initially diagnosed with ES-SCLC, while the remaining 30% present with LS-SCLC (Blackhall et al., 2023, Zhu et al., 2023). Although limited-stage SCLC is potentially curable, with 20% to 30% of patients alive at 5 years and a median OS (mOS) ranging between 25 to 30 months (García-Campelo et al., 2023), ES-SCLC is deemed uncurable. Treatment is

therefore palliative in nature and the disease has a poor mOS, between 8 and 13 months, and a 5-year survival rate of less than 5% (Bebb et al., 2023, Blackhall et al., 2023, García-Campelo et al., 2023).

Patients with ES-SCLC experience a substantial impact on multiple physical and social aspects of their life, including the completion of daily activities (e.g., obtaining groceries, playing with grandchildren), hobbies, and work (Bebb et al., 2023). Disease symptoms have a high impact on physical, social, and emotional aspects.

1.3.7.2 Humanistic burden

In addition to the physical burden of ES-SCLC, patients' mental health is impacted substantially. The lack of treatment options and the inherently progressive nature of the disease leave patients feeling afraid of dying, and hoping to go into remission as a means of gaining more time (Bebb et al., 2023).

Looking to caregiver implications, a study by Feliciano et al. on the family-centred concerns of lung cancer revealed that caregivers experience a wide range of barriers involving psychological, emotional, and technical aspects, while helping their affected person (Feliciano et al., 2020). Their responsibilities occupy a significant portion of their time, and they often live with the patient (Bebb et al., 2023). Duties can be considered overwhelming, impacting their careers, family, and hobbies. Caregivers often express a desire for external support as they feel isolated while helping their family member (Bebb et al., 2023, Feliciano et al., 2020).

1.3.7.3 Economic burden

Direct costs for SCLC patients are those associated with chemotherapy, diagnosis (e.g., screening methods), and treatment (e.g. treatment administration, medication, surgical). Treatment costs include hospitalisations, nurse visits, emergency room visits, follow-up appointments, and outpatient care (Enstone et al., 2018).

A systematic literature review (SLR) of evidence on the economic and humanistic burden of ES-SCLC found no evidence on the economic burden of ES-SCLC in the UK (see Appendix J) (Accord Data on File, 2024b). In Australia, in a study addressing the direct costs of modern lung cancer management, the results found that hospitalisation is the predominant cost driver of ES-SCLC treatment, with a

median hospital stay of 25 days, accounting for approximately 44% of all costs (Kang et al., 2012). Similarly, in the US, a study reporting the healthcare costs per patient for ES-SCLC and metastatic NSCLC found that SCLC disease-related costs were a larger percentage of the total (all-cause) costs compared with NSCLC (62.6% vs 56.4%) (Karve et al., 2014).

There is limited information on the indirect costs of SCLC. The loss of productivity due to premature death was reported in Turkey by Cakir et al. 2007**.** It accounted for a total of $866,870, representing 59% of the total lung cancer costs. The study also found that the indirect costs experienced by patients varied widely, ranging from $500 to $99,000 (Cakir Edis and Karlikaya, 2007).

1.3.8 Diagnosis and staging

Diagnosis

Lung cancer symptoms may be mild or mistaken for common respiratory issues, often leading to a delayed diagnosis. Patients typically present with a short duration of symptoms and frequently with metastatic disease (Bernhardt and Jalal, 2016, World Health Organization, 2025b). As of April 2021, the ESMO Guidelines for SCLC (Dingemans et al., 2021) and WHO criteria (please see below) serve as the recommended standard followed by most European countries, including the UK (Appendix M). ESMO instructions state that a diagnosis should be made based on the WHO criteria. These include:

- Physical examination
- Imaging (such as chest X-rays, CT scans, and MRI)
- Bronchoscopy to examine the inside of the lung
- Taking a biopsy for a histopathology examination that defines the lung cancer subtype
- Molecular testing to identify specific genetic mutations or biomarkers

Although NICE guidelines recommend a series of diagnostic steps for the diagnosis of lung cancer, with no specific guidelines for ES-SCLC, there is significant overlap between NICE guidelines, ESMO guidelines and WHO criteria (National Institute of Health and Care Excellence, 2019).

Currently, no predictive biomarker is available, and PD-L1 and TMB testing are not recommended in routine clinical practice for SCLC specifically. ESMO highlights that for a pathological diagnosis, histology is preferred over cytology (Dingemans et al., 2021).

Factors that may be assessed to identify risk factors or symptoms include smoking history, physical examination, comorbidities, performance status (PS), laboratory tests, and potential autoimmune-mediated paraneoplastic neurological symptoms. Poor prognostic factors include impaired performance status, weight loss, increased age, and male sex. The screening of paraneoplastic neurological symptoms is important when considering immunotherapy for patients. A complete blood count, as well as tests for liver enzymes, sodium, potassium, calcium, glucose, lactate dehydrogenase (LDH), and renal function, should be carried out in a laboratory analysis. Elevated LDH and low sodium are poor prognostic factors in SCLC. In case of an abnormal blood count or signs of blood-bone marrow infiltration, a bone marrow aspiration and biopsy are recommended (in patients with no known additional metastases) to confirm bone marrow involvement (Dingemans et al., 2021).

Imaging tests are used to visualise the lungs and detect abnormalities. A contrast-enhanced CT of the chest and abdomen is recommended, with fluorodeoxyglucose-position emission tomography (FDG-PET) used optionally. If FDG-PET is used for decision-making, its results should be confirmed through pathology (biopsy) due to false-positive results of metastasis with this technology. In cases of suspected bone metastasis and no other metastasis where FDG-PET is unavailable, a bone scan should be performed. When dealing with advanced-stage cancer without certain prophylactic cranial irradiation (PCI), obtaining an MRI of the brain is advised to check for any potential issues in the brain. In case a suspected solitary metastasis cannot be adequately diagnosed, or a diagnosis significantly delays the start of treatment, the lesion can be re-evaluated after two cycles of chemotherapy to confirm the metastatic disease diagnosis (Dingemans et al., 2021).

Staging and risk assessment

After characterising the lung cancer type, cancer staging is performed by identifying the cancer's location, size, and spread. Staging is important to determine the available treatment options (American Lung Association, 2025c). Staging is based on the results of the diagnostic examinations, including physical exams, biopsies, imaging tests, and other tests. In practice, most clinicians use the two-stage (VALSG) system to separate LS-SCLC from ES-SCLC based on the cancer spread and the administered treatment. LS-SCLC implies localised cancer (e.g., one side of the chest) and can be treated with a single radiation field. ES-SCLC indicates a widespread cancer affecting multiple areas of the lung or other parts of the body. For ES-SCLC patients, chemotherapy (cisplatin or carboplatin) in combination with etoposide and immunotherapy (such as atezolizumab) is likely to be the best option for disease control; however, most people with ES-SCLC see their cancer return at some point (American Lung Association, 2025c).

The ESMO guideline recommends using the 8th edition of the TNM staging system, shown in Table 3. NICE also uses the TNM system, with its guidelines defining ES-SCLC as "broadly corresponding to T1-4, N0-3, M1a/b". The latest ESMO Clinical Practice Guidelines for SCLC from 2021 uses the terms 'limited' and 'extensive' SCLC, as in clinical trials, to define eligibility (Dingemans et al., 2021).

Table 3: Clinical TNM classification of SCLC

T – Primary Tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Tis	Carcinoma in situ	
T1	Tumour ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscope 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. T2 tumours with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm.	
	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	
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, or 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	
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	
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[a]
	M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
	M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

***Notes**: [a]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 judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor*
***Abbreviations**: M, distant metastasis; N, regional lymph nodes; SCLC, small cell lung cancer; T, primary tumour.*
***Source**: (Dingemans et al., 2021)*

[redacted]

1.3.9 Clinical pathway of care

1.3.9.1 Treatment pathway

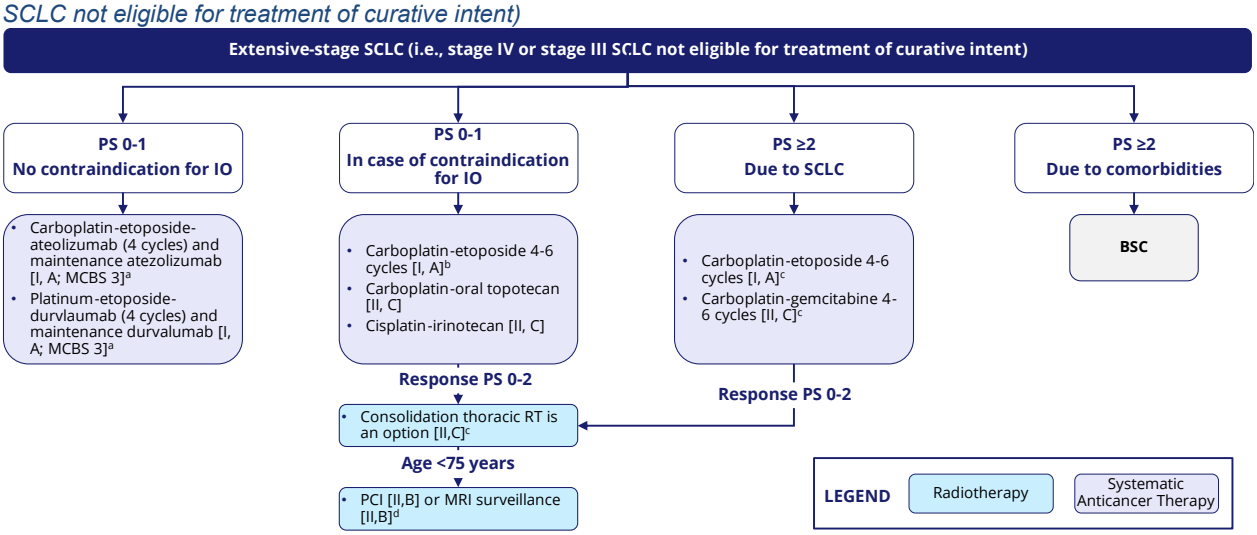
Whereas LS-SCLC is sometimes treated with curative intent, ES-SCLC is deemed incurable, and treatment is palliative in nature (Bebb et al., 2023). Platinum-based chemotherapy and etoposide has been a long-established first-line treatment (Dingemans et al., 2021, Montanino et al., 2021). A median OS of 9 to 10 months and a median progression-free survival (PFS) of 5 to 6 months is linked to this treatment regimen, although platinum-based chemotherapy has serious undesirable effects, including dose-limiting toxicity (Wlodarczyk et al., 2018, Zhang et al., 2022, Dingemans et al., 2021). The specific toxicity profiles of different platinum-based chemotherapies should also be considered in treatment decision-making; cisplatin is associated with non-haematological toxicity (e.g., nausea, vomiting and renal toxicity), while carboplatin leads to myelosuppression (Dingemans et al., 2021).

Atezolizumab in combination with platinum-based therapy represents an alternative

treatment. Atezolizumab is an immune checkpoint inhibitor that targets the PD-L1 protein, a molecule present on the surface of many cancer cells, and as such prevents the interaction between the PD-L1 protein on cancer cells and the PD-1 protein on T-cells (European Medicines Agency, 2024c, European Medicines Agency, 2024e).

Figure 4 presents the ESMO treatment algorithm for patients with ES-SCLC.

Figure 3: ESMO treatment algorithm for SCLC in patients with extensive-stage disease (i.e., Stage IV or Stage III SCLC not eligible for treatment of curative intent)



***Notes**: [a]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA or FDA. The score has been calculated by the ESMO-MCBS working group and validated by the ESMO guidelines committee; [b]Carboplatin may be replaced by cisplatin in patients <70 years of age or based on the toxicity profile; [c]In patients with a PS of more than 2, consider ChT dose reduction and/or G-CSF prophylaxis; [d]No brain metastasis on MRI before PCI I*
***Abbreviations:** BSC. best supportive care; ChT, chemotherapy; G-CSF, granulocyte colony-stimulating factor; IO, immunotherapy; MCBS, ESMO-Magnitude of Clinical Benefit Scale; PS, performance status; RT, radiotherapy; SCLC, small cell lung cancer*
***Source:** (Dingemans et al., 2021)*

The standard clinical pathway for ES-SCLC outlined in the NICE guidelines for lung cancer is similar to the ESMO treatment algorithm, with platinum-based combination chemotherapy as a first-line treatment option, followed by thoracic radiotherapy or PCI as second-line treatment (Dingemans et al., 2021):

- Offer platinum-based combination chemotherapy to people with extensive-stage disease SCLC (broadly corresponding to T1–4, N0–3, M1a/b – including cerebral metastases) if they are fit enough.
- Assess the person's condition before each cycle of chemotherapy for extensive-stage disease SCLC (broadly corresponding to T1–4, N0–3, M1a/b) and offer up to a maximum of 6 cycles, depending on response and toxicity.

- Consider thoracic radiotherapy with PCI for people with extensive-stage disease SCLC who have had a partial or complete response to chemotherapy within the thorax and at distant sites.
- Consider PCI for people with extensive-stage disease SCLC and WHO performance status 0 to 2, if their disease has responded to first-line treatment.

NICE does not recommend maintenance treatment for SCLC at any time outside of clinical trials (National Institute of Health and Care Excellence, 2019).

In addition, NICE TA638 recommends atezolizumab with carboplatin and etoposide as an option for untreated ES-SCLC in adults with an ECOG performance status of 0 or 1 (National Institute of Health and Care Excellence, 2020). However, the NICE lung cancer guidelines have not been updated to reflect the reimbursement of atezolizumab (National Institute of Health and Care Excellence, 2019).

At the time of submission development, NICE does not recommend the use of durvalumab for ES-SCLC (National Institute of Health and Care Excellence, 2019). Final recommendation is expected on the 19th February 2025, and durvalumab has therefore not been included as a relevant comparator for serplulimab.

[redacted]

1.3.9.2 Unmet need

SCLC presents with an aggressive clinical course with rapid progression, frequently with widespread metastases at diagnosis (Coutinho et al., 2019, Bennett et al., 2017). This, combined with the fact that diagnoses often occur in the later stage of the disease due to non-specific symptoms, as it is often asymptomatic until the cancer has progressed to a more advanced stage (Bennett et al., 2017, Blackhall et al., 2023), results in the need for an effective method for early detection or screening

of SCLC (Pietanza et al., 2015). Additionally, the low adoption rate of lung cancer screening programmes, together with the aggressive nature of the disease, leads to a lack of early diagnosis and poor life expectancy (Blackhall et al., 2023, Poon et al., 2023).

SCLC is deemed incurable, and treatment is palliative in nature (Bebb et al., 2023). People diagnosed with ES-SCLC are often dismayed at their lack of treatment options as therapeutic options have not changed for decades (Mak et al., 2019, Schwendenwein et al., 2021, García-Campelo et al., 2023). New launches in SCLC have been limited in contrast to NSCLC, which has had more focus on innovations and diverse therapeutic options. Additionally, patients are aware of the success of immunotherapy for treating other cancers (National Institute of Health and Care Excellence, 2020).

The established first-line treatment for ES-SCLC is platinum-based chemotherapy. This is associated with significant side effects such as non-haematological toxicity (e.g., nausea, vomiting and renal toxicity) for cisplatin and myelosuppression for carboplatin (Dingemans et al., 2021). Patients express a desire for regaining a level of independence and the ability to continue their life as close to normal as possible (Bebb et al., 2023). More time to plan end-of-life care could help improve HRQoL for patients and families (National Institute of Health and Care Excellence, 2020). Lastly, patients often respond to platinum-based chemotherapy (chemo-sensitive patients) but relapse later and become resistant to treatment. Clinical studies have not captured this response pattern or the specific population subgroup (Mak et al., 2019). Patients require therapies with longer OS, as well as a more effective and safe profile without relying on chemotherapy; this would allow them to enjoy a higher QoL and can continue the activities they enjoy the most (Bebb et al., 2023).

Overall, the lack of screening programme adoption rates, the lack of an early diagnosis, rapid development of resistance to chemotherapy treatment, platinum chemotherapy side effects, low 5-year survival rates, and low quality of end-of-life care, underline the unmet need in terms of available treatments, especially for patients with ES-SCLC (Enstone et al., 2018, Blackhall et al., 2023).

[redacted]

1.3.9.3 Introduction to serplulimab

Serplulimab (formerly HLX10) is a humanised monoclonal IgG4 antibody which binds to the PD-1 receptor and blocks its interaction with ligands PD-L1 and programmed cell death-ligand 2 (PD-L2). The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in 16 antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Serplulimab potentiates T-cell responses, including anti-tumour responses, through the blockade of PD-1 binding to PD-L1 and PD-L2.

A Phase 1 study was conducted on 29 Chinese patients with advanced solid tumours to evaluate the PD-1 receptor occupancy on peripheral T-cells and the in vitro interleukin-2 (IL-2) release capability of serplulimab in vitro. Patients received single and multiple doses of serplulimab at 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg. The results showed that serplulimab could maintain the saturation state of receptor occupation stably and sustained functional blockage at the dosage from 0.3 mg/kg to 10 mg/kg every 2 weeks (Accord Data on File, 2024a).

The clinical value of serplulimab for the first-line treatment of ES-SCLC has been evaluated in the randomised, double-blind, placebo control, global Phase 3 trial, ASTRUM-005. The objective of the ASTRUM-005 clinical trial was to evaluate the efficacy and adverse event (AE) profile of the PD-1 inhibitor, serplulimab and chemotherapy (consisting of etoposide plus carboplatin (EpC)), compared with placebo plus EpC in untreated ES-SCLC patients. (Cheng et al., 2022a). Serplulimab plus chemotherapy showed consistent benefits in OS, PFS, objective response rate (ORR), and Duration of response (DoR) versus placebo plus chemotherapy. Long-term efficacy benefits were also observed, with patients in the serplulimab group

showing significantly longer median OS versus patients in the placebo group (Cheng et al., 2022b).

The results of the clinical trial support the use of serplulimab plus chemotherapy as the first-line treatment among patients with previously untreated ES-SCLC, making it the first PD-1 inhibitor in combination with chemotherapy showing OS benefits licenced in this indication.

1.3.9.4 Proposed placement in treatment pathway

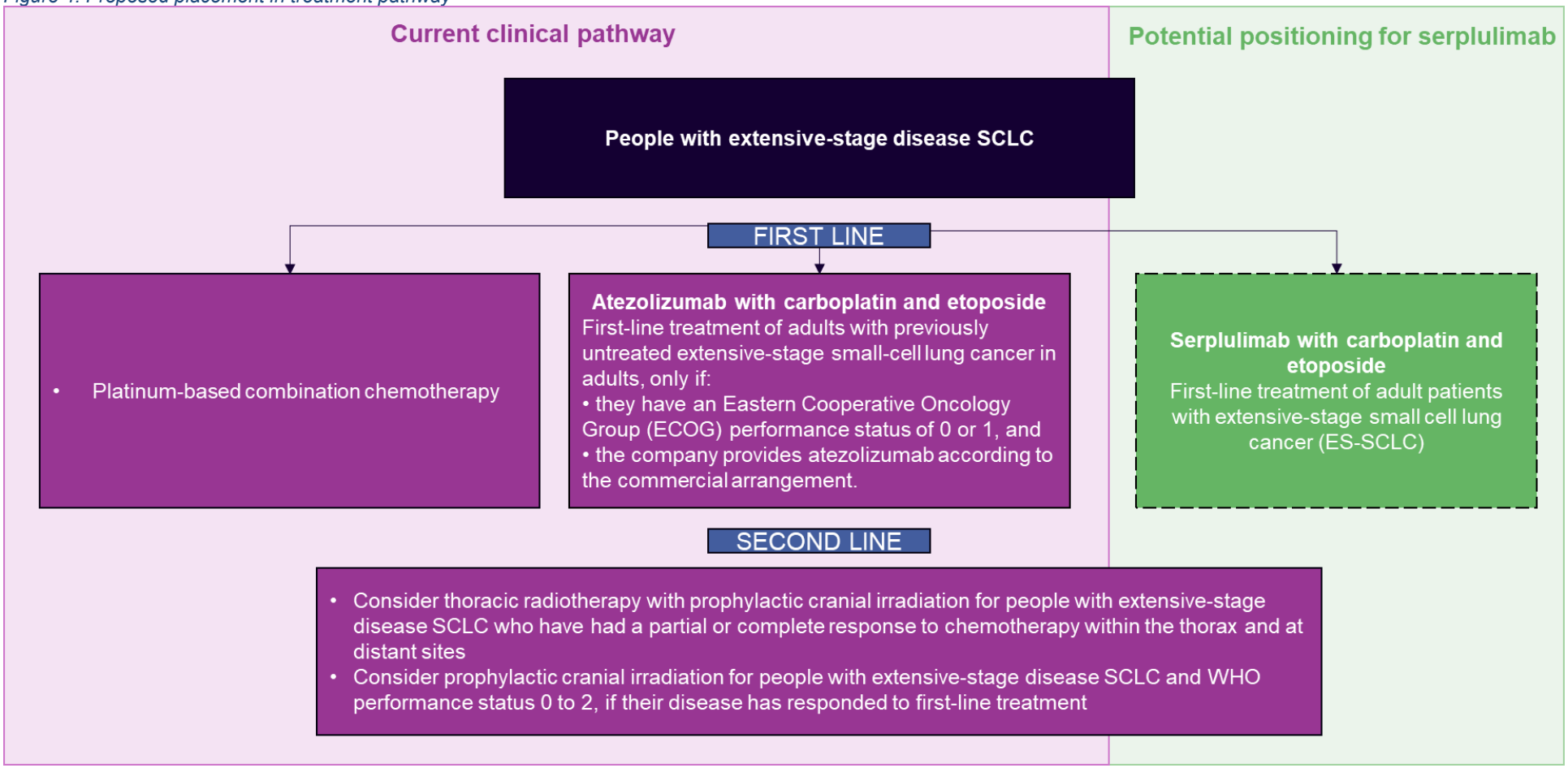
Serplulimab in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with ES-SCLC. As such, it is intended to be an alternative to existing first-line treatments in the UK, that is, platinum-based combination therapy or, for patients with an ECOG performance status of 0 or 1, atezolizumab in combination with carboplatin and etoposide. In 2022, the EMA granted orphan drug designation for serplulimab for the treatment of patients with SCLC (EMA/OD/0000099427), indicating that there exists no satisfactory method of prevention or treatment of ES-SCLC and/or that the serplulimab will be of significant benefit to those affected by ES-SCLC (European Medicines Agency, 2024b, European Union, 1999). The proposed clinical pathway is shown in Figure 4. Serplulimab in combination with carboplatin and etoposide has been shown to significantly improve OS and PFS compared with etoposide and carboplatin alone in patients with previously untreated ES-SCLC. In addition, serplulimab in combination with carboplatin and etoposide demonstrates a manageable safety profile similar to carboplatin and etoposide alone, which does not compromise patients' health-related quality of life (Cheng et al., 2022b).

In indirect treatment comparisons, serplulimab in combination with carboplatin and etoposide has also been found to have superior survival outcomes (OS, PFS, and ORR) over carboplatin and etoposide alone compared to other PD-L1 inhibitors, most notably atezolizumab in combination with carboplatin and etoposide (Accord Data on File, 2022). Carboplatin and etoposide is representative of 'platinum-based chemotherapy' more broadly in the UK.

[redacted]

[redacted]

Figure 4: Proposed placement in treatment pathway



Abbreviations: *ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small cell lung cancer; SCLC, small cell lung cancer; WHO, World Health Organization*
Source: *Partially adapted from (National Institute of Health and Care Excellence, 2019)*

1.4 Equality considerations

[redacted] However, this is not expected to impact the availability of serplulimab and does not impact the submission.

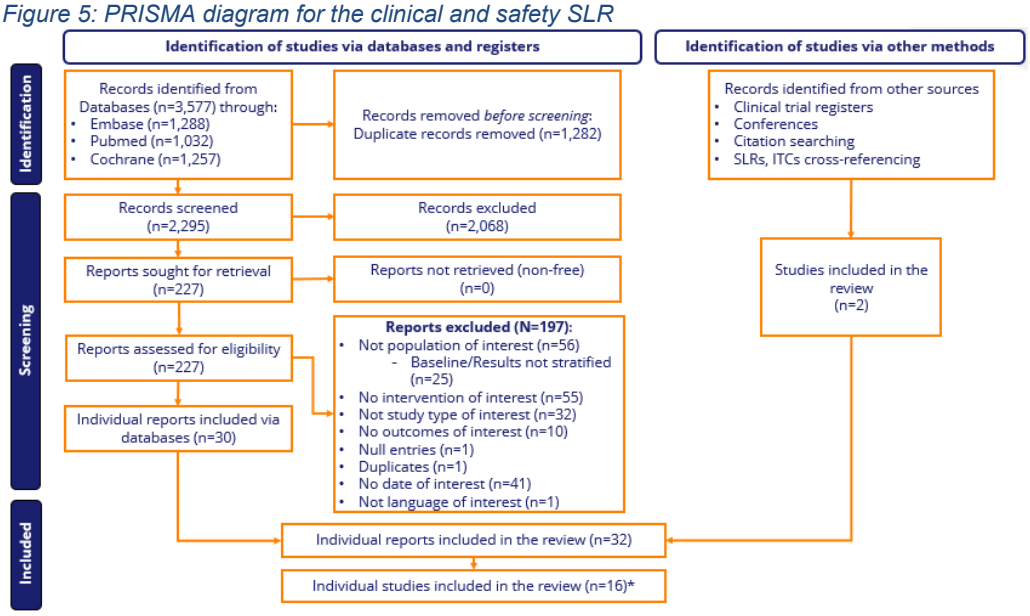
2 Clinical effectiveness

2.1 Identification and selection of relevant studies

An SLR was conducted to identify and collect key clinical efficacy and safety evidence for treatments for adults with untreated ES-SCLC listed in ESMO treatment guidelines (Dingemans et al., 2021). The SLR was conducted in accordance with guidelines provided by the Cochrane collaboration and the Centre for Reviews and Dissemination (CRD), as well as NICE requirements. The methodology and results were reported as per PRISMA guidelines. Full details of the SLR search strategy, study selection process, results, and narrative synthesis are presented in Appendix D.

Electronic searches were conducted across key biomedical databases on 5th April 2024, identifying 3,577 records. 1,282 were duplicates and 2,068 were excluded following title and/or abstract screening. All remaining 227 references were retrieved for full publication screening. However, 197 articles failed to meet the population, intervention, comparator, outcomes, study (PICOS) inclusion criteria and were excluded. Thirty publications identified through database searching were included in the review, with two additional references being identified through supplementary searches for published and unpublished literature. These 32 articles published relevant information on 16 individual studies. The PRISMA flow diagram representing the study identification and selection process is presented in Figure 5.

Figure 5: PRISMA diagram for the clinical and safety SLR



*Notes: *In total, 32 individual publications were identified from the SLR, corresponding to 16 single studies relevant for the ITC (CASPIAN n=10, IMPower133 n=4, ASTRUM-005 n=4, JCOG1201 n=2)*
Abbreviations: ITC, indirect treatment comparison; SLR, systematic literature review.

Although 16 individual studies were identified to report on relevant efficacy, safety, and HRQoL results for treatments for untreated or chemo-naïve ES-SCLC patients, the double-blind, Phase 3, randomised ASTRUM-005 trial was the only trial which provided a comparison of serplulimab plus chemotherapy (carboplatin plus etoposide) to chemotherapy (carboplatin plus etoposide). Other studies compared carboplatin plus etoposide to irinotecan plus cisplatin, topotecan plus cisplatin, irinotecan plus carboplatin, durvalumab plus platinum-etoposide, or atezolizumab plus carboplatin and etoposide.

The primary trials of interest for this appraisal were those of serplulimab. As such, studies were further screened during the preparation of this submission to exclude trials where there were no comparisons with serplulimab. Therefore, of the identified SLR clinical evidence base, the ASTRUM-005 trial is the sole source of relevant data on the clinical efficacy and safety of serplulimab plus chemotherapy (carboplatin plus etoposide) versus chemotherapy alone.

2.1 List of relevant clinical effectiveness evidence

The key clinical study to demonstrate the efficacy and safety of serplulimab as a treatment for adults with ES-SCLC, ASTRUM-005, is detailed in Table 4. ASTRUM-005 is a randomised, double-blind, placebo-controlled, global Phase 3 trial to compare the clinical efficacy and safety of serplulimab with chemotherapy versus placebo with chemotherapy in previously untreated patients with ES-SCLC (Cheng et al., 2022a). Furthermore, serplulimab was awarded an ESMO-MCBS score of 4 (compared with a score of 3 for atezolizumab and durvalumab in the treatment of ES-SCLC), highlighting the substantial benefit of treatment associated with serplulimab. (European Society for Medical Oncology, 2024)

Table 4: Clinical effectiveness evidence (ATRUM-005)

Study	ASTRUM-005
Study design	ASTRUM-005 was a randomised, double-blind, placebo-controlled, multicentre, Phase 3 study to compare the clinical efficacy, safety, and tolerability of serplulimab (recombinant humanised anti-PD-1 monoclonal antibody injection) with placebo in combination with chemotherapy in

Study	ASTRUM-005
	patients with previously untreated ES-SCLC, to obtain pharmacokinetic parameters, and to investigate the biomarkers related to efficacy.
Population	Previously untreated patients with ES-SCLC
Intervention(s)	Serplulimab and chemotherapy (carboplatin-etoposide)
Comparator(s)	Placebo and chemotherapy (carboplatin-etoposide)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Pivotal study evidencing the efficacy and safety of serplulimab for the treatment of patients with untreated ES-SCLC
Reported outcomes specified in the decision problem	The outcome measures to be considered are: • OS • PFS • Response rates • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	Additional outcomes included in the model: • Time-to-off treatment • Relative dose intensity

***Abbreviations**: ES-SCLC, extensive-stage small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival*

2.3. Summary of methodology of the relevant clinical effectiveness evidence

2.3.1. Trial design

ASTRUM-005 is a randomised, double-blind, placebo-controlled, global Phase 3 trial to compare the clinical efficacy and safety of serplulimab with chemotherapy versus placebo with chemotherapy in previously untreated patients with ES-SCLC (Cheng et al., 2024).

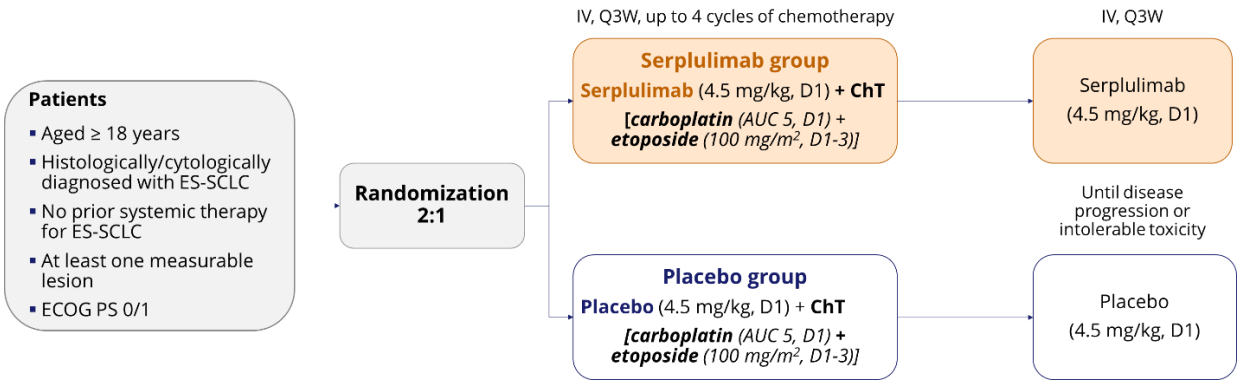
Figure 6 displays the study design of the ASTRUM-005 trial. Blinding was performed by the Statistical Unit during study treatment. The subjects, investigator, sponsor, and designated personnel were unaware of the randomisation and treatment allocation. This study was to be unblinded after the last subject completed the end of study visit or under the condition of interim analysis (see Table 9), as determined by the Independent Data Monitoring Committee (IDMC). During the study, unblinding was allowed only in case of emergency (when emergency rescue could only be conducted if the type of randomised drug received by the subject was known) or as required by regulatory authorities. Otherwise, blinding was to be maintained. All randomisation numbers were unblinded only after all data were entered into the

database, all data queries were resolved, and subjects were included in analysis sets.(Shanghai Henlius Biotech, 2024)

This submission includes efficacy data from the final data cutoff of the trial (7th May 2024) (Shanghai Henlius Biotech, 2024).

A total of 894 patients were screened, of which 309 were ineligible. This left a total of 585 patients to be randomised 2:1 to receive either 4.5 mg/kg of serplulimab (n=389) with chemotherapy or placebo with chemotherapy (n=196) every 3 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent, or other reasons specified in the trial protocol. All patients received 100 mg/m^2 of etoposide on Days 1, 2, and 3, and carboplatin within the area under the serum drug concentration time curve of 5 mg (mL/min (up to 750 mg) on Day 1 of each cycle for up to four cycles via IV infusions (every 3 weeks for up to 12 weeks).(Cheng et al., 2022a). Chemotherapy was administered for the first 4 cycles in combination with either serplulimab or placebo, after which serplulimab or placebo maintenance was continued (see Figure 6).

Figure 6: ASTRUM-005 study design



***Abbreviations**: AUC, area under the curve; ChT, chemotherapy; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; IV, intravenous; Q3W, every 3 weeks.*
***Source**: Cheng et al., 2022 (Cheng et al., 2022a)*

The end of the study, defined as the final analysis of OS, was to be performed when a target number of OS events (approximately 342) was observed and for final analysis the α was 0.046 (two-sided) based on the O'Brien-Fleming alpha spending function. Alternatively, the end of the study was defined as the date when all subjects enrolled completed the safety follow-up, 90 days after the end of treatment visit. (Shanghai Henlius Biotech, 2024)

2.3.2. Eligibility criteria

The inclusion criteria include the following: age ≥18 years; histologically or cytologically confirmed ES-SCLC according to the VALSG staging system; no prior systemic therapy for ES-SCLC; ≥1 measurable lesion(s) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1; ECOG PS score of 0 or 1; adequate organ function; and a life expectancy of 12 weeks or longer. Exclusion criteria included mixed-stage SCLC, active central nervous system metastases or carcinomatous meningitis, and autoimmune diseases. Patients with asymptomatic and stable brain metastases were included, defined as no evidence of new or enlarging brain metastases for ≥2 months confirmed by two radiological examinations at least 4 weeks apart after treatment and discontinuation of steroid use 3 days prior to study drug administration. Full details on exclusion and inclusion criteria are presented in Table 5. (Shanghai Henlius Biotech, 2024)

Table 5: Summary of inclusion and exclusion criteria for ASTRUM-005

Inclusion criteria	Exclusion criteria
• Voluntary participation in clinical studies; patients fully understood and were informed about the study and had signed the ICF; willingness to follow and ability to complete all trial procedures • Male or female aged ≥ 18 years at the time of signing the ICF • Histologically or cytologically diagnosed with ES-SCLC (according to the VALSG staging system) • No prior systemic therapy for ES-SCLC (including systemic chemotherapy, molecular targeted therapy, biological therapy, and other investigational therapies) • Patients who had received chemoradiotherapy for previous limited-stage SCLC had to have been treated with curative intent and had had a treatment-free interval of at least 6 months from the last course of chemotherapy, radiotherapy, or chemoradiotherapy to the diagnosis of extensive-stage SCLC • At least one measurable lesion as assessed by the independent radiology review committee (IRRC) according to RECIST 1.1 within 4 weeks prior to randomisation • Patients had to provide tumour tissues that met the requirements for the determination of PD-L1 expression levels. Patients were assessed for an evaluable PD-L1 expression category (negative: tumour proportion score (TPS) <1%, positive: TPS ≥1%, or not evaluable/not available) by the central laboratory for randomisation. • Prior antineoplastic therapy had been given ≥ 2 weeks before the first dose in this study and any previous treatment-related AEs had	• Histologically or cytologically confirmed mixed SCLC • Other active malignancies within 5 years or at the same time. Localised tumours that had been cured, such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder cancer, prostate carcinoma in situ, cervical cancer in situ, and breast cancer in situ were acceptable. • Patients who were preparing for or had received an organ or bone marrow transplant • Pleural or pericardial effusion requiring clinical intervention, or ascites • Patients with known or documented active central nervous system (CNS) metastases and/or carcinomatous meningitis at screening. However, the following subjects were allowed to be enrolled: 1) Subjects with asymptomatic brain metastases (i.e., no progressive CNS symptoms caused by brain metastases, no requirement for corticosteroids, and lesion size ≤ 1.5 cm) could be included but were required to receive regular brain imaging as a site of lesion. 2) Subjects with treated brain metastases which had been stable for at least 2 months (as confirmed by 2 radiological examinations at least 4 weeks apart after treatment of brain metastases), with no evidence of new or enlarging brain metastases, and with discontinued steroids 3 days prior to study drug administration. Stable brain metastases here had to be confirmed before the first dose of the study drug. • Subjects with spinal cord compression that had not been radically treated with surgery and/or radiotherapy • Patients with myocardial infarction within half a year before the first dose of the study drug, poorly controlled arrhythmia (including QTc intervals ≥ 450 ms for male patients and ≥ 470 ms for female patients) (QTc intervals were calculated by Fridericia's formula) • Class III to IV cardiac insufficiency according to the New York Heart Association classification or a left ventricular ejection fraction < 50% by cardiac colour Doppler

Inclusion criteria	Exclusion criteria
resolved to CTCAE Grade ≤ 1 (except for Grade 2 alopecia) • An ECOG PS score of 0 or 1 • An expected survival ≥ 12 weeks • Patients with prior denosumab use were able and willing to switch to bisphosphonate therapy for bone metastases starting prior to randomisation and throughout treatment • Normal major organ functions as defined by the following criteria (no blood transfusions, or treatment with albumin, recombinant human thrombopoietin, or colony-stimulating factor within 14 days prior to the first dose in this study) • Female patients had to meet one of the following conditions: ○ Menopause (defined as no menses for at least 1 year and no confirmed cause other than menopause), or ○ Surgically sterilised (removal of the ovaries and/or uterus), or ○ Of childbearing potential, but had to meet the following: ▪ Serum pregnancy test had to be negative within 7 days prior to randomisation, and ▪ Agreed to use birth control methods with an annual failure rate of <1% or maintain abstinence (avoid heterosexual intercourse) (from the signing of ICF to at least 6 months after the final dose of study drug) (birth control methods with an annual failure rate of <1% include bilateral tubal ligation, male sterilisation, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine contraceptive devices and copper containing intrauterine contraceptive devices or condoms), and ▪ Not breast-feeding • Male patients had to agree to abstinence (avoid heterosexual intercourse) or take contraception measures as follows: ○ Male patients with a pregnant partner or a partner of childbearing potential must remain abstinent or use a condom to prevent embryonic exposure during study treatment and for at least 6 months after the last dose of study drug. Periodic abstinence (e.g., contraceptive methods based on calendar day, ovulation, basal body temperature or post-ovulation) and external ejaculation are ineligible methods of contraception.	• Subject had uncontrolled or symptomatic hypercalcaemia (> 1.5 mmol/L ionised calcium or calcium > 12 mg/dL or corrected serum calcium > ULN) • Subject with peripheral neuropathy ≥ Grade 2 by CTCAE • Human immunodeficiency virus (HIV) infection, positive test for HIV antibody • Active or latent pulmonary tuberculosis • Subjects with previous and concurrent interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis and severe impaired pulmonary function that might interfere with the detection and management of suspected drug-related pulmonary toxicity, as judged by the investigator • Hepatitis B (positive test for HbsAg or HbcAb and positive test for HBV-DNA) or Hepatitis C (positive tests for HCV antibody and HCV-RNA). Hepatitis B and C co-infection (positive test for HbsAg or HbcAb and positive test for HCV antibody) • Known active or suspected autoimmune diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy were allowed to enrol. • Treatment with live vaccines and all COVID-19 vaccines (fully administered to the required number of doses) within 28 days prior to study drug administration; inactivated viral vaccines for seasonal influenza were allowed. • Subjects requiring treatment with systemic corticosteroids (> 10 mg/day prednisone efficacy dose) or other immunosuppressive drugs within 14 days prior to the first dose or during the study. However, in the absence of active autoimmune disease, subjects were allowed to use topical or inhaled steroids and adrenal hormone replacement therapy at doses equivalent to ≤ 10 mg/day of prednisone efficacy. • Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration or subjects with a positive reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 infection at randomisation. Subjects with a history of COVID-19 infection had to have a negative RT-PCR test prior to the first dose of the study drug. • Major surgery within 28 days prior to the first dose of the study drug, defined as surgeries requiring at least 3 weeks of recovery to be able to receive treatment in this study • Radical radiation therapy within 3 months prior to study medications • The subject had previously received other antibodies/drugs against immune checkpoints, such as PD-1, PD-L1, cytotoxic T-lymphocyte associated protein 4 (CTLA4) • Participation in any other ongoing clinical studies, or less than 14 days from the end of the previous clinical study treatment to the start of this trial • Known history of severe allergy to any monoclonal antibody • Known hypersensitivity to carboplatin or etoposide • Pregnant or lactating women • Known history of psychotropics abuse or drug abuse • In the judgement of the investigator, the subject had any other factors that might lead to a premature discontinuation

Abbreviations*: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; CNS, central nervous system; COVID-19, coronavirus disease 2019; CTLA4, cytotoxic T-lymphocyte-associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung*

cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HbsAg, hepatitis B surface antigen; HbcAb, hepatitis B core antibody; ICF, informed consent form; IRRC, independent radiology review committee; ITT, intention-to-treat; MAIC, matched adjusted indirect comparison; NYHA, New York Heart Association; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; QTc, corrected QT interval; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCLC, small cell lung cancer; TPS, tumor proportion score; ULN, upper limit of normal; VALSG, Veterans Administration Lung Study Group.

2.3.3. Settings and locations

The trial was conducted globally; patients enrolled from 114 hospital sites in six countries (China, Georgia, Poland, Russia, Turkey, and Ukraine) from 12th September 2019 (Cheng et al., 2022a). The last patient enrolled was on April 27th, 2021, and the data cutoff date was the 7th May, 2024 (Shanghai Henlius Biotech, 2024).

2.3.4. Trial drugs

The investigational product in this study was either serplulimab or placebo. Both were administered intravenously. Dosing regimen and preparation for each treatment cycle was every 3 weeks (every 21 days). The study drug was administered as follows:
Investigational product (serplulimab or placebo):

- Serplulimab: 4.5 mg/kg, intravenous (IV) infusion for 30 to 90 minutes, administered on Day 1 of each cycle, once every 3 weeks
- Placebo: IV infusion, administered on Day 1 of each cycle, once every 3 weeks (21 days)

The infusion of investigational product was completed between 30 minutes and 90 minutes if there was not any infusion reaction. The diluted drug solution was recommended to be used within 6 hours of preparation and was stable for up at 24 hours. The diluted drug solution needed to be stored at approximately 2-8 °C, for no longer than 24 hours, and kept from light if not used within 6 hours. (Shanghai Henlius Biotech, 2024)

- Other study drugs (chemotherapy):
- Etoposide: 100 mg/m^2, IV infusion, on Days 1, 2, and 3 of each cycle. On Day 1, etoposide was administered following infusion of carboplatin.

- Carboplatin: AUC = 5, up to a dose of 750 mg, IV infusion, on Day 1 of each cycle. The dose of carboplatin was calculated according to the following Calvert formula: $Dose\ of\ carboplatin\ (mg)\ =\ target\ AUC\ \times\ [(CrCl\ (mL/min)\ +\ 25)]$. CrCl was calculated according to the Cockroft-Gault formula on the basis of the subject's most recent serum creatinine and body weight.
    - Note: If CrCl calculated by the Cockroft-Gault formula was >125 mL/min, CrCl was to be calculated using an alternative formula in accordance with the standard of the study site or capped at 125 mL/min.

As mentioned previously, the combination of serplulimab or placebo with carboplatin and etoposide was administered in a 3-week treatment cycle. Carboplatin and etoposide were administered for a maximum of 4 cycles. In each 3-week cycle, the subjects were to receive an IV infusion of serplulimab or placebo, followed by the IV infusion of carboplatin, then etoposide on the first day of dosing with close monitoring of vital signs. The administration of serplulimab/placebo was blinded, while carboplatin and etoposide were openly administered. Subjects continued to receive etoposide on Days 2 and 3. The treatment continued until disease progression as assessed per RECIST 1.1, intolerable toxicity, discontinuation decided by the subject or the investigator, death, withdrawal of informed consent, pregnancy, noncompliance with protocol or procedure requirements, administrative reasons, or other reasons specified in the protocol, whichever occurred first. If a subject had the first disease progression and was clinically stable, and intended to receive second-line chemotherapy treatment subsequently (the selection of second-line chemotherapy may refer to the NCCN guidelines or the ESMO guidelines (Dingemans et al., 2021)), it was at the discretion of the investigator to continue treating the subject with blinded serplulimab or placebo assignment per protocol in addition to the second-line chemotherapy (Shanghai Henlius Biotech, 2024).

Subjects who met the following conditions could continue the treatment after appropriate discussion with the subject and obtaining the supplementary informed consent:

- Subjects who had received serplulimab or placebo in combination with chemotherapy, who might benefit from continuing serplulimab/placebo treatment despite progression, could be able to receive serplulimab or placebo therapy in the post-PD treatment.
- Subjects eligible for continued treatment in the post-PD treatment period, as judged by the investigator.
- The subject was requested to sign the supplementary informed consent form to receive investigational product with second-line chemotherapy.
- The subject was clinically stable, defined as:
    - No clinical signs and/or symptoms (including worsening of laboratory findings) that might indicate disease progression
    - A stable ECOG performance status score
    - No rapid disease progression or tumour progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression)

The dosing window was ±3 days from the scheduled date of administration (from the date of the first dose). (Shanghai Henlius Biotech, 2024)

Administration of drugs outside the dosing window was considered a delayed dose, and subsequent doses were to be administered according to the actual date of last administration. If chemotherapy was not used due to toxicity or other reasons in a certain cycle, it was not counted as the number of combined chemotherapy cycles. After completing four cycles of chemotherapy would not be continued, even if the subject did not meet the above criteria (Shanghai Henlius Biotech, 2024).

2.3.5. Baseline characteristics

Baseline characteristics were balanced between both groups. The median ages in the serplulimab and placebo groups were 63 and 62, respectively. In both groups most participants were male: 81.5% in the serplulimab group and 83.7% in the placebo group. Similarly, the Asian population was 67.4% in the serplulimab group and 70.9% in the placebo group. In both groups, most participants were former or current smokers, with 79.2% in the serplulimab group and 82.2% in the placebo group. Also, in both groups most participants were ECOG PS 1 (81.7% serplulimab, 83.7% placebo). There was a greater proportion of participants with liver metastases (25.4% serplulimab, 26.0% placebo) than brain metastases (12.9% serplulimab,

14.3% placebo). More details on patient baseline characteristics can be found in Table 6 (Shanghai Henlius Biotech, 2024).

Table 6: Summary of baseline characteristics of patients who participated in the ASTRUM-005 trial

Characteristics	Serplulimab group (n=389)	Placebo group (n=196)
Age at screening (years)		
Min, max	28, 76	31, 83
Mean (SD)	61.0 (8.64)	61.1 (8.75)
Median (Q1, Q3)	63.0 (56.0, 67.0)	62.0 (55.0, 68.0)
<65 years	235 (60.4)	119 (60.7)
Gender, n (%)		
Male, n (%)	317 (81.5)	164 (83.7)
Female, n (%)	72 (18.5)	32 (16.3)
Race, n (%)		
Asian	262 (67.4)	139 (70.9)
Non-Asian	127 (32.6)	57 (29.1)
Ethnicity, n (%)		
Hispanic or Latino	0	0
Not Hispanic or Latino	366 (94.1)	184 (93.9)
Other	23 (5.9)	12 (6.1)
Smoking status, n (%)		
Current	102 (26.2)	48 (24.5)
Former	206 (53.0)	113 (57.7)
Never	81 (20.8)	35 (17.9)
Baseline ECOG Performance Status Scale score [a]		
0	71 (18.3)	32 (16.3)
1	318 (81.7)	164 (83.7)
Prior anti-cancer therapy, n (%)		
Chemotherapy[2]	9 (2.3)	3 (1.5)
Other[3]	1 (0.3)	2 (1.0)
PD-L1 expression levels, n (%)		
Negative, TPS<1%	317/379 (83.6)	152/186 (81.7)
Positive, TPS≥1%	62/379 (16.4)	34/186 (18.3)
Brain metastases, n (%)	50 (12.9)	28 (14.3)
Liver metastasis, n (%)	99 (25.4)	51 (26.0)

***Notes**: [1]Carboplatin + etoposide; [2]11 patients received prior treatment for limited-stage SCLC (treatment-free interval ≥6 months). 1 patient received prior treatment for gastric cancer (>5 years ago); [3]Other treatments included herbal or Traditional Chinese Medicine and immunostimulant lentinan*
***Abbreviations**: CPS, continued positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; SOD, sum of diameters; TPS, tumour proportion score.*
***Source**: (Cheng et al., 2022a, Cheng et al., 2022b)*

2.3.6. Prior and concomitant therapy

The investigator could, at their discretion, administer any drugs that they deemed necessary for the treatment of subjects and not expected to interfere with the evaluation of the study drugs (i.e., the best supportive care). Prophylactic and other supportive treatments for nausea and vomiting could be given to subjects according to local medical practice before and after carboplatin and etoposide administration (Shanghai Henlius Biotech, 2024).

All concomitant medications (including start/end dates, total daily doses, and indications) had to be documented in the subject's source document and the corresponding section in the eCRF. Full details on medications that were permitted and not permitted during the trial are provided in Table 7 (Shanghai Henlius Biotech, 2024).

Table 7: Permitted and prohibited medications during the ASTRUM-005 trial

Medications or treatments prohibited during the study treatment period	Medications or treatments permitted during the study
• Any other systemic chemotherapy, radiotherapy, immunotherapy, biological therapy, molecular targeted therapy with anti-tumour effects or modern Chinese medicine preparations in anti-tumour therapy approved for marketing by National Medical Products Administration during the initial treatment period, immunomodulators with adjuvant anti-tumour effects (e.g., thymosin, lentinan, interleukin-12, etc.) that has anti-tumour effect. Local remission of an isolated lesion (other than the target lesion) was acceptable (e.g., local surgery or radiotherapy for bone metastasis). • Any other clinical trial drugs. Other immunosuppressive drugs, including but not limited to systemic glucocorticoids with a dose of more than 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-inhibitors, except for the following situations: ○ The use of immunosuppressive drugs to treat study treatment-related AEs ○ Where they were used for short-term prophylaxis in subjects who were expected to receive chemotherapy, and the use of glucocorticoids in subjects who had hypersensitivity reactions required by the prescription information on the drug ○ Used in subjects allergic to contrast agents ○ The use of inhaled, topical, and intranasal glucocorticoids was permitted. If clinical indications were present and the investigator considered it necessary to carry out disease management for the subject, the use of short-term glucocorticoids (e.g., to control COPD, radiotherapy, nausea, etc.) was permitted. • Live vaccine administration within 4 weeks prior to the first dose of study drug and during the study. Live vaccines included but were not limited to measles, epidemic parotitis, rubella, varicella, yellow fever, rabies, Bacillus Calmette-Guerin, typhoid fever vaccines. Injectable inactivated seasonal influenza vaccines were allowed, but intranasal live attenuated influenza vaccines were not allowed.	• Treatment for complications, AEs, or symptoms (including blood products, blood transfusions, infusions, antibiotics, anti-diarrhoeal medications), with the exception of medications/therapies that were expected to interfere (or interact) with the evaluation of the study • Antiemetics • Nutritional support • Medication or therapy necessary for previous disease

Abbreviations: *AE, adverse event*
Source*: ASTRUM-005 CSR (Shanghai Henlius Biotech, 2024)*

2.3.7. All reported outcomes in the ASTRUM-005 trial

The outcomes of ASTRUM-005 trial are presented in Table 8 and Section B2.7.

Table 8: All reported outcomes in the ASTRUM-005 trial

Objectives	Endpoints
Primary: to compare the clinical efficacy of serplulimab in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated	**Primary efficacy endpoint** • OS
	Key secondary efficacy endpoints • PFS, assessed by the IRRC based on RECIST 1.1 • PFS, assessed by the investigator based on RECIST 1.1 and the modified RECIST 1.1 for immune-based therapeutics (iRECIST) • PFS2, assessed by the investigator based on RECIST 1.1 • ORR, assessed by the IRRC and investigator based on RECIST 1.1 • DoR, assessed by the IRRC and the investigator based on RECIST 1.1

Objectives	Endpoints
patients with ES-SCLC	
Secondary: to compare the safety and tolerability of serplulimab in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated patients with ES-SCLC and evaluate pharmacokinetics (PK), immunogenicity, and biomarkers	**Safety** • AEs (including serious adverse events [SAEs]), laboratory tests (routine blood test, blood chemistry, coagulation function, urinalysis, myocardial function and thyroid function), 12-lead electrocardiogram (ECG), vital signs, and physical examination, etc.
	Pharmacokinetic (PK) endpoint • Concentration of serplulimab in serum
	Immunogenicity endpoint • serplulimab anti-drug antibody (ADA) positive rate
	Biomarker endpoint • Relationship between PD-L1 expression, MSI, TMB in tumour tissue and efficacy
	Quality of life assessment • EQ-5D-5L (5-level EQ-5D) scale, European Organisation for Research and Treatment of Cancer Quality of Life Scale (EORTC QLQ-C30) scale, and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13) scale
Exploratory: to determine the relationship between SCLC subtypes and the treatment outcome and to determine the biomarkers which potentially respond to serplulimab treatment	Screening biomarkers: achaete-scute homolog 1 (ASCL1), neurogenic differentiation 1(NEUROD1), pan cytokeratin (pan-CK), cluster of differentiation 8 (CD8), forkhead box P3 (FOXP3), PD-L1. To find panels of novel protein markers in circulating proteins in blood with the Olink ultra-sensitive proteomics platform. This study will focus on, (but not limited to) 14 protein biomarkers: leukaemia inhibitory factor, interleukin-6 (IL6), interleukin-8 (IL8), melanoma inhibitory activity, growth-differentiation factor 15 (GDF-15), PD-L1, mesenchymal-epithelial transition factor, epidermal growth factor receptor (EGFR), B-cell lymphoma-2 (BCL2), tumour protein p53 (TP53), L-Serine/L-Threonine kinase 11 (STK11), stromal cell-derived factor-1 (CXCL12), matrix metallopeptidase 9 (MMP9) and SLIT2-related protein (SLIT2).

Abbreviations*: ADA, anti-drug antibody; AEs, adverse events; DoR, duration of response; ECG, electrocardiogram; EORTC QLQ-LC13, Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Scale; ES-SCLC, end-stage small cell lung cancer; IRRC, Independent radiology review committee; ORR, Objective response rate; OS, overall survival; PFS, Progression-free survival; PK, Pharmacokinetic; RECIST, Response Evaluation Criteria; Response Evaluation Criteria for immune-based therapeutics (iRECIST); SAEs, serious adverse events; TMB, tumour mutation burden*
Source*: ASTRUM-005 CSR (Shanghai Henlius Biotech, 2024)*

2.3.8. Pre-planned subgroups

To assess the consistency of the study prespecified outcomes OS, PFS, and PFS2, subgroup analyses were conducted (Shanghai Henlius Biotech, 2024). The following subgroups were considered:

- Age (≥65 years versus <65 years)
- Sex (male versus female)
- Race (Asian versus non-Asian)
- Ethnicity (Hispanic or Latino versus non-Hispanic or Latino)
- Baseline ECOG performance status (0 versus 1)
- Baseline smoking status

- Baseline brain metastasis (yes versus no)

To explore the efficacy under different PD-L1 expression level, the following subgroups were examined:

- PD-L1 expression level based on TPSs (positive TPS ≥1% versus negative TPS < 1%)
- PD-L1 expression level based on combined positive score (CPS) (positive CPS ≥1% versus negative CPS < 1%)

Results of the non-Asian subgroup are provided as part of Appendix E.

2.3.9. Modified Delphi panel

A 2-round modified Delphi panel was conducted to gather expert clinical consensus on key areas of clinical uncertainty in order to support the upcoming UK and Irish HTA submissions in ES-SCLC. More detail is provided in Appendix M.

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

A summary of the statistical analysis of the ASTRUM-005 trial is shown in Table 9.

Table 9: Summary of the statistical analysis carried out in the ASTRUM-005 trial.

Hypothesis objective	***Primary efficacy endpoint*** • OS ***Secondary efficacy endpoints*** • PFS, assessed by the IRRC based on RECIST 1.1 • PFS, assessed by the investigator based on RECIST 1.1 and the modified RECIST 1.1 for immune-based therapeutics (iRECIST) • PFS2, assessed by the investigator based on RECIST 1.1 • ORR, assessed by the IRRC and investigator based on RECIST 1.1 • DoR, assessed by the IRRC and the investigator based on RECIST 1.1
Interim analysis	The interim analysis was conducted when 66% (approximately 226) of OS events were observed (actual 246 OS events). The efficacy results at interim analysis met the prespecified stopping boundary, as determined by the IDMC. Therefore, the sponsor performed a database lock (data cutoff: 22nd October 2021), unblinded the study, and conducted statistical analyses to evaluate the efficacy and safety of serplulimab in combination with chemotherapy versus placebo in combination with chemotherapy in patients with previously untreated ES-SCLC.
Statistical analysis	***Primary efficacy analyses*** This study was designed to test for superiority of serplulimab to placebo. For the time-to-event endpoints (e.g., PFS, OS), the null hypothesis (H_0) and the alternative hypothesis (H_1) could be expressed as follows: H_0: $S_A(t) = S_B(t)$ for all t H_1: $S_A(t) \neq S_B(t)$ for some t where SA(t) and SB(t) are the rates of time-to-event for Arm A (serplulimab + chemotherapy) and Arm B (placebo + chemotherapy) at time $t, t > 0$. The comparison of the time-to-event between the two arms was performed by a two-sided stratified log-rank test and the prespecified stratification factors. Time-to-event distributions were estimated using the Kaplan-Meier product-limit method. If median event time was evaluated, the corresponding two-sided 95% CI was to be computed using the Brookmeyer-Crowley approach. The standard error of the survival rate at a fixed time point (e.g., PFS rate at 6 months) was estimated using Greenwood's

	formula. The HR and its 95% CI were estimated by stratified Cox proportional hazards model. Efron's method was used to handle ties. All CIs were presented to one more decimal place than the point estimate. For binomial proportions endpoints (e.g., ORR), considering the stratified randomisation, the stratified Cochran-Mantel-Haenszel method is used to test the between-group variation in the ORR and to estimate the odds ratio and its 95% CI. For each single arm, the 95% CI for the proportion was derived using Clopper-Pearson method. Considering the stratified randomisation, the stratified Cochran-Mantel-Haenszel method was used to test the between-group variation in the ORR and to estimate the odds ratio and its 95% CI. The estimates for ORR and 95% Clopper-Pearson CI were presented. Efficacy analyses were performed primarily on the intention to treat population (ITT), supported by the per protocol set (PPS). ***Safety*** Safety analyses were primarily based upon summaries of the data rather than formal statistical inference. All safety summaries and analyses used the Safety Set. ***Pharmacokinetics and immunogenicity analysis*** Serplulimab concentrations and ADA status were listed by individual subjects and summarised in tables and figures. The accumulation index (RCmax* and RCtrough*, ratio of serplulimab drug cumulation) following multiple serplulimab dosing were calculated by the nominal sampling time, listed, and summarised by descriptive statistics. ***Biomarker analysis*** The OS and PFS assessed by the IRRC and by the investigator based on RECIST 1.1 were analysed based on their relationship with biomarkers.
Sample size	The sample size was estimated based on the assumption that the median OS for treatment with placebo with chemotherapy (carboplatin and etoposide) was 10 months and the HR of (serplulimab with chemotherapy) group versus the placebo group was 0.7. It was further assumed that when the enrolment period was 24 months and the whole study period was 34 months, to achieve a confidence level of 85% at an overall significance level of $\alpha = 0.05$ (two-sided), at least 342 OS events had to have been observed. Considering a dropout rate of 20%, a total of 567 subjects (378 in treatment arm and 189 in control arm) needed to be enrolled in the 2 arms.
Missing data handling	For an AE where the event date was partial or missing, the event was to be assumed to be treatment-emergent, unless there was clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study treatment. For other unspecified analyses, missing data were not imputed. In the situation where the event date was partial or missing, the date was to appear partial or missing in the listings
Participant discontinuation or withdrawal from the study	***Management of premature discontinuations*** The reasons for premature discontinuations had to be documented in the electronic case report form (eCRF) by the investigator. All subjects who discontinued the trial prematurely (except patients who withdrew informed consent) and agreed to continued follow-up of associated clinical outcome information, were to undergo an end of treatment (EOT) visit and be followed up for safety and survival. Subjects who discontinued the trial for reasons other than disease progression and agreed to continue follow-up of associated clinical outcome information were to be radiologically followed up until disease progression, withdrawal of informed consent, death, or start of a new antineoplastic therapy. All AEs present at the time of discontinuation had to be followed up until the outcomes of the AEs. In case of an enrolled subject's withdrawal for any reason, no subject replacement was permitted. ***Participant discontinuation/withdrawal*** A subject could withdraw from the study at any time at his/her own request or could be withdrawn at any time at the discretion of the investigator for safety, behavioural, or administrative reasons. If the subject withdrew consent for disclosure of future information, the sponsor could retain and continue to use any data collected before such a withdrawal of consent. If a subject withdrew from the study, he/she could request destruction of any samples taken and not tested, and the investigator had to document this in the site study records. If a subject developed fever or symptoms suspected of being a result of COVID-19 during the study, they were to be instructed to report them to their regular healthcare provider or follow the instructions for suspected COVID-19 cases per their local health authority. A subject was to discontinue treatment based on discussion with the sponsor and Medical Monitor under the following circumstances: any suspected or confirmed COVID-19 case was to be immediately discontinued from study treatment for up to 12 weeks after the last study drug administration; subjects who recovered from the infection within 12 weeks from the last study drug administration could continue treatment following sponsor's confirmation. ***Loss to follow-up***

	A subject was to be considered lost to follow-up if they repeatedly failed to return for scheduled visits and was unable to be contacted by the study site. The following actions had to be taken if a subject failed to return to the clinic for a required study visit: • The site was required to attempt to contact the subject and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wished to and/or should continue in the study. • If a subject was deemed lost to follow-up, the investigator or designee was required to make every effort to regain contact with the subject (where possible, three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts had to be documented in the subject's medical record/CRF. • If the subject continued to be unreachable, he/she was to be considered to have withdrawn from the study.

Notes: *Red cell maximum concentration [RCmax] is the highest concentration of a drug measured in red blood cells within a dosing interval, and the red cell trough concentration [RCtrough] which is the lowest concentration of the drug in red blood cells before the next dose is administered*
Abbreviations*: AEs, adverse events; CI, confidence interval; CRD, case report form; eCRD, electronic case report form; DoR, duration of response; ES-SCLC, end-stage small cell lung cancer; EOT, end of treatment; IRRC, independent radiology review committee; ITT, intention to treat population; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, Progression-free survival; PK, Pharmacokinetic; PPS, Per Protocol Set; RECIST, Response Evaluation Criteria; Response Evaluation Criteria for immune-based therapeutics (iRECIST); SAEs, serious adverse events.*
Source*: ASTRUM-005 CSR (Shanghai Henlius Biotech, 2024)*

2.4.1. Description of the study populations in ASTRUM-005

Table 10 contains a description of all the analysis sets in ASTRUM-005.

Table 10: The analysis sets in the ASTRUM-005 trial

Population	Definition
Enrolled	All participants who signed the ICF (including screening failures)
ITT	Comprised of all subjects who were randomised. Statistical analyses were based on study intervention groups as per randomisation, irrespective of the study intervention actually received. The ITT population served as the primary population of efficacy assessment in this study. The ITT population was analysed based on planned treatment arms.
PPS	Comprised a subset of the ITT. The PPS consisted of all randomised subjects without any major protocol deviation that significantly impacted the primary efficacy. The PPS was used to demonstrate robustness of results for the primary efficacy endpoint. The protocol deviations that significantly affect evaluation for the primary efficacy were determined based on a blinded data review prior to interim/final database lock. Analyses for the PPS were based on actual treatment received. PPS analysis supplements the ITT analysis as supporting analysis to demonstrate robustness of results for the efficacy endpoint.
Safety Set	All subjects who received at least one dose of study intervention. Subjects in the Safety Set were analysed according to the study intervention they actually received. The Safety Set was the primary population for safety endpoint analysis.
PKS	Consisted of all participants who received at least one dose of serplulimab with at least one measurable post-dose concentration at scheduled PK time points without any major protocol deviation that could impact the PK assessment significantly. The PKS was used for PK analysis.

Abbreviations*: ICF, informed consent form; ITT, intention to treat; PFS, progression-free survival; PK, pharmacokinetics; PKS, Pharmacokinetics Set; PPS, Per Protocol Set*
Source*: ASTRUM-005 CSR (Shanghai Henlius Biotech, 2024)*

2.4.2. Patient disposition in ASTRUM-005

Subject disposition is summarised in Table 11. A total of 894 patients were screened for study participation, 309 of which were screen failures, resulting in 585 eligible subjects who were randomised. Of these subjects, 389 were randomly assigned to

the serplulimab with carboplatin and etoposide group (hereafter referred to as the serplulimab group), and 196 were randomly assigned to the placebo with carboplatin and etoposide group (hereafter referred to as the placebo group) (Shanghai Henlius Biotech, 2024).

As of the cutoff date of 7th May 2024, [redacted] subjects had discontinued the study treatment. The most common reason for discontinuing study treatment was progressive disease, which occurred in a higher proportion of subjects in the placebo group ([redacted] than in the serplulimab group ([redacted] Furthermore, [redacted] in the placebo group and [redacted] in the serplulimab group withdrew from study treatment, and [redacted] in the placebo group and [redacted] in the serplulimab group discontinued study treatment due to AEs. As of the data cutoff date, 89 (15.2%) subjects had completed the study, and 496 (84.8%) subjects had discontinued the study. The most common reason for discontinuing the study was death (76.4%), which occurred in a higher proportion of subjects in the placebo group (84.7%) than in the serplulimab group (72.2%) (Shanghai Henlius Biotech, 2024).

A total of [redacted] subjects in the serplulimab group and [redacted] subjects in the placebo group received serplulimab/placebo treatment after the first disease progression (Shanghai Henlius Biotech, 2024).

Table 11: Summary of participant disposition

	Serplulimab group	Placebo group	Total
Screened, n	-	-	894
Screen fail	-	-	309
Randomised, n	389	196	585
Did not receive any study treatment, n (%)	[redacted]	[redacted]	[redacted]
Treatment ongoing, n (%)	[redacted]	[redacted]	[redacted]
Treatment discontinued, n (%)	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Poor compliance of study drug administration	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Study terminated by sponsor	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Signed inform consent for post-PD treatment, n (%)	[redacted]	[redacted]	[redacted]

	Serplulimab group	Placebo group	Total
Ever received treatment (serplulimab/placebo) after progressive disease, n (%)	[redacted]	[redacted]	[redacted]
Discontinued the study, n (%)	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]
Study terminated by sponsor	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Completed study	[redacted]	[redacted]	[redacted]

***Abbreviations**: PD, progressive disease*
***Source**: ASTRUM-005 CSR Table 10 (Shanghai Henlius Biotech, 2024)*

2.5. Critical appraisal of the relevant clinical effectiveness evidence

Please see Appendix B for the complete quality assessment for the ASTRUM-005 trial. Table 12 assesses the relevant clinical effectiveness evidence, using criteria taken from the NICE User Guide. For more information, please see Appendix D.

Table 12: Quality assessment for ASTRUM-005

Quality assessment criteria	Response
Was the method used to generate random allocations adequate?	Yes
Was the allocation adequately concealed?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Unclear – double-blinded
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – methods for missing data imputation appropriate
Did the study authors declare any conflicts of interest?	Yes – authors employees of Shanghai Henlius Biotech, Inc.

***Source**: Appendix D.*

2.6. Clinical effectiveness results of the relevant studies

SUMMARY

Serplulimab plus chemotherapy showed consistent benefits in OS, PFS, ORR, and DoR outcomes compared to placebo plus chemotherapy. Data from the Phase 3, placebo-controlled ASTRUM-005 trial shows that serplulimab plus chemotherapy:

- Provides a significant improvement in OS for patients with ES-SCLC vs those treated with placebo plus chemotherapy (15.8 months vs 11.1 months, HR=0.60 [95%CI: 0.49, 0.73], p<0.001)

- Significantly reduces the risk of progressive disease or death for patients with ES-SCLC vs those treated with placebo plus chemotherapy by 53% (5.8 months vs 4.3 months, HR=0.47 [95% CI: 0.38, 0.57; p<0.001])
- Provides a significant improvement in mDOR for patients with ES-SCLC vs those treated with placebo plus chemotherapy who had a confirmed objective response (6.8 months vs 4.17 months, HR=0.45 (95%CI: 0.35, 0.58), p<0.001)
- Provides a numerical improvement in confirmed ORR according to RECIST 1.1 by IRRC for patients with ES-SCLC vs those treated with placebo plus chemotherapy (68.9% vs 58.7%, OR=1.58 [95% CI: 1.10, 2.26])
- Provides a numerical improvement in patient quality of life at Week 18 vs baseline for the QLQ-C30 functional and symptom domains, QLQ-LC13 symptom domains, and EQ-5D-5L visual analogue scale (VAS), which was similar to that of placebo plus chemotherapy
- Provides a numerical improvement in patient quality of life at Week 18 vs baseline for the 'pain in other parts' symptom domain of QLQ-C30, QLQ-LC13, and EQ-5D-5L, which was significantly greater than that seen with placebo plus chemotherapy (Least squares mean change -6.37 [95% CI: -11.59, -1.15; p=0.0170])

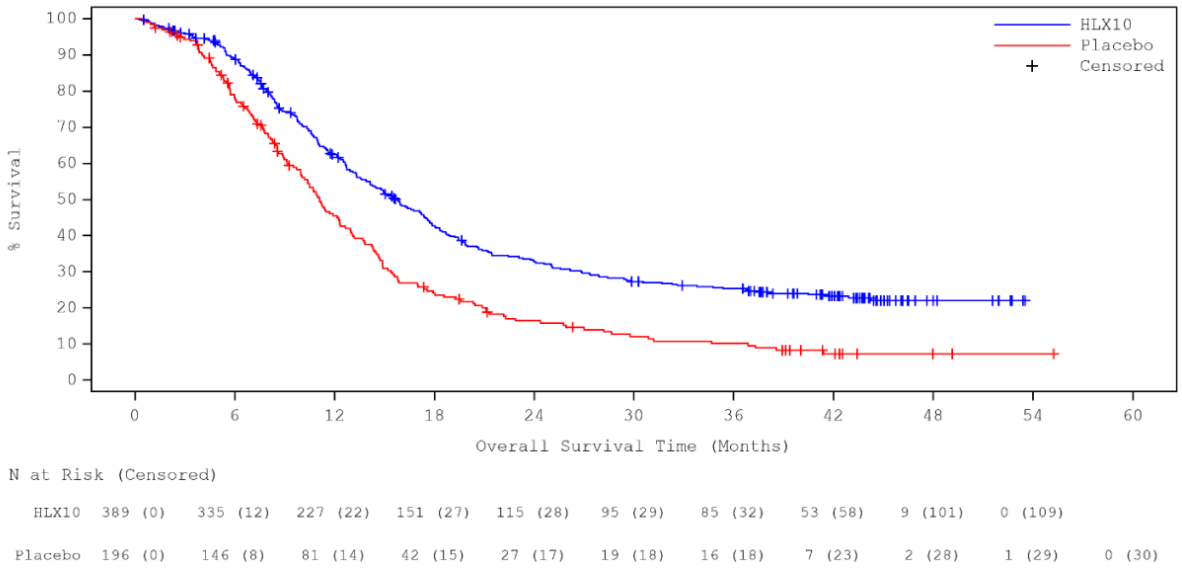
2.6.1. Primary endpoint, meaningful improvements in overall survival: Serplulimab with carboplatin and etoposide significantly improves OS compared with carboplatin and etoposide alone among patients with previously untreated ES-SCLC

SCLC (made up of LS-SCLC and ES-SCLC) is the most aggressive form of lung cancer (Dingemans et al., 2021), characterised by an exceptionally high proliferative rate and a strong propensity for early metastasis (Basumallik and Agarwal, 2023, Dingemans et al., 2021). ES-SCLC has a particularly poor prognosis, with a median survival of only 4 months, and less than 5% of patients surviving for 5 years after diagnosis (Khakwani et al., 2014). Being such an aggressive disease with such a poor prognosis means that any potential to extend OS is of critical importance to patients.

The OS benefit of serplulimab treatment compared to placebo was sustained at the end of study analysis data cutoff (7th May 2024), which had a median follow-up of 42.38 months. Serplulimab treatment had an OS benefit of 15.77 months versus 11.10 months for placebo (HR=0.60 [95% CI: 0.50, 0.73; p<0.001]). The OS rate at 1 year was superior for the serplulimab group, with a survival rate of 62.5% (95% CI 57.3%, 67.2%) versus 45.4% (95% CI: 38.1%, 52.5%) for the placebo group. At 2 years, the increase in survival rates for the serplulimab group versus placebo was sustained, with an OS rate of 32.7% (95% CI: 27.9%, 37.6%) for the serplulimab group versus 16.4% for the placebo group (95% CI: 11.4%, 22.3%) (Figure 7 and Table 63). At 3 years, the increase in survival rates for the serplulimab group versus

placebo again was sustained, with an OS rate of 25.3% (95% CI: 20.9%, 29.9%) for the serplulimab group versus 10.1% for the placebo group (95% CI: 6.2%, 15.3%). Finally, at 4 years, serplulimab again saw sustained increases in OS rates: 21.9% (95% CI: 17.6%, 26.6%) versus 7.2% (95% CI: 3.8%, 12.1%) for the placebo group (Shanghai Henlius Biotech, 2024).

Figure 7: Overall survival in the intention to treat population (data cutoff: 7th May 2024)



Note: HLX10 is serplulimab's previous name.
Abbreviations: *CI, confidence interval; HR, hazard ratio; ITT, intention to treat; mo, month; OS, overall survival; yr, year.*
Source*: ASTRUM-005 CSR (Shanghai Henlius Biotech, 2024)*

Table 13: Primary efficacy analysis: OS (ITT)

	Serplulimab-chemotherapy (n=389)	**Placebo-chemotherapy (n=196)**
Events (deaths)[a], n (%)	280 (72.0)	166 (84.7)
Median OS (95% CI)[b], mo	15.8 (13.9, 17.4)	11.1 (10.0, 12.4)
Stratified HR (95% CI)[c]; p-value[d]	0.60 (0.49, 0.73); p<0.001	
1-yr OS rate (95% CI)[e]	62.5 (57.3, 67.2)	45.4 (38.1, 52.5)
2-yr OS rate (95% CI) [e]	32.7 (27.9, 37.6)	16.4 (11.4, 22.3)
3-yr OS rate (95% CI) [e]	25.3 (20.9, 29.9)	10.1 (6.2, 15.3)
4-yr OS rate (95% CI) [e]	21.9 (17.6, 26.6)	7.2 (3.8, 12.1)

Notes: *aThe OS for patient 11009001 in the serplulimab group is censored since the month of death date is missing. b The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS. c Stratification factors: PD-L1 expression level (TPS < 1%, TPS ≥ 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years). The HR and its 95% CI were estimated by Cox proportional hazards model. Efron's method was used to handle ties. d The comparison of OS between the two arms was performed by a two-sided stratified log-rank test. e The standard error of the survival rate was calculated using Greenwood's formula.*
Abbreviations*: CI, confidence interval; ITT, intention to treat; OS, overall survival; PD-L1, programmed death-ligand-1; TPS, tumour proportion score; yr, year.*
Source: *ASTRUM-005 CSR Table 61 (Shanghai Henlius Biotech, 2024)*

2.6.2. Secondary endpoints: Serplulimab with carboplatin and etoposide demonstrated improvement in clinical outcomes (mPFS, PFS2 ORR,

DoR) compared with carboplatin and etoposide alone among patients with previously untreated ES-SCLC

There were 13 secondary outcomes, including PFS, ORR, and DoR (all three endpoints were assessed by both an IRRC and by the investigators using version 1.1 of RECIST), as well as the relationship between PD-L1 expression and serplulimab efficacy. (Cheng et al., 2022a)

2.1.1.1 Progression-free survival

The median PFS (mPFS) assessed by the IRRC was longer in the serplulimab group (5.82 months [95% CI: 5.55, 6.93]) than in the placebo group (4.34 months [95% CI: 4.21, 4.43]) with an HR of 0.47 (95% CI: 0.38, 0.57; p<0.001). Thus, treatment with serplulimab reduced the risk of progressive disease or death by 53%.

The PFS rate was [redacted] and [redacted] in the serplulimab and placebo groups, respectively, at 1 year; [redacted] and [redacted] respectively, at 2 years; and [redacted] and [redacted] respectively, at 3 years. Full results of the secondary outcomes, assessed by the independent radiology group, can be found in **Error! Reference source not found.** and Table 64. (Shanghai Henlius Biotech, 2024)

[redacted]

Note: HLX10 is serplulimab's previous name.
Abbreviations: *IRRC, Independent Radiology Review Committee; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors*
Source: *ASTRUM-005 CSR Figure 66 (Shanghai Henlius Biotech, 2024)*

Table 14: Secondary outcomes assessed by the independent radiology review committee

	Serplulimab (n=389)	Placebo (n=196)
PFS events, n (%)[a]	[redacted]	[redacted]
Median PFS (95% CI), mo	5.82 (5.552, 6.932)	4.34 (4.205, 4.435)
Stratified HR (95% CI); p-value	0.47 (0.380, 0.572); p<0.001	
1-yr PFS rate (95% CI)	[redacted]	[redacted]
2-yr PFS rate (95% CI)	[redacted]	[redacted]
3-yr PFS rate (95% CI)	[redacted]	[redacted]
4-yr PFS rate (95% CI)	[redacted]	[redacted]
Confirmed ORR, n (%) [95% CI]	[redacted]	[redacted]
Median DoR (95% CI), mo	[redacted]	[redacted]
Stratified HR (95% CI); p-value	[redacted]	

Notes: *[a] PFS assessed per Response Evaluation Criteria in Solid Tumours version 1.1*
Abbreviations: *CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; mo, month; NE, not evaluated; PD, progressive disease; PR, partial response; ORR, objective response rate; PFS, progression-free survival.*
Source: *ASTRUM-005 CSR, Supplementary Table 14.2.2.3.1 (p1313) (Shanghai Henlius Biotech, 2024)*

2.1.1.2 Progression-free survival 2

PFS2 was defined as the time from randomisation to second or subsequent objective tumour progression on next-line treatment or death from any cause. If a subject died without any progression event, the subject's PFS and PFS2 event dates were equivalent. If a subject died after his/her primary PFS event but prior to the initiation of subsequent anti-cancer therapy, the date of death was still considered the PFS2 event. A subject who was alive and for whom a second PD had not been observed was censored on the last tumour assessment date. PFS2 was analysed using the same method as the analysis of PFS (analysis set: ITT, PPS) (Shanghai Henlius Biotech, 2024).

The median PFS2 was [redacted] (95% CI: [redacted]) months in the serplulimab group and [redacted] (95% CI: [redacted]) months in the placebo group. The stratified HR was [redacted] (95% CI: [redacted]). Investigators' analysis of the PPS of PFS2 according to RECIST 1.1 showed results consistent with the ITT analysis (Shanghai Henlius Biotech, 2024).

2.1.1.3 Objective response rate: Unconfirmed

Tumour assessment results according to RECIST 1.1 at each cycle included overall response, response of target lesion, sum of tumour diameter, response of non-target lesion, and response of new lesion. Tumour response according to iRECIST was assessed by investigators at each visit (Shanghai Henlius Biotech, 2024).

The unconfirmed ORR refers to the proportion of patients whose tumours had decreased in size (partial response) or disappeared entirely (complete response), but for whom the responses had not yet been confirmed by follow-up evaluations. Unconfirmed best overall responses according to RECIST 1.1 by IRRC are summarised in Table 15. In the serplulimab group, [redacted] subjects and [redacted] subjects had unconfirmed CR and PR, respectively, compared with [redacted] and [redacted] in the placebo group. The unconfirmed ORR was [redacted] in the serplulimab group and [redacted] in the placebo group, resulting in an odds ratio of [redacted] (95% CI: [redacted]). (Shanghai Henlius Biotech, 2024)

Table 15: Unconfirmed best overall response according to RECIST 1.1 by IRRC (ITT)

	Serplulimab (n=389)	Placebo (n=196)
Unconfirmed best overall response, n (%)		
CR	[redacted]	[redacted]

	Serplulimab (n=389)	Placebo (n=196)
PR	[redacted]	[redacted]
SDi	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE or NA	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Unconfirmed ORR (CR + PR), n (%) [a]	[redacted]	[redacted]
95% CI (%) [b]	[redacted]	[redacted]
Odds Ratio (95% CI) [c]	[redacted]	

Notes: *[a] stratification factor: PD-L1 expression level (TPS < 1%, TPS ≥ 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years). [b] Clopper-Pearson method. [c] The odds ratio of ORR and its 95% CI were estimated by the Cochran-Mantel-Heanszel statistics.*
Abbreviations: *CI, confidence interval; CR, complete response; IRRC, Independent Radiology Review Committee; ITT, intention to treat; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SDi, stable disease.*
Source: *ASTRUM-005 CSR Table 64 (Shanghai Henlius Biotech, 2024).*

Unconfirmed best overall responses according to RECIST 1.1 by the investigators are summarised in Table 16. In the serplulimab group, [redacted]) and [redacted] subjects had unconfirmed CR and PR, respectively, compared with [redacted] and [redacted] in the placebo group. The unconfirmed ORR was [redacted] in the serplulimab group and [redacted] in the placebo group, resulting in an odds ratio of [redacted]) (Shanghai Henlius Biotech, 2024).

Table 16: Unconfirmed best overall response according to RECIST 1.1 by investigators (ITT)

	Serplulimab (n=389)	Placebo (n=196)
Unconfirmed best overall response, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SDi	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE or NA	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Unconfirmed ORR (CR + PR), n (%) [a]	[redacted]	[redacted]
95% CI (%) [b]	[redacted]	[redacted]
Odds ratio (95% CI) [c]	[redacted]	

Notes: *[a] Stratification factor: PD-L1 expression level (TPS < 1%, TPS ≥ 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years). [b] Clopper-Pearson method. [c] The odds ratio of ORR and its 95% CI were estimated by the Cochran-Mantel-Heanszel statistics.*
Abbreviations: *CI, confidence interval; CR, complete response; IRRC, Independent Radiology Review Committee; ITT, intention to treat; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SDi, stable disease.*
Source: *ASTRUM-005 CSR Table 65 (Shanghai Henlius Biotech, 2024)*

The results of the unconfirmed best overall response analyses on the PPS were consistent with the ITT analysis set (Shanghai Henlius Biotech, 2024).

*2.1.1.4 **Objective response rate: Confirmed***

The confirmed ORR is the percentage of patients who showed a measurable, sustained reduction in tumour size, either partially or completely. It required that an initial response be validated through follow-up assessments, ensuring the effect was not temporary. Confirmed best overall responses according to RECIST 1.1 by IRRC

are summarised in Table 17. In the serplulimab group, 9 (2.3%) subjects and 259 (66.6%) had confirmed CR and PR, respectively, compared with 0 and 115 (58.7%) in the placebo group. The confirmed ORR was 68.9% in the serplulimab group and 58.7% in the placebo group, resulting in an odds ratio of 1.58 (95% CI: 1.099, 2.260) (Shanghai Henlius Biotech, 2024).

Table 17: Confirmed best overall response according to RECIST 1.1 by IRRC (ITT)

	Serplulimab (n=389)	Placebo (n=196)
Confirmed best overall response, n (%)		
CR	9 (2.3)	0
PR	[redacted]	[redacted]
SDi	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE or NA	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Confirmed ORR (CR + PR), n (%) [a]	268 (68.9)	115 (58.7)
95% CI (%) [b]	[redacted]	[redacted]
Odds ratio (95% CI) [c]	1.58 (1.099, 2.260)	

***Notes**: [a] Stratification factor: PD-L1 expression level (TPS < 1%, TPS ≥ 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years). [b] Clopper-Pearson method. [c] The odds ratio of ORR and its 95% CI were estimated by the Cochran-Mantel-Heanszel statistics.*
***Abbreviations**: CI, confidence interval; CR, complete response; IRRC, Independent Radiology Review Committee; ITT, intention to treat; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SDi, stable disease.*
Source: *ASTRUM-005 CSR Table 66 (Shanghai Henlius Biotech, 2024)*

Confirmed best overall responses according to RECIST 1.1 by the investigators are summarised in Table 18. In the serplulimab group, [redacted] subjects and [redacted] had confirmed CR and PR, respectively, compared with [redacted] and [redacted] in the placebo group. The confirmed ORR was [redacted] in the serplulimab group and [redacted] in the placebo group, resulting in an odds ratio of [redacted] (95% CI: [redacted]). (Shanghai Henlius Biotech, 2024)

Table 18: Confirmed best overall response according to RECIST 1.1 by investigators (ITT)

	Serplulimab (n=389)	Placebo (n=196)
Confirmed best overall response, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SDi	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE or NA	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Confirmed ORR (CR + PR), n (%) [a]	[redacted]	[redacted]
95% CI (%) [b]	[redacted]	[redacted]
Odds Ratio (95% CI) [c]	[redacted]	

***Notes**: [a] Stratification factor: PD-L1 expression level (TPS < 1%, TPS ≥ 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years). [b] Clopper-Pearson method. [c] The odds ratio of ORR and its 95% CI were estimated by the Cochran-Mantel-Heanszel statistics.*
***Abbreviations**: CI, confidence interval; CR, complete response; IRRC, Independent Radiology Review Committee; ITT, intention to treat; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SDi, stable disease.*
Source: *ASTRUM-005 CSR Table 67 (Shanghai Henlius Biotech, 2024)*

2.1.1.5 Duration of response – unconfirmed

The Kaplan-Meier curve of response over time in patients who had an unconfirmed objective response according to RECIST 1.1, as assessed by IRRC, is displayed in **Error! Reference source not found.**. The median DoR in patients who had an u nconfirmed objective response was [redacted] (95% CI: [redacted]) months in the serplulimab group and [redacted] (95% CI: [redacted]) months in the placebo group. The stratified HR was [redacted] (95% CI: [redacted]). (Shanghai Henlius Biotech, 2024)

[redacted]

***Notes**: DoR was derived from patients who had an unconfirmed objective response. HLX10 is serplulimab's previous name.*
***Abbreviations**: IRRC, Independent Radiology Review Committee; ITT, intention to treat; RECIST, Response Evaluation Criteria in Solid Tumors.*
***Source**: ASTRUM-005 CSR Figure 84 (Shanghai Henlius Biotech, 2024)*

The Kaplan-Meier curve of response over time in patients who had an unconfirmed objective response according to RECIST 1.1, as assessed by investigators, is displayed in **Error! Reference source not found.**. The median DoR in patients who h ad an unconfirmed objective response was [redacted] (95% CI: [redacted]) months in the serplulimab group and [redacted] (95% CI: [redacted]) months in the placebo group. The stratified HR was [redacted] (95% CI: [redacted]) (Shanghai Henlius Biotech, 2024).

[redacted]

***Notes**: DoR was derived from patients who had an unconfirmed objective response. HLX 10 is serplulimab's previous name.*
***Abbreviations**: IRRC, Independent Radiology Review Committee; ITT, intent to treat; RECIST, Response Evaluation Criteria in Solid Tumors.*
Source: *ASTRUM-005 CSR Figure 85 (Shanghai Henlius Biotech, 2024)*

2.1.1.6 Duration of response: Confirmed

DoR in patients who had a confirmed objective response according to RECIST 1.1, as assessed by IRRC

The median DoR in patients who had a confirmed objective response according to RECIST 1.1 as assessed by IIRC was 6.8 (95% CI: 5.52, 8.35) months in the serplulimab group and 4.17 (95% CI: 3.06, 4.21) months in the placebo group. The stratified HR was 0.45 (95% CI 0.35, 0.58; p<0.001) (Shanghai Henlius Biotech, 2024).

DoR in patients who had a confirmed objective response according to RECIST 1.1, as assessed by investigators

The median DoR in patients who had a confirmed objective response according to RECIST 1.1 as assessed by the investigators was [redacted] (95% CI: [redacted]) months in the serplulimab group and [redacted] (95% CI: [redacted]) months in the placebo group. The stratified HR was [redacted] (95% CI: [redacted]) (Shanghai Henlius Biotech, 2024).

2.6.3. Patient-reported outcomes: PROs were not adversely impacted, and pain in other parts was significantly improved for patients treated with serplulimab (Cheng et al., 2024). The time to deterioration (TTD) was comparable between the treatment arms

Three questionnaires were used to evaluate patient-reported outcomes (PROs): the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), which assesses both functional and symptom domains; the EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13), which focuses on lung cancer-specific symptoms; and the European Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L), which measures overall health status via a VAS (Cheng et al., 2024).

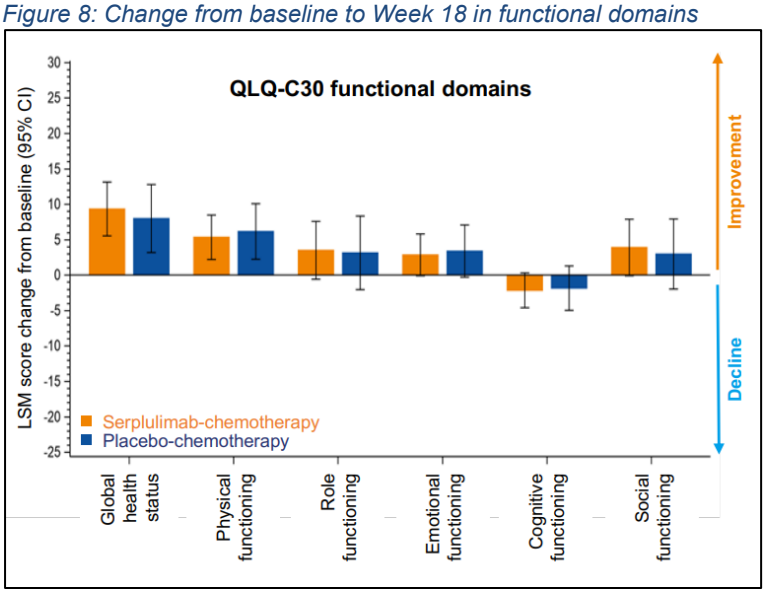
Quality of life scales were evaluated prior to the first dose and every other subsequent dosing cycle (i.e., pre-dose in Cycles 1, 3, 5, 7, etc.) until EOT. A quality of life assessment was required at the EOT visit if no assessment had been performed within the past 3 weeks. Quality of life assessment could be performed either on Day -7 to Day -1 of the screening period, or prior to dosing in Cycle 1.

By-visit longitudinal changes in all domains were comparable between treatment groups for all three questionnaires. Least square mean changes from baseline to Week 18 in QLQ-C30 functional and symptom domains, QLQ-LC13 symptom domains, and EQ-5D-5L VAS were similar and generally improved in both groups (Figure 8, Figure 9, and Figure 10). More pronounced and persistent amelioration was observed in the “pain in other parts” symptom domain for the serplulimab group (Figure 8, Figure 9, Figure 10, and Table 19). This was indicated by a least squares mean (LSM) change difference of -6.37 (95% CI: -11.59, -1.15; p=0.0170). (Cheng et

al., 2024). At the end of the study, patients in the serplulimab group had higher scores than the placebo group on the global health status domain of the EORTC QLQ-C30 (4.85 vs 4.68) (Shanghai Henlius Biotech, 2024).

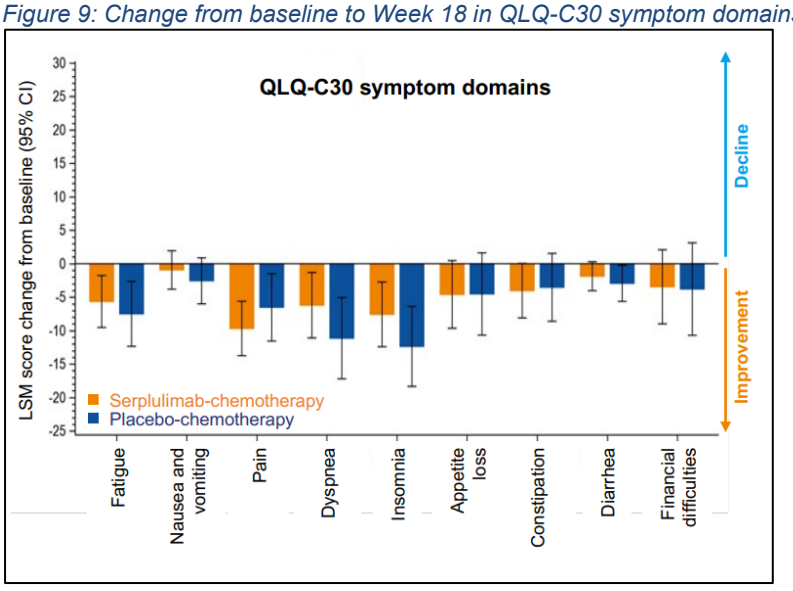
The TTD was comparable between the treatment arms, with the median not reached (NR) in both groups for global health status/quality of life (HR 0.90; 95% CI: 0.59, 1.39), physical functioning (HR 1.01; 95% CI: 0.61, 1.65), and role functioning (HR: 1.17; 95% CI 0.74, 1.87) Please see Table 20 for further details (Cheng et al., 2024).

Figure 8: Change from baseline to Week 18 in functional domains



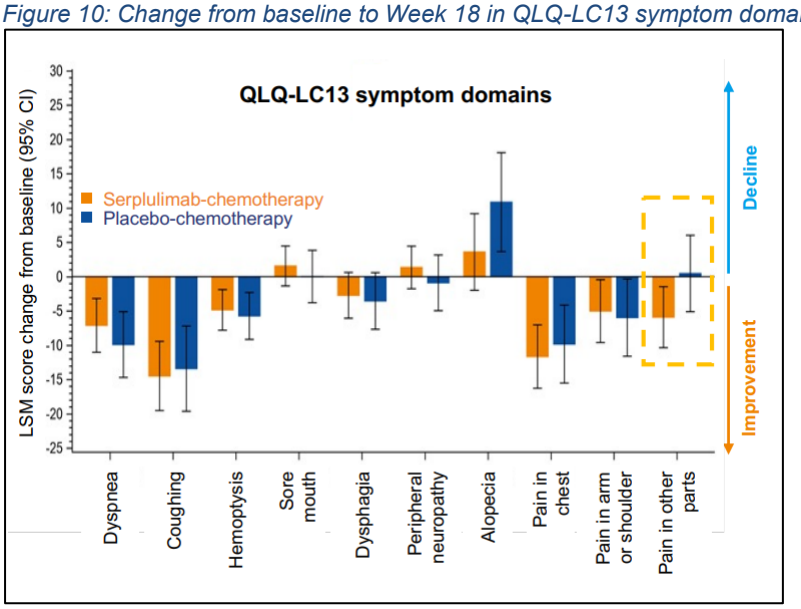
***Abbreviations**: CI, confidence interval; LSM, least square mean; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30*
***Source**: Cheng et al., 2024 (Cheng et al., 2024)*

Figure 9: Change from baseline to Week 18 in QLQ-C30 symptom domains



***Abbreviations**: CI, confidence interval; LSM, least square mean; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30*
***Source**: Cheng et al., 2024 (Cheng et al., 2024)*

Figure 10: Change from baseline to Week 18 in QLQ-LC13 symptom domains



Abbreviations: *CI, confidence interval; LSM, least square mean; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13*
Source: *Cheng et al., 2024 (Cheng et al., 2024)*

Table 19: Change from baseline to Week 18 in 'pain in other parts' domain of EORTC QLQ-LC13

"Pain in other parts" in EORTC QLQ-LC13	**Serplulimab (n=389)**	**Placebo (n=196)**
Change from baseline to Week 18 LSM (95% CI)	-5.91 (-10.36, 1.46)	0.46 (-5.11, -6.03)
Difference in LSM (95% CI)	-6.37 (-11.59, -1.15)	
Nominal p-value	0.0170	

Abbreviations: *CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, European Quality of Life-5 Dimension-5 Level; LSM, least square mean; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13.*
Source: *Cheng et al., 2024 (Cheng et al., 2024)*

Table 20: Time to deterioration

Median time to deterioration	**Serplulimab (n=389)**	**Placebo (n=196)**
Global health status/quality of life, mo (95% CI)	NR (26.84, NE)	NR (NE, NE)
HR (95% CI)	0.90 (0.59, 1.39)	
Physical functioning, mo (95% CI)	NR (NE, NE)	NR (N, NE)
HR (95% CI)	1.01 (0.61, 1.65)	
Role functioning, mo (95% CI)	NR (26.84, NE)	NR (NE, NE)
HR (95% CI)	1.17 (0.74, 1.87)	

Abbreviations: *CI, confidence interval; mo, month; NE, not evaluable.*
Source: *Cheng et al., 2024 (Cheng et al., 2024)*

2.7 Subsequent treatments used in the relevant studies

If a subject had first disease progression, was clinically stable in ASTRUM-005, and intended to receive second-line chemotherapy treatment subsequently (the selection of second-line chemotherapy may refer to the NCCN guidelines or the ESMO guidelines), it was at the discretion of the investigator to continue treating the subject with blinded serplulimab or placebo assignment per protocol in addition to the

second-line chemotherapy, until the second disease progression, intolerable toxicity, death, withdrawal of consent, or loss to follow-up. Any other anti-PD-1 and anti-PD-L1 therapy were not allowed.(Shanghai Henlius Biotech, 2024) Data on subsequent therapy was available in the interim CSR (data cut-off: 13th June 2022). 44.2% of subjects in the serplulimab arm and 43.4% in the placebo arm had subsequent treatment, respectively. (Cheng et al. 2022).

2.8 Pre-planned subgroup analysis

To assess the consistency of the study prespecified OS, PFS, and PFS2, subgroup analyses were conducted (Shanghai Henlius Biotech, 2024). The following subgroups were considered:

- Age (≥ 65 years versus < 65 years)
- Sex (male versus female)
- Race (Asian versus non-Asian)
- Ethnicity (Hispanic or Latino versus non-Hispanic or Latino)
- Baseline ECOG performance status (0 versus 1)
- Baseline smoking status
- Baseline brain metastasis (yes versus no)

To explore the efficacy under different PD-L1 expression level, the following subgroups were examined:

- PD-L1 expression level based on TPS (positive TPS ≥1% versus negative TPS <1%)
- PD-L1 expression level based on CPS (positive CPS ≥1% versus negative CPS <1%)

Summaries of OS, PFS, and PFS2, including unstratified HRs estimated from Cox proportional hazards models, were displayed in forest plots in the ASTRUM-005 CSR. Kaplan-Meier estimates of median OS, PFS, and PFS2 were produced separately for each level of the categorical variables for the comparisons between treatment arms. The survival curve and median survival time were estimated by the Kaplan-Meier approach for subgroups (including age, baseline brain metastasis, PD-L1 expression level based on TPS, and CPS). The Brookmeyer-Crowley method

was used to construct the 95% CI for the median survival time. All the subgroup analyses were summarised using the ITT and PPS datasets. OS analyses of the PPS produced similar results as the analyses of the ITT set (Shanghai Henlius Biotech, 2024).

OS

Subgroup analysis results of the OS, including age, sex, race, ethnicity, baseline ECOG performance status score, brain metastasis, and baseline PD-L1 expression levels are shown in Figure 11. The HRs consistently favoured serplulimab over placebo across all subgroups (Shanghai Henlius Biotech, 2024).

PFS

In subgroup analyses of the PFS according to RECIST 1.1 evaluated by both investigators and IRRC, HRs consistently favoured serplulimab over placebo across all subgroups (Shanghai Henlius Biotech, 2024).

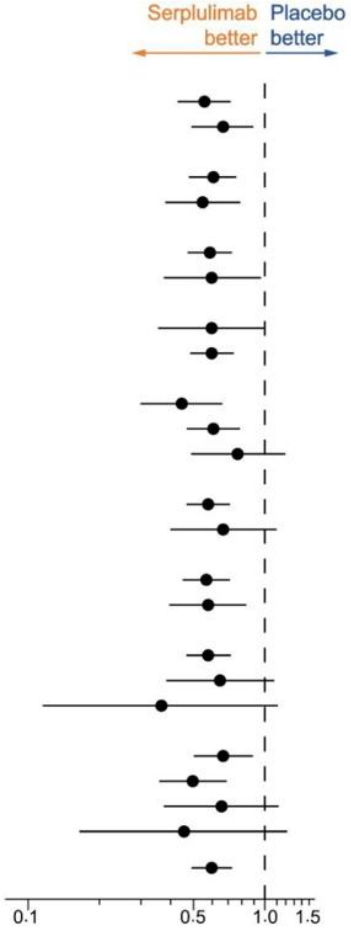
PFS2

In subgroup analyses on the ITT of PFS2 according to RECIST 1.1 by investigators, the HRs consistently favoured serplulimab over placebo across all subgroups (Shanghai Henlius Biotech, 2024).

Overall, subgroup analysis showed consistent OS benefit of serplulimab treatment over placebo regardless of age, sex, race, ethnicity, baseline ECOG performance status, brain metastasis, or baseline PD-L1 expression level (Shanghai Henlius Biotech, 2024).

Figure 11: Subgroup analysis for the primary outcome of overall survival (extended follow-up analysis – data cutoff 7th May 2024))

Subgroup	Number of events/patients		Median OS (months)		HR (95% CI)
	Serplulimab	Placebo	Serplulimab	Placebo	
Age					
< 65 years	160/235	97/119	16.8	11.7	0.56 (0.43–0.72)
≥ 65 years	120/154	69/77	14.9	10.0	0.67 (0.49–0.90)
Race					
Asian	194/262	119/139	15.8	11.1	0.61 (0.48–0.76)
Non-Asian	86/127	47/57	15.6	11.2	0.55 (0.38–0.79)
Sex					
Male	228/317	139/164	15.5	10.9	0.59 (0.48–0.73)
Female	52/72	27/32	16.6	13.8	0.60 (0.38–0.96)
Baseline ECOG performance status					
0	46/71	22/32	19.7	11.1	0.60 (0.36–0.99)
1	234/318	144/164	14.8	11.1	0.60 (0.49–0.74)
Smoking history					
Current	64/102	43/47	15.5	10.7	0.45 (0.30–0.67)
Former	154/206	96/114	16.3	10.9	0.61 (0.47–0.79)
Never	62/81	27/35	14.4	13.1	0.77 (0.49–1.22)
Brain metastasis					
No	241/339	142/168	15.9	11.3	0.58 (0.47–0.72)
Yes	39/50	24/28	13.9	9.1	0.67 (0.40–1.12)
Liver metastasis					
No	196/290	121/145	17.7	12.2	0.57 (0.45–0.72)
Yes	84/99	45/51	10.8	7.8	0.58 (0.40–0.84)
PD-L1 expression level (TPS)					
TPS < 1%	236/322	133/154	15.8	10.5	0.58 (0.47–0.72)
TPS ≥ 1%	38/58	24/32	15.1	12.9	0.65 (0.39–1.10)
Not evaluable/ Not available	6/9	9/10	17.3	11.4	0.37 (0.12–1.14)
PD-L1 expression level (CPS)					
CPS < 1	135/175	74/90	14.2	10.0	0.67 (0.50–0.89)
1 ≤ CPS < 10	94/131	64/71	15.9	11.1	0.50 (0.36–0.69)
CPS ≥ 10	43/70	18/25	19.7	14.7	0.66 (0.38–1.14)
Not evaluable/ Not available	8/13	10/10	17.3	12.8	0.46 (0.17–1.24)
Overall	**280/389**	**166/196**	**15.8**	**11.1**	**0.60 (0.49–0.73)**



***Abbreviations**: chemo, chemotherapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; HR, hazard ratio; m, median; mo, month; OS, overall survival; PD-L1, programmed death-ligand-1; PROs, patient-reported outcomes; TPS, tumour proportion score.*

***Source**: Cheng et al., 2025 (Cheng et al., 2025)*

2.7. Meta-analysis

The efficacy and safety of serplulimab in combination with carboplatin and etoposide for the first-line treatment of adult patients with ES-SCLC has been investigated in one RCT: the ASTRUM-005 trial. Therefore, no meta-analyses were conducted for this appraisal.

2.8. Indirect and mixed treatment comparisons

The final scope issued by NICE for this appraisal states the relevant comparators as:

- Platinum-based combination chemotherapy
- Atezolizumab with carboplatin and etoposide (for people with Eastern Cooperative Oncology Group performance status of 0 or 1)

Platinum-based combination chemotherapy

In the appraisal of atezolizumab with carboplatin and etoposide for untreated ES-SCLC (TA638), platinum-based combination chemotherapy was listed as the comparator in the final scope issued by NICE. However, UK-practising clinical experts advised the submitting company that carboplatin-etoposide best reflects NHS standard of care; therefore, only carboplatin-etoposide was considered as the relevant comparator in the decision problem addressed in TA638 (National Institute of Health and Care Excellence, 2020). Further expert opinion obtained to inform the current appraisal showed that carboplatin is the most widely used platinum-based therapy in SCLC in the UK.

[redacted].

Because of the higher chance of long-term response and survival and the addition of immune checkpoint inhibitors to chemotherapy, carboplatin is now being more frequently used to avoid acute and late toxicities associated with cisplatin, as in NSCLC.

[redacted] Furthermore, according to expert clinical opinion supporting TA638 (National Institute of Health and Care Excellence,

2020), carboplatin-etoposide is preferred for its lower toxicity profile compared with cisplatin-etoposide, as well as its shorter administration period (2 hours compared with 10 hours for cisplatin-etoposide).Therefore, carboplatin-etoposide is considered as the comparator of relevance for this appraisal to best reflect UK clinical practice.

It is important to note that not considering other platinum-based regimens (such as cisplatin-etoposide) as relevant comparators is of little consequence due to their poor comparative efficacy with carboplatin-etoposide. A large meta-analysis of 4 studies (including >600 LD and ED patients), performed by Rossi et al 2012 (Rossi et al., 2012), showed similar efficacy between carboplatin- and cisplatin-containing regimens; median OS was 9.6 months for cisplatin and 9.4 months for carboplatin (HR=1.08; 95% CI: 0.92, 1.27; p=0.37). ORR in this analysis was 67.1% for cisplatin and 66.0% for carboplatin (RR=0.98; 95% CI: 0.84, 1.16; p=0.83). Older reviews (Go (Go and Adjei, 1999, Hotta et al., 2004) also report similar conclusions. Furthermore, a network meta-analysis (NMA) carried out in TA638 compared the relative efficacy of cisplatin with etoposide and carboplatin with etoposide and demonstrated that both regimens have equivalent efficacy profiles.

Therefore, it was not deemed appropriate or necessary to conduct an NMA to account for the various platinum-based treatment regimens, as the carboplatin-etoposide regimen is best reflective of NHS standard of care, and other platinum-based regimens such as cisplatin-etoposide are not used frequently for SCLC and have equivalent efficacy profiles to carboplatin-etoposide.

Atezolizumab with carboplatin and etoposide (for people with Eastern Cooperative Oncology Group performance status of 0 or 1)

The comparative efficacy of serplulimab and atezolizumab (both in combination with carboplatin and etoposide) has not been directly investigated as part of the same RCT. Therefore, a matched-adjusted indirect comparison (MAIC) was performed using data from the ASTRUM-005 and IMpower133 trials (NCT02763579). As described in NICE TSD18 (Phillippo et al., 2016), population-adjusted indirect comparisons such as MAICs have a distinct advantage over more standard methods such as NMAs. This is because they do not rely on the assumption that there is no difference between the trials in the distribution of effect-modifying variables, as any

differences are adjusted for as part of the analysis. Furthermore, a MAIC was deemed most appropriate in this context as there is only one key trial for each of serplulimab and atezolizumab (ASTRUM-005 and IMpower133, respectively). In networks consisting of only one or two trials per treatment, network meta-analyses are highly vulnerable to systematic variation resulting from imbalances in effect modifier distributions (Phillippo et al., 2016).

2.8.1. Summary of included evidence and assessment of comparability

The MAIC utilized individual patient data from ASTRUM-005 and published aggregate data from the IMpower133 clinical trial. The design, population, and outcomes of ASTRUM-005 are described in detail in Sections 2.3 to 2.7. A comparison of ASTRUM-005 and IMpower133 is presented in Table 21.

Table 21: Summary of ASTRUM-005 and IMpower133

	ASTRUM-005 (HLX10-005-SCLC301)	**IMpower133**
Intervention	Serplulimab + carboplatin + etoposide	Atezolizumab + carboplatin + etoposide
Comparator	Placebo + carboplatin + etoposide	Placebo + carboplatin + etoposide
Target	PD-1	PD-L1
Study design	Randomised, double-blind, multicentre, Phase 3 study	Randomised, Phase 1/3, multicentre, double-blinded, placebo-controlled study
Key inclusion criteria	Histologically or cytologically diagnosed with ES-SCLC No prior systemic therapy for ES-SCLC Patients who had received chemoradiotherapy for previous limited-stage SCLC had to have been treated with curative intent and be treatment-free for 6 months At least one measurable lesion as assessed by the independent radiology review committee An ECOG PS score of 0 or 1 Normal major organ functions as defined by the following criteria (no blood transfusions, or treatment with albumin, recombinant human thrombopoietin, or colony-stimulating factor within 14 days prior to the first dose in this study)	Histologically or cytologically confirmed ES-SCLC No prior systemic treatment for ES-SCLC ECOG performance status of 0 or 1 Measurable disease, as defined by RECIST v1.1 Adequate hematologic and end organ function Treatment-free for at least 6 months since last chemo/radiotherapy, among those treated (with curative intent) with prior chemo/radiotherapy for limited-stage SCLC
Primary endpoints	OS	OS, Investigator-assessed PFS
Sample size	585 (Active arm: 389, Control arm: 196)	403 (Active arm: 201, Control arm: 202)
Primary outcomes	OS: 15.77 mon vs. 11.10 mon HR=0.60 (95% CI: 0.49, 0.73; p<0.001) 2-year OS rate: 32.7% vs. 16.4% median follow-up: 42.38 months (Cutoff date: 7th May 2024) PFS (assessed by Investigator): 5.49 mon vs. 4.34 mon HR=0.57 (95% CI: 0.47, 0.69; p<0.001)	OS: 12.3 mon vs. 10.3 mon HR=0.76 (95% CI: 0.60, 0.95; p=0.0154) 2-year OS rate: Both < 25% median follow-up: 22.9 mon (Cutoff date: 24th January 2019) PFS (assessed by Investigator): 5.2 mon vs. 4.3 mon HR=0.77 (95% CI: 0.62,0.96; p=0.02)

	ASTRUM-005 (HLX10-005-SCLC301)	IMpower133
	Confirmed ORR (assessed by investigator): [redacted] Confirmed DOR (assessed by investigator): [redacted]Median follow-up: 42.38 months (Cutoff date: 7th May 2024)	Confirmed ORR (assessed by investigator): 60.2% vs. 64.4% Confirmed DOR (assessed by investigator): 4.2 mon vs. 3.9 mon Median follow-up: 13.9 mon (Cutoff date: 24th April 2018)

***Abbreviations**: CI, confidence interval; DOR, duration of response; ECOG PS, European Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; HR, hazard ratio; mon, month; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progresision-free survival*
***Source**: (Henlius, 2024, Liu et al., 2021b)*

ASTRUM-005 and IMpower133 were both Phase 3, randomised, double blinded, placebo-controlled studies. IMpower133 was designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin plus etoposide in comparison with placebo and carboplatin plus etoposide. The trial enrolled chemotherapy-naive participants with ES-SCLC. Patients were randomized in a 1:1 ratio to each study arm, receiving treatment on 21-day cycles for four cycles in the induction phase followed by maintenance with atezolizumab or placebo until progressive disease based on investigator assessment. ASTRUM-005 and IMpower133 both evaluated the efficacy of the investigational product in comparison with placebo and carboplatin plus etoposide, and consequently, indirect estimates of treatment efficacy can be anchored via the control arms of each study. Dosing schedules of carboplatin plus etoposide were consistent between studies, with administration every three weeks, up to a maximum of 12 weeks.

Similarly, based on a comparison of study inclusion and exclusion criteria, no material discrepancies were identified in the patient populations that would be eligible for enrollment in ASTRUM-005, and IMpower133. Both the ASTRUM-005 study and IMpower133 study enrolled patients aged >18 years, with ECOG performance status 0 or 1, having received no prior systemic treatment for ES-SCLC, with normal major organ functions, without uncontrolled intercurrent illness, and without active immune diseases.

2.8.2. Patient characteristics

A summary of patient characteristics for ASTRUM-005 and IMpower133 is presented in Table 21. There were notable imbalances in patient characteristics between the study populations of ASTRUM-005 and IMpower133: patients in ASTRUM-005 were typically younger, more likely to be male, more likely to be of Asian ethnicity, more

likely to have ECOG performance status of 1 versus 0, less likely to be smokers, more likely to have existing brain metastases, less likely to have liver metastases, and less likely to have received previous anticancer treatments. Data describing disease stage and PD-L1 status were not reported for IMpower133, and consequently, the potential impact of imbalances in these factors is unknown.

Table 22: Summary of patient baseline characteristics in ASTRUM-005 and IMpower133

	ASTRUM-005		IMpower133	
	Serplulimab	**Control**	**Atezolizumab**	**Control**
Age group (≥65 yr), %	39.6	39.3	44.8	47.5
Sex (Male), %	81.5	83.7	64.2	65.3
Race (Asian), %	67.4	70.9	16.4	17.8
Disease stage (IV), %	81.7	79.1	NR	NR
ECOG (PS 1), %	81.7	83.7	63.7	66.8
Smoking status (Current/former smoker), %	79.2	82.1	95.5	98.5
Brain metastases (Yes), %	12.9	14.3	8.5	8.9
Liver metastases (Yes), %	25.4	26.0	38.8	35.6
Blood-based tumor mutational burden ≥10 mutations/Mb, %	11.3 (195 pts)	3.6 (110 pts)	59.0 (173 pts)	61.8 (178 pts)
PD-L1 TPS >1%, %	16.4 (379 pts)	18.3 (186 pts)	NR	NR
Previous anticancer treatments, %	2.6	2.6	32.8	32.2

***Note**: In cases where data was not evaluable for some patients, the number of patients for which it was evaluable is indicated in brackets.*
***Abbreviations**: ECOG PS, European Cooperative Oncology Group performance status; Mb, mutational burden; NR, not recorded; PD-L1, programmed death-ligand 1; pts, patients; TPS, tumour proportion score.*
***Source**: (Shanghai Henlius Biotech, 2024, Liu et al., 2021b)*

As described in NICE TSD18 (Phillippo et al., 2016), differences in patient characteristics between studies have the potential to bias indirect estimates of efficacy. As such, characteristics were assessed for population adjustment based on the following factors:

1. Availability of data or aggregated results from the studies being compared.
2. Significant impact on the treatment effect. Clinical experts' recommendations will play a crucial role.
3. Imbalance in distribution across studies.
4. The number of cases with a particular characteristic is at least 10% of the total cases, without leading to an excessively low ESS.

Based on these principles, patient characteristics were selected for adjustment based on the rationale presented in Table 23.

Table 23: Rationale for variable selection for population adjustment

	Adjusted	Rationale
Age group (≥65 yr)	Yes	Imbalance in patient age between ASTRUM-005 and IMpower133.

Sex	No	Subgroup analysis in ASTRUM-005 showed no impact of sex on treatment effect.
Race	No	Adjustment would lead to excessively low ESS resulting in unreliable outcomes, furthermore subgroup analysis in ASTRUM-005 showed no impact of race on treatment effect.
Disease stage	No	Not reported in IMpower133.
ECOG	Yes	Imbalance in patient ECOG status between ASTRUM-005 and IMpower133.
Smoking status	Yes	Imbalance in patient smoking status between ASTRUM-005 and IMpower133.
Brain metastases	Yes	Imbalance in the presence of brain metastases between ASTRUM-005 and IMpower133.
Liver Metastases	Yes	Imbalance in the presence of liver metastases between ASTRUM-005 and IMpower133.
Blood-based tumor mutational burden	No	Not tested in all participants.
PD-L1	No	Not reported in IMpower133.
Previous anticancer treatments	No	Adjustment would lead to excessively low ESS resulting in unreliable outcomes.

Abbreviations*: ECOG PS, European Cooperative Oncology Group performance status; Mb, mutational burden; NR, not recorded; PD-L1, programmed death-ligand 1*.

2.8.3. Outcomes for assessment

Outcomes considered in the indirect treatment comparison were OS and investigator assessed PFS, representing primary and secondary endpoints of both ASTRUM-005 and IMpower133. Analysis was based on the latest data cut from ASTRUM-005, with median follow-up of 42.38 months, in comparison with median follow-up of 22.9 months and 13.9 months in IMpower133 for OS and PFS analysis, respectively. HRs for OS and PFS for patients treated with atezolizumab in comparison with placebo in IMpower133 that informed indirect treatment comparisons are presented in Table 21

2.8.4. Statistical methods

An anchored comparison was performed, using individual patient data from ASTRUM-005 and aggregate data from IMpower133, as both trials share a common comparator arm (placebo plus carboplatin and etoposide). Unadjusted HRs for serplulimab in comparison with atezolizumab were first estimated under an assumption that differences in patient characteristics between the trials would not impact the estimated treatment effect of serplulimab. This analysis was conducted utilising the Bucher method for indirect treatment comparisons on the log scale for HRs. However, the Bucher method may produce biased estimates of comparative efficacy where imbalances in treatment effect modifying factors existing between the two studies.

Consequently, population adjusted methods were also conducted using the matched-adjusted indirect comparison (MAIC) described by Signorovitch et al., 2010 (Signorovitch et al., 2010). This approach is suitable when individual patient data from the intervention trial are available, and only aggregate data are available for the comparator trial. For this analysis, key baseline characteristic variables from the ASTRUM-005 study were centralised based on the aggregate summary data from the comparator studies according to Signorovitch's method. For example, the representative value for each patient's respective age group (0 for <65 years, 1 for ≥65 years) in the ASTRUM-005 study was subtracted by the proportion of patients aged ≥65 years in the IMpower133 study (0.448 for the active arm and 0.475 for the control arm). Weights for each patient in the ASTRUM-005 study were calculated using the Newton-Raphson optimization procedure. The weighted baseline characteristics for the patients were then verified to ensure that they matched those aggregate characteristics from IMpower133 and calculated effective sample size (ESS). MAIC analyses were then conducted to obtain the relative HR and 95% CI for OS and PFS. Analysis used a Cox proportional hazards model with weights to obtain the weighted hazard ratios (HRs) for the ASTRUM-005 study, then compared with the IMpower133 study to determine the relative HR and 95% CI.

2.8.5. Analysis results

Unadjusted analysis showed that treatment with serplulimab was anticipated to improve both OS and PFS in comparison with atezolizumab,

[redacted]

In the matched analysis, patient characteristics for matching variables were well aligned between study populations (Table 24).

[redacted]

Table 24: Patient characteristics in matched analysis

Baseline Variables	ASTRUM-005		ASTRUM-005 - Adjusted		IMpower133	
	Serplulimab (N = 389)	Placebo (N = 196)	Serplulimab (ESS = 240)	Placebo (ESS = 126)	Placebo (N = 202)	Atezolizumab (N = 201)
Age Group, n (%)						
≥ 65 years	154 (39.6)	77 (39.3)	108 (44.8)	60 (47.5)	96 (47.5)	90 (44.8)
< 65 years	235 (60.4)	119 (60.7)	132 (55.2)	66 (52.5)	106 (52.5)	111 (55.2)
Sex, n (%)						

Baseline Variables	ASTRUM-005		ASTRUM-005 - Adjusted		IMpower133	
	Serplulimab (N = 389)	Placebo (N = 196)	Serplulimab (ESS = 240)	Placebo (ESS = 126)	Placebo (N = 202)	Atezolizumab (N = 201)
Male	317 (81.5)	164 (83.7)	216 (90.2)	117 (92.9)	132 (65.3)	129 (64.2)
Female	72 (18.5)	32 (16.3)	24 (9.8)	9 (7.1)	70 (34.7)	72 (35.8)
Race, n (%)						
Asian	262 (67.4)	139 (70.9)	150 (62.6)	84 (66.4)	36 (17.8)	33 (16.4)
Non-Asian	127 (32.6)	57 (29.1)	90 (37.4)	42 (33.6)	166 (82.2)	168 (83.6)
Disease Stage, n (%)						
IV	318 (81.7)	155 (79.1)	204 (84.8)	100 (79.3)	NR	NR
III or other	71 (18.3)	41 (20.9)	36 (15.2)	26 (20.7)	NR	NR
ECOG, n (%)						
PS 1	318 (81.7)	164 (83.7)	**153 (63.7)**	**84 (66.8)**	**135 (66.8)**	**128 (63.7)**
PS 0	71 (18.3)	32 (16.3)	**87 (36.3)**	**42 (33.2)**	**67 (33.2)**	**73 (36.3)**
Smoking Status, n (%)						
Current/former smoker	308 (79.2)	161 (82.1)	**229 (95.5)**	**124 (98.5)**	**199 (98.5)**	**192 (95.5)**
Never	81 (20.8)	35 (17.9)	**11 (4.5)**	**2 (1.5)**	**3 (1.5)**	**9 (4.5)**
Brain Metastasis, n (%)						
Yes	50 (12.9)	28 (14.3)	**20 (8.5)**	**11 (8.9)**	**18 (8.9)**	**17 (8.5)**
No	339 (87.1)	168 (85.7)	**220 (91.5)**	**115 (91.1)**	**184 (91.1)**	**184 (91.5)**
Liver Metastasis, n (%)						
Yes	99 (25.4)	51 (26.0)	**92 (38.3)**	**45 (35.6)**	**72 (35.6)**	**77 (38.3)**
No	290 (74.6)	145 (74.0)	**148 (61.7)**	**81 (64.4)**	**130 (64.4)**	**124 (61.7)**
Tumor Mutational Burden, n (%)						
≥10 mutations/Mb	22/195 (11.3)	4/110 (3.6)	13/120 (10.5)	2/71 (2.7)	110/178 (61.8)	102/173 (59.0)
<10 mutations/Mb	173/195 (88.7)	106/110 (96.4)	107/120 (89.5)	69/71 (97.3)	68/178 (38.2)	71/173 (41.0)
Previous Anticancer Treatments, n (%)						
Yes	10 (2.6)	5 (2.6)	6 (2.4)	3 (2.0)	65 (32.2)	66 (32.8)
No	379 (97.4)	191 (97.4)	234 (97.6)	123 (98.0)	137 (67.8)	135 (67.2)

Bold *data indicate matching variables.*
Abbreviations*: ECOG PS, European Cooperative Oncology Group performance status; Mb, mutational burden; NR, not recorded.*
Source*: (Shanghai Henlius Biotech, 2024, Liu et al., 2021b)*

The distribution of patient weights was consistent with expectations, with [redacted] patients having a weight of zero, and only [redacted] of patients having a weight in excess of one indicating that indirect efficacy estimates are not being biased by disproportionate weighting in ASTRUM-005. Histograms of estimated weights and rescaled weights for both study arms, and summary statistics of the weights are presented in Figure 12 and Table 25, respectively.

Table 25: Distribution of patient weights

	ASTRUM-005 vs. IMpower133	
	Active arm (N=389)	Control arm (N=196)
Weights		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
= 0, n(%)	[redacted]	[redacted]
>0 and <=0.1, n(%)	[redacted]	[redacted]
>0.1 and <=0.5, n(%)	[redacted]	[redacted]
>0.5 and <=1, n(%)	[redacted]	[redacted]
>1, n(%)	[redacted]	[redacted]

Abbreviations*: SD, standard deviation.*

Figure 12: Distribution of patient weights

[redacted]

In matched analysis, treatment with serplulimab was estimated to result in improved OS and PFS in comparison with atezolizumab,

[redacted]

[redacted]Improvements in PFS were statistically significant (Table 26).

Table 26: Results of indirect treatment comparison based on ASTRUM-005 and IMpower133

	Bucher	Matched
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

***Abbreviations**: PFS, progression free survival; OS, overall survival.*

2.8.6. Interpretation of evidence

Overall, the results of the MAIC demonstrate improvements in both PFS and OS with serplulimab + carboplatin-etoposide (ASTRUM-005) compared to atezolizumab + carboplatin-etoposide (IMpower133), regardless of the adjustments for baseline characteristics. In general, greater improvements were observed after adjustments, especially for OS. This may be attributed to the higher percentage of patients with ECOG PS 1 and brain metastasis enrolled in ASTRUM-005, both of which are associated with poor prognosis (Foster et al., 2009, Franco et al., 2021, Fukui et al., 2016, Paz-Ares et al., 2019). Improvements in PFS were statistically significant, supporting the findings of improvements in OS, given that PFS is predictive of OS in SCLC. This was despite ASTRUM-005 being powered to detect differences in treatment effect in comparison with placebo, rather than an active comparator, and loss of sample size in the matching process.

2.8.7. Uncertainties in the indirect and mixed treatment comparisons

It is important to note that a key assumption of the MAIC is that the target population is well represented by the baseline characteristics of the IMpower133 trial, to which the baseline characteristics of the ASTRUM-005 trial are adjusted to. The population in ASTRUM-005 was associated with a higher percentage of patients with ECOG PS 1 and brain metastasis, which are associated with poor prognosis (Foster et al., 2009, Franco et al., 2021, Fukui et al., 2016, Paz-Ares et al., 2019), compared to IMpower133. This likely explains why adjusting to IMpower133 gives a more favourable HR for serplulimab.

[redacted]

2.9. Adverse reactions

SUMMARY
In ASTRUM-005, serplulimab showed a manageable safety profile with the incidence and severity of TEAEs similar between the two groups • Data from the Phase 3, placebo-controlled ASTRUM-005 RCT shows that serplulimab plus chemotherapy is well tolerated, with fewer TEAEs compared with placebo plus chemotherapy ([redacted] • The incidence of drug-related TEAEs was higher with serplulimab compared to placebo plus chemotherapy ([redacted] • The incidence of SAEs ([redacted] was higher in the serplulimab arm, but there was a higher incidence of AEs leading to death in the placebo arm ([redacted]

The serplulimab group of ASTRUM-005 received a median of 8 treatment cycles (range: [redacted]), compared to 6 cycles (range: [redacted]) in the placebo group (Shanghai Henlius Biotech, 2024). The median total numbers of treatment cycles of carboplatin and etoposide were both 4 cycles in both groups as specified per the protocol. The mean (SD) relative dose intensity was [redacted] for serplulimab and [redacted] for placebo (Shanghai Henlius Biotech, 2024).

2.9.1. TEAEs that occurred in ≥20% of all subjects

The most common TEAEs with an incidence ≥20% in the serplulimab group were anaemia (serplulimab vs placebo: 72.2% vs 71.4%), neutrophil count decreased (56.6% vs 51.5%), alopecia (54.2% vs 56.6%), white blood cell count decreased (54.2% vs 51.0%), platelet count decreased (41.6% vs 44.9%), nausea (36.2% vs 43.9%), neutropenia (30.1% vs 32.1%), decreased appetite (28.3% vs 28.6%),

hyponatraemia (25.4% vs 13.3%), leukopenia (24.4% vs 20.4%), constipation (24.7% vs 29.6%), and vomiting (20.3% vs 29.6%) (Shanghai Henlius Biotech, 2024).

Many of the common TEAEs had incidences in the serplulimab group similar to or lower than those in the placebo group. The common TEAEs that occurred more frequently in the serplulimab group were anaemia, neutrophil count decrease, white blood cell count decrease, hyponatraemia, and leukopenia. (Shanghai Henlius Biotech, 2024).

2.9.2. TEAEs that occurred in ≥5% of all subjects

Please see Appendix G for a full list of the TEAEs occurring in ≥5% of all subjects.

2.9.3. Study drug-related TEAEs

The most common TEAEs (incidence ≥10% in the serplulimab group) considered related to serplulimab/placebo were anaemia (serplulimab group vs placebo group: [redacted] white blood cell count decreased ([redacted] neutrophil count decreased ([redacted] platelet count decreased ([redacted] hypothyroidism ([redacted] nausea ([redacted] alanine aminotransferase increased ([redacted]), hyperthyroidism ([redacted], aspartate aminotransferase increased ([redacted]and decreased appetite ([redacted]) (Shanghai Henlius Biotech, 2024).

Please see Appendix G for a full list of the study-related TEAEs occurring in ≥5% of all subjects.

2.9.4. TEAEs by severity

TEAEs are summarised according to their severity in Table 14.3.1.3 in the ASTRUM-005 CSR (Shanghai Henlius Biotech, 2024). Common and severe TEAEs related to serplulimab/placebo were reported in 35.0% vs 29.1% subjects. Of these TEAEs, only neutrophil count decreased had a slightly higher incidence in the serplulimab group ([redacted] than in the placebo group ([redacted] (Shanghai Henlius Biotech, 2024).

2.9.5. Deaths

All-cause

As of the cutoff date (7th May 2024), [redacted] subjects had died: [redacted] in the serplulimab group and [redacted] in the placebo group. The causes of these deaths, as reported on the eCRF, included progressive disease (serplulimab group vs placebo group: [redacted] AEs ([redacted]), and other ([redacted] (Shanghai Henlius Biotech, 2024).

TEAEs leading to death

TEAEs leading to death occurred in 10.0% of subjects in the serplulimab group and 13.8% in the placebo group. The TEAEs leading to death with an incidence ≥1% (in the serplulimab group) were disease progression (serplulimab group vs placebo group: [redacted] and death ([redacted]). TEAEs leading to death, excluding disease progression, were reported in [redacted] of subjects in the serplulimab group and [redacted] in the placebo group. TEAEs leading to death, excluding disease progression and COVID-19, were reported in 5.4% of subjects in the serplulimab group and 7.7% in the placebo group. Please see Appendix G for more details (Shanghai Henlius Biotech, 2024).

[redacted] subjects had TEAEs considered related to serplulimab/placebo that resulted in death.

[redacted] Please see Appendix G for more details (Shanghai Henlius Biotech, 2024).

2.9.6. Serious AEs

A total of 232 (39.7%) subjects experienced serious TEAEs during the study, including 155 (39.8%) subjects in the serplulimab group and 77 (39.3%) in the placebo group. The serious TEAEs with an incidence ≥2% (in the serplulimab group) were platelet count decreased (serplulimab group vs placebo group: [redacted] neutrophil count decreased ([redacted] white blood cell count decreased ([redacted]), disease progression ([redacted]), pneumonia ([redacted]), neutropenia ([redacted]), thrombocytopenia ([redacted]), and leukopenia ([redacted]) (Shanghai Henlius Biotech, 2024).

SAEs considered related to serplulimab or placebo were reported in [redacted] of subjects in the serplulimab group and [redacted] in the placebo group (Table 98). The serious TEAEs related to serplulimab or placebo with an incidence ≥2% in the serplulimab group were platelet count decreased (serplulimab group vs placebo group: [redacted]), white blood cell count decreased ([redacted]), and neutrophil count decreased ([redacted]) Please see Appendix G for more details. (Shanghai Henlius Biotech, 2024).

2.9.7. TEAEs that led to interruptions of serplulimab/placebo

Overall, [redacted] of subjects in the serplulimab group and [redacted] of subjects in the placebo group had TEAEs that led to the interruption of serplulimab/placebo. The most common TEAEs (incidence ≥5% in the serplulimab group) that led to serplulimab/placebo interruption were neutrophil count decreased (serplulimab vs placebo: [redacted] neutropenia ([redacted] platelet count decreased ([redacted] anaemia ([redacted] and white blood cell count decreased ([redacted] (Shanghai Henlius Biotech, 2024).

2.9.8. TEAEs that led to study drug discontinuation

A total of [redacted] subjects had at least one TEAE that led to the discontinuation of serplulimab/placebo during the study: [redacted] subjects in the serplulimab group and [redacted] in the placebo group. TEAEs related to serplulimab/placebo that led to the discontinuation of serplulimab/placebo are summarised in Appendix G. The number of subjects who discontinued serplulimab/placebo due to TEAEs related to serplulimab/placebo was small, including [redacted] subjects in the serplulimab group and [redacted] in the placebo group, which suggests that serplulimab was not associated with any substantial risk of treatment discontinuation (Shanghai Henlius Biotech, 2024).

Treatment-emergent infusion reaction

Treatment-emergent infusion reactions were reported by the investigators and occurred in [redacted] of subjects in the serplulimab group and [redacted] in the placebo group. Of note is that [redacted] subjects in the serplulimab group and [redacted] in the placebo group had an anaphylactic reaction. Please see Appendix G for more details (Shanghai Henlius Biotech, 2024).

Immune-related TEAEs

Immune-related TEAEs occurred in 38% of subjects in the serplulimab group and 18.9% of subjects in the placebo group. The most common (incidence ≥3% in the serplulimab group) immune-related AEs were hypothyroidism (serplulimab vs placebo: [redacted] hyperthyroidism ([redacted]), and rash ([redacted] Please see Appendix G for more information (Shanghai Henlius Biotech, 2024).

For additional information on all AEs, please see the ASTRUM-005 clinical study report (Shanghai Henlius Biotech, 2024).

Ongoing studies

Table 27 lists all ongoing trials for serplulimab in any indication.

Table 27: Ongoing trials of serplulimab in ES-SCLC

No.	URL	Trial ID	Interventions	Trial status	Title
1	https://clinicaltrials.gov/study/NCT06497530	NCT06497530	Serplulimab, lurbinectedin, carboplatin, etoposide	Not yet recruiting	Maintenance Lurbinectedin in Combination with Serplulimab for Patients With ES-SCLC
2	https://clinicaltrials.gov/study/NCT06350162	NCT06350162	Serplulimab, chest radiation	Recruiting	Testing the Addition of Radiation Therapy to the Immune Therapy Treatment for ES-SCLC
3	https://clinicaltrials.gov/study/NCT05765825	NCT05765825	Serplulimab, thoracic radiation therapy, carboplatin, etoposide, cisplatin	Recruiting	Study of Low-Dose Radiotherapy Concurrent Chemotherapy With Serplulimab for Patients With ES-SCLC
4	https://clinicaltrials.gov/study/NCT05468489	NCT05468489	Serplulimab + chemotherapy (carboplatin-etoposide), Atezolizumab + chemotherapy (carboplatin-etoposide)	Recruiting	To Evaluate Efficacy and Safety of Serplulimab + Chemotherapy (Carboplatin-Etoposide) in US Patients With ES-SCLC
5	https://clinicaltrials.gov/study/NCT06554535	NCT06554535	Serplulimab, Platinum-based Chemotherapy, Aspirin	Not yet recruiting	Efficacy and Safety of Serplulimab With Chemotherapy and Aspirin in Untreated Extensive-Stage Small Cell Lung Cancer
6	https://clinicaltrials.gov/study/NCT06497530	NCT05882630	Surufatinib, Serplulimab, Etoposide, Carboplatin	Not yet recruiting	Surufatinib Combined With Serplulimab Plus Chemotherapy in the Treatment of Extensive-stage Small Cell Lung Cancer

7	https://clinicaltrials.gov/study/NCT05873790	NCT05873790	Serplulimab plus chemotherapy	Not yet recruiting	Minimal Residual Disease Dynamic Monitoring in First-Line Serplulimab Plus Chemotherapy in Treatment of Extensive SCLC: An Observational Study
8	https://clinicaltrials.gov/study/NCT06462105	NCT06462105	Irinotecan Hydrochloride Liposome Injection, Carboplatin Injection, Serplulimab Injection	Not yet recruiting	Liposomal Irinotecan Combination Regimen for First-line Treatment of Small Cell Lung Cancer
9	https://www.clinicaltrials.gov/study/NCT04063163	NCT04063163	Serplulimab (HLX10), carboplatin, etoposide, placebo	Completed	A Randomized, Double-blind, Placebo Controlled Phase III Study to Investigate Efficacy and Safety of HLX10 + Chemotherapy (Carboplatin- Etoposide) in Patients With Extensive Stage Small Cell Lung Cancer (ES-SCLC)

***Abbreviations**: ES-SCLC, extensive-stage small cell lung cancer*

Please note no additional results are expected to become available within the timeframe of the appraisal.

2.10. Interpretation of clinical effectiveness and safety evidence

2.10.1. Summary of efficacy data

The clinical value of serplulimab for the first-line treatment of ES-SCLC has been evaluated in the randomised, double-blind, placebo control, global Phase 3 trial, ASTRUM-005 (Cheng et al., 2024, Cheng et al., 2022b, Cheng et al., 2022a, Shanghai Henlius Biotech, 2024).

Serplulimab demonstrated significant improvements in OS benefits for patients with ES-SCLC:

- The median OS for serplulimab combined with chemotherapy at a 42.38-month median follow-up was 15.77 months, statistically significantly higher than placebo with chemotherapy, which achieved 11.1 months (HR=0.60; 95% CI: 0.49, 0.73; p<0.001) (Shanghai Henlius Biotech, 2024).
- Treatment with serplulimab combined with chemotherapy versus placebo with chemotherapy reduced the risk of death or progression by 53%, with an OS rate of 21.9% (95% CI: 17.6%, 26.6%) vs 7.2% (95% CI: 3.8%, 12.1%) at 4 years, and a PFS rate of [redacted] vs [redacted] at 3 years (Shanghai Henlius Biotech, 2024).

The subgroup analysis by race showed similar trends of a prolonged mOS for the serplulimab group in Asians (stratified HR=[redacted]) and non-Asians (all were White; stratified HR=[redacted]) (Shanghai Henlius Biotech, 2024, Cheng et al., 2022b). Similarly, for the subgroup analysis by smoking history, prolonged mOS was reported in the serplulimab group for non-smokers (HR=[redacted]), current smokers (HR=[redacted]), and former smokers (HR=[redacted]) (Shanghai Henlius Biotech, 2024, Cheng et al., 2024).

Serplulimab demonstrated extended survival benefits:

- The mPFS for patients in the serplulimab group was 5.8 months (95% CI: 5.6, 6.9), compared with 4.3 months (95% CI: 4.2, 4.4) in the placebo group (HR=0.47; 95% CI: 0.38, 0.57; p<0.001) (Shanghai Henlius Biotech, 2024, Cheng et al., 2022b).
- The confirmed ORR was 68.9% (95% CI: 64.0%, 73.5%) in the serplulimab group, compared with 58.7% (95% CI: 51.4%, 65.6%) in the placebo group (Shanghai Henlius Biotech, 2024, Cheng et al., 2022b).
- Among patients with complete or partial response, the median DoR (mDoR) was 6.8 months (95% CI: 5.5, 8.35) in the serplulimab group compared with 4.2 months (95% CI: 3.1, 4.2) in the placebo group (Shanghai Henlius Biotech, 2024, Cheng et al., 2022b).
- Serplulimab combined with chemotherapy achieved a superior 4-year OS rate compared with chemotherapy: 21.9% (95% CI: 17.6, 26.6) versus 7.2% (95% CI: 3.8, 12.1) (Shanghai Henlius Biotech, 2024).

In the ASTRUM-005 trial, serplulimab combined with chemotherapy demonstrated a significant improvement in PFS compared with chemotherapy alone. The mPFS in the serplulimab group was 5.8 months (95% CI: 5.6, 6.9), compared with 4.3 months (95% CI: 4.2, 4.4) in the placebo group. This difference was statistically significant, with a HR of 0.47 (95% CI: 0.38, 0.57; p<0.001) (Shanghai Henlius Biotech, 2024).

The confirmed ORR was 68.9% (95% CI: 64.0%, 73.5%) in the serplulimab group compared with 58.7% (95% CI: 51.4%, 65.6%) in the placebo group. In the serplulimab group, [redacted] and [redacted] subjects had confirmed complete and partial responses, respectively, compared with [redacted] and [redacted] in the placebo group. Among patients with complete or partial response, the mDoR was 6.8 months (95% CI: 5.5, 8.35) in the serplulimab group compared with 4.2 months (95% CI: 3.1, 4.2) in the placebo group (Shanghai Henlius Biotech, 2024, Cheng et al., 2022b). A longer DoR is clinically beneficial as it indicates a more sustained treatment effect and delayed disease progression from the patient's perspective (Delgado et al., 2021).

Survival rates were superior in the serplulimab group compared with the placebo group. Serplulimab in combination with chemotherapy demonstrated a superior 1-year OS rate compared with chemotherapy: 62.5% (95% CI: 57.3%, 67.2%) versus 45.4% (95% CI: 38.1%, 52.5%). This superiority was also superior at 2 years and 3 years. The 4-year OS rate was 21.9% (95% CI: 17.6%, 26.6%) and 7.2% (95% CI: 3.8%, 12.1%) (Shanghai Henlius Biotech, 2024).

Patient-reported outcomes were comparable between groups:

- Serplulimab provides a numerical improvement in patient quality of life at Week 18 versus baseline for the QLQ-C30 functional and symptom domains, QLQ-LC13 symptom domains, and EQ-5D-5L VAS, which was similar to that of placebo plus chemotherapy (Cheng et al., 2024).

- Serplulimab provides a numerical improvement in patient quality of life at Week 18 versus baseline in the ‘pain in other parts’ symptom domain of QLQ-LC13, which was significantly greater than that seen with placebo plus chemotherapy (LSM change: -6.37 [95% CI: -11.59, -1.15; p=0.017]) (Cheng et al., 2024).

The analysis of LSM changes from baseline to Week 18 in the ASTRUM-005 trial, encompassing functional and symptomatic dimensions of EORTC QLQ-C30 and QLQ-LC13, alongside EQ-5D-5L-VAS, demonstrated a uniform and generally enhanced trend in both the serplulimab and the placebo arm. Within the serplulimab arm, a more notable and sustained improvement was discerned in the ‘pain in other

parts' symptom domain, delineated by a significant difference in LSM change of -6.37 (95% CI: -11.59, -1.15; p=0.017) (Cheng et al., 2024).

Moreover, the investigation into TTD unveiled similar patterns between the treatment groups. Specifically, median TTD was NR for both arms across various metrics, including Global Health Status/quality of life (HR=0.90; 95% CI: 0.59, 1.39), physical functioning (HR=1.01, 95% CI: 0.61, 1.65), and role functioning (HR=1.17; 95% CI: 0.74, 1.87), further underscoring the similarity in clinical outcomes between the two therapeutic arms (Cheng et al., 2024).

An indirect treatment comparison demonstrated improvements in OS and PFS with serplulimab compared to atezolizumab

A MAIC was performed to assess the efficacy of serplulimab with carboplatin-etoposide compared to atezolizumab with carboplatin-etoposide using IPD from the ASTRUM-005 trial, and aggregate data from IMpower133. Improvements in the estimated HRs for OS and PFS were observed for serplulimab compared to atezolizumab both before and after adjusting for differences in baseline characteristics between the two trials. The observed improvements were greater after adjustment, especially for OS. This may be attributed to the higher percentage of patients with ECOG PS 1 and brain metastasis enrolled in ASTRUM-005, both of which are associated with poor prognosis (Paz-Ares et al., 2019; Franco et al., 2021; Fukui et al., 2016; Foster et al., 2009).

2.10.2. Summary of safety data

Serplulimab was well tolerated in ASTRUM-005, with no new safety signals identified:

- Treatment-related AEs (TRAEs) were reported in [redacted] of patients in the serplulimab group, compared with [redacted] of patients in the placebo group (Shanghai Henlius Biotech, 2024, Cheng et al., 2022a).
- Grade 3 or higher TRAEs occurred in [redacted] of patients in the serplulimab group, compared with [redacted] of patients in the placebo group (Shanghai Henlius Biotech, 2024, Cheng et al., 2022a).

- Serplulimab combined with chemotherapy reported [redacted] of serious TEAEs related to the study drug, compared with [redacted] in the placebo arm. However, only 10% of TEAEs led to death in the serplulimab arm, compared with 13.8% in the placebo arm (Shanghai Henlius Biotech, 2024).
- Incidence of immune-related TEAEs was higher in the serplulimab group compared with the placebo group with the largest difference in endocrine disorders ([redacted] which are commonly reported with anti-PD-1/PD-L1 therapies (Cheng et al., 2022, Goldman et al., 2021, Liu et al., 2021b, Shanghai Henlius Biotech, 2024).

In the ASTRUM-005 clinical trial, the safety profile was similar between the two groups, the serplulimab group and the placebo group. TRAEs were reported in [redacted] of patients in the serplulimab group compared with [redacted] of patients in the placebo group. TRAEs grade 3 or higher occurred in [redacted] of patients in the serplulimab group compared with [redacted] of the patients in the placebo group. The most common TEAEs with an incidence ≥20% in the serplulimab group were anaemia (serplulimab vs placebo: 72.2% vs 71.4%), neutrophil count decreased (56.6% vs 51.5%), alopecia (54.2% vs 56.6%), white blood cell count decreased (54.2% vs 51.0%), platelet count decreased (41.6% vs 44.9%), nausea (36.2% vs 43.9%), neutropenia (30.1% vs 32.1%), decreased appetite (28.3% vs 28.6%), hyponatraemia (25.4% vs 13.3%), leukopenia ([redacted]), constipation (24.7% vs 29.6%), and vomiting (20.3% vs 29.6%) (Shanghai Henlius Biotech, 2024).

The incidence of immune-related TEAEs was higher in the serplulimab group compared with the placebo group with the largest difference in endocrine disorders ([redacted] which are commonly reported with anti-PD-1/PD-L1 therapies (Cheng et al., 2022, Goldman et al., 2021, Liu et al., 2021b, Shanghai Henlius Biotech, 2024).

2.10.3. Conclusion

In the UK, platinum-based chemotherapy is the current standard of care for first-line ES-SCLC (National Institute of Health and Care Excellence, 2019). This offers patients a median OS of 9 to 10 months and has serious undesirable effects,

including dose-limiting toxicity (Dingemans et al., 2021, Wlodarczyk et al., 2018, Zhang et al., 2022).

In patients with previously untreated EC-SCLC, serplulimab plus chemotherapy has demonstrated meaningful and consistent benefits over chemotherapy alone in OS, PFS, overall response rate, and DoR (Shanghai Henlius Biotech, 2024). Serplulimab has been shown to be well tolerated, with no new safety signals identified in the ASTRUM-005 study (Shanghai Henlius Biotech, 2024). Subgroup analysis has also shown consistent OS benefit of serplulimab treatment over placebo regardless of age, sex, race, ethnicity, baseline ECOG performance status, brain metastasis, and baseline PD-L1 expression levels (Shanghai Henlius Biotech, 2024).

The MAIC conducted for this submission showed improvements in the estimated HRs for OS and PFS for serplulimab compared to atezolizumab. Serplulimab also provided a numerical improvement in patient quality of life at Week 18 vs baseline for the QLQ-C30 functional and symptom domains, QLQ-LC13 symptom domains, and EQ-5D-5L VAS, which was similar to that of placebo plus chemotherapy In addition, serplulimab provided a numerical improvement in patient quality of life at Week 18 versus baseline in the ‘pain in other parts’ symptom domain of QLQ-LC13, which was significantly greater than that seen with placebo plus chemotherapy (LSM change: -6.37 [95% CI: -11.59, -1.15; p=0.017]) (Cheng et al., 2024).

Overall, serplulimab has demonstrated to be more effective than current therapies in improving OS, an especially critical outcome for ES-SCLC patients who typically have a very poor prognosis. Serplulimab with chemotherapy also demonstrated longer-lasting effectiveness with no new safety signals compared to chemotherapy alone. At Week 18, serplulimab also led to quality of life improvements across multiple domains, notably reducing pain more effectively than placebo plus chemotherapy (Cheng et al., 2024). Furthermore, serplulimab was awarded an ESMO-MCBS score of 4 (compared with a score of 3 for atezolizumab and durvalumab in the treatment of ES-SCLC), highlighting the substantial benefit of treatment associated with serplulimab (European Society for Medical Oncology, 2024). It is therefore crucial that serplulimab be considered for reimbursement so that these patients can gain access to a treatment that has displayed multiple

meaningful and consistent benefits compared to the current therapies that are available in the UK.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

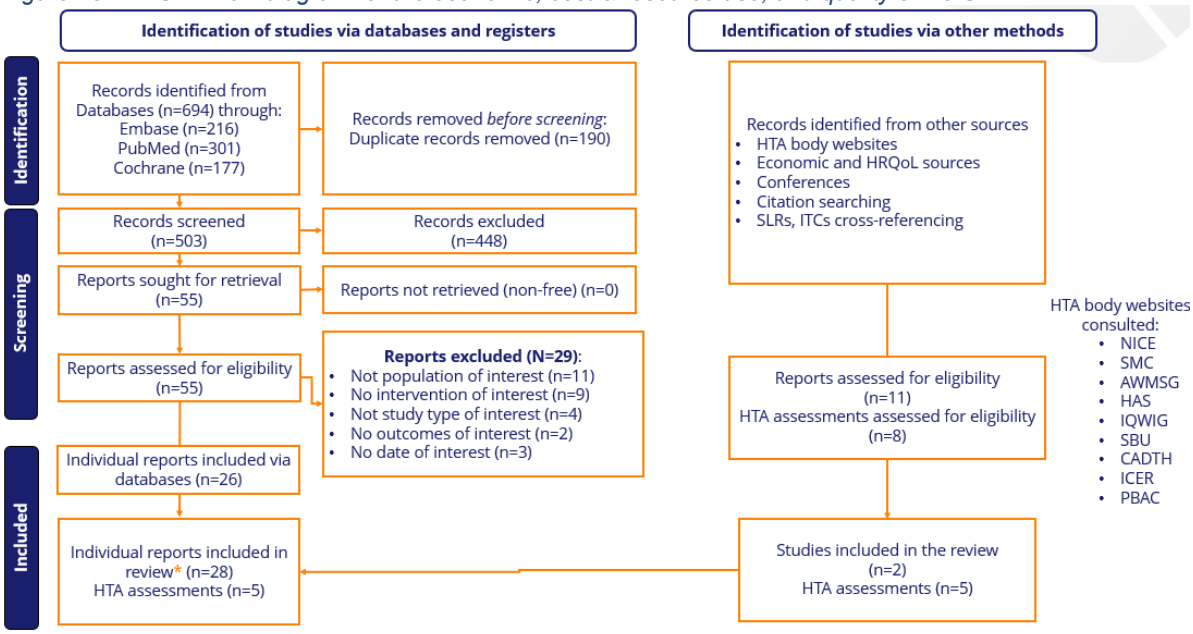
An SLR was conducted to identify and collect evidence on economic evaluations, healthcare resource utilisation (HCRU), associated costs, and quality of life related to treatments for adults with untreated ES-SCLC. The SLR was conducted in accordance with guidelines provided by the Cochrane collaboration and the CRD, as well as NICE requirements, with methodology and results being reported as per PRISMA guidelines. Full details of the SLR search strategy, study selection process, results, and narrative synthesis are presented in Appendix H.

Electronic searches were conducted across key biomedical databases on 7th May 2024. 694 records were identified, of which 190 were duplicates and 448 were excluded following title/ abstract screening. All remaining 55 references were retrieved for full publication screening; 29 articles failed to meet the PICOS inclusion criteria and were excluded. 26 publications identified through database searching were included in the review, with 7 additional articles being identified through supplementary searches for published and unpublished economic and quality of life literature. In total, 28 individual studies and 5 health technology assessment (HTA) assessments were included in the review. The PRISMA flow diagram representing the study identification and selection process is presented in Figure 13.

Of the included references, 22 were economic modelling studies. These studies were conducted in China (n=11), the US (n=9), Portugal (n=1), and Russia (n=1). Most of the economic evaluations used a Markov model (n=8) or partitional survival model (PSM) (n=8) structure. Other studies were conducted with a combination of models (n=5) or did not report the type of model structure (n=1). 7 modelling studies compared the intervention of interest to this appraisal, serplulimab plus etoposide and carboplatin to EpC (see Table 28). Of the 5 HTA assessments identified, 4 evaluated the cost-effectiveness of atezolizumab in addition to carboplatin and etoposide compared to carboplatin and etoposide, with the other being an appraisal of durvalumab in addition to carboplatin and etoposide compared to carboplatin and etoposide (with cisplatin + etoposide as a second comparator). See Appendix H for

further information on the published cost-effectiveness evaluations of serplulimab plus etoposide and carboplatin, and comparator technologies.

Figure 13: PRISMA flow diagram for the economic, cost & resource use, and quality of life SLR



***Abbreviations**: AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; HAS, Haute Autorité de Santé; HTA, health technology assessment; HRQoL, health-related quality of life; ICER, Institute for Clinical and Economic Review; IQWIG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SBU, Swedish Agency for Health Technology Assessment and Assessment of Social Services; SMC, Scottish Medicine Consortium.*

Table 28: Summary list of published cost-effectiveness studies of serplulimab

Study	Year	Summary of model	Average patient population age	QALYs (intervention, comparator)	Costs (USD) (intervention, comparator)	ICER (USD per QALY gained)
Liang et al., 2023	2021	Partitioned survival model, 10-year time horizon, 1-week cycle length, PFS, progressive disease, death health states	61.1 years	1.207, 0.771	90,659, 38,327	120,149
Shao et al., 2023	2022	Partitioned survival model, lifetime horizon, 3-week cycle length, PFS, progressive disease, death health states	NA	1.39, 0.81	33,616.66, 14,247.49	33,392.41
Zhu et al., 2023	2022	Decision tree and Markov model, 10-year time horizon, 6-week cycle length, PFS, progressive disease, death health states	61 years	1.217, 0.885	11,202, 7,194	12,077
Kang et al., 2023	2021	Mathematical model combined with decision tree and partitioned survival model, 10-year time horizon, 3-week cycle length, PFS, progressive disease, death health states	NA	0.98, 0.73	54,592.48, 17,023.17	147,908.74
Xiang et al., 2023	2022	Markov model, lifetime horizon, 3-week cycle length, PFS, 1st disease progression, 2nd and subsequent disease progression, death health states	61.1 years	0.79, 0.64	26,402, NA	179,161
Long et al., 2023	2022	Partitioned survival model, 10-year time horizon, 3-week cycle length, PFS, progressive disease, death health states	NA	1.22, 0.88	52,510.45, 10,827.82	122,378.86
Zheng et al., 2024	2022	Partitioned survival model, 10-year time horizon, 3-week cycle length, PFS, progressive disease, death health states	61.1 years	1.172, 0.546	31,020.152, 20,126.157	17,402.548

***Abbreviations**: ICER, incremental cost-effectiveness ratio; NA, not available; PFS, progression-free survival, QALYs, quality-adjusted life years; USD, United States Dollar.*

3.2 Economic analysis

The cost-effectiveness studies identified in Section 3.1 and described in Appendix H, as well as the previous NICE technology appraisal for atezolizumab plus carboplatin and etoposide in first-line ES-SCLC (TA638) (National Institute of Health and Care Excellence, 2020), were reviewed for their potential to inform the submission dossier and cost-effectiveness model. A similar approach to the atezolizumab submission was adopted, with many of the key assumptions also informed by the ASTRUM-005 trial and engagement of clinical experts treating ES-SCLC patients in the UK.

The model inputs of efficacy, safety, and tolerability are based on the pivotal ASTRUM-005 trial for serplulimab plus carboplatin and etoposide (Shanghai Henlius Biotech, 2024). Model results are reported in terms of cost per life year gained (LYG) and cost per quality-adjusted life year (QALY) gained. These reflect the decision problem summarised in Section 1.1.

3.2.1 Patient population

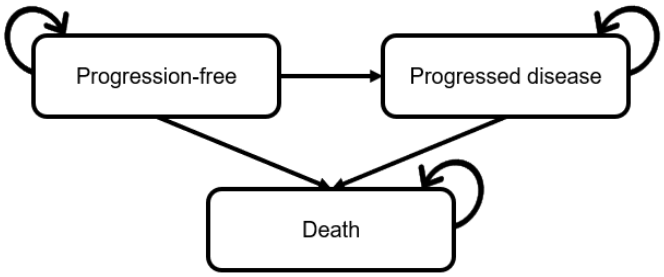
The patient population included in the model is that of the ASTRUM-005 trial (Shanghai Henlius Biotech, 2024). The ITT population is modelled in the base-case; a subgroup analysis of the non-Asian subgroup, which was a prespecified subgroup of interest, was also explored. This population is consistent with the NICE scope, the decision problem, and the SmPC (Accord Data on File, 2024a).

The results of ASTRUM-005 were assessed for consistency between the ITT population and non-Asian subgroup in terms of demographics (age and sex) and baseline prognostic characteristics (smoking status, ECOG PS, and presence of brain and/or liver metastases). Although minor differences are present in the long-term outcomes in these populations, the ITT population is a more generalisable cohort with increased statistical power, allowing for more robust parameter estimates (Shanghai Henlius Biotech, 2024). Clinician feedback also suggested that the ITT population is the most relevant population to the NHS in England (see Appendix M). To minimise uncertainty, the ITT population was used to generate the HR in the MAIC. As a result, the ITT population was modelled in the base-case. Cost-effectiveness results of the non-Asian subgroup are reported in Section 3.10.

3.2.2 Model structure

The cost-effectiveness model used in this appraisal is a partitioned survival model, based on three health states (progression-free, progressed disease, and death), with health state occupancy derived directly from the OS and PFS curves of the ASTRUM-005 trial for serplulimab and carboplatin-etoposide. Health state occupancy for the atezolizumab arm is derived from the MAIC, adjusting the OS and PFS curves from the serplulimab arm using HRs. This model structure is consistent with the NICE appraisal for atezolizumab in ES-SCLC (National Institute of Health and Care Excellence, 2020), as well as many other submissions in oncology. The approach is based on NICE Technical Support Document 19 (TSD19) (Woods et al., 2017). A schematic of the model is presented in Figure 14.

Figure 14: Economic model structure



Patients start in the progression-free state, and progress to the progressed disease state consistently with the rate of disease progression in the ASTRUM-005 trial. Mortality is estimated directly from the OS curve. Although health state transitions are not explicitly modelled as part of this model structure, the proportion of patients in each health state is driven by parametric survival curves. The parametric survival curves are varied in the scenario analysis, with parameters varied in the sensitivity analysis. Not all events were observed within the ASTRUM-005 trial; therefore, long-term survival is modelled using standard parametric methods for extrapolation. The plausibility of the selected extrapolation methods was confirmed by clinical opinion (Appendix M).

The time-to-off treatment (TTOT) curves derived from the ASTRUM-005 trial data are incorporated to capture the time on treatment of patients in each arm of ASTRUM-005, with HRs from the MAIC informing the TTOT curve for atezolizumab. Time on treatment measured in ASTRUM-005 is applied directly in the model to

accurately capture the costs associated with serplulimab, as maintenance therapy with serplulimab was allowed beyond evidence of first disease progression at the discretion of the investigators if prespecified criteria were met (see Section 2.3.4). Similarly, maintenance with atezolizumab monotherapy was allowed to continue beyond evidence of disease progression in IMpower133, the pivotal trial for atezolizumab, until loss of clinical benefit if certain criteria were met, as described in TA638 (National Institute of Health and Care Excellence, 2020). This approach is consistent with TA638.

The selected cycle length is weekly to accurately capture the three-weekly drug administration and acquisition costs, with half-cycle correction applied.

There is one previous assessment for first-line atezolizumab plus carboplatin + etoposide, published by NICE in 2020, TA638 (National Institute of Health and Care Excellence, 2020). A summary of the key features of this assessment is presented in Table 29.

The model perspective is that of the NHS and PSS in England, as per the reference case (National Institute of Health and Care Excellence, 2023). A time horizon of a lifetime was selected (corresponding to 20 years in the model, consistent with TA638) to ensure all costs and outcomes associated with treatment are captured. Discounting is in line with the NICE reference case at 3.5% for costs and outcomes. Costs and outcomes are disaggregated as follows:

- Costs (total and incremental):
    - Total costs
    - Drug acquisition costs
    - Drug administration costs
    - Resource use costs
    - AEs costs
    - Incremental cost-effectiveness ratio (ICER)
- Effectiveness (total and incremental):
    - Life years (LYs)

- QALYs
- QALY decrements due to AEs

- Sensitivity analyses:
  - One-way sensitivity analysis (OWSA)
  - Probabilistic sensitivity analysis (PSA)
  - Scenario analysis

Table 29: Features of the economic analysis

Factor	Previous evaluations		Current evaluation
	TA638	Chosen values	Justification
Time horizon	Lifetime (20 years)	Lifetime (20 years)	This corresponds to the NICE reference case (National Institute of Health and Care Excellence, 2023) and the time horizon used in TA638.
Cycle length	1 week	1 week	In line with TA638 and previous oncology models to accurately model drug administration based on weekly cycles
Half-cycle correction	Included	Included	In line with TA638 and other oncology/lung cancer appraisals to improve the accuracy of patients moving from one state to the next at any point, rather than at the beginning of each cycle
Were health effects measured in QALYs?	Yes	Yes	NICE reference case (National Institute of Health and Care Excellence, 2023). Only direct health effects related to patients were considered, with no wider societal impact or impact on carers included.
Discount for outcomes and costs	3.5%	3.5%	NICE reference case (National Institute of Health and Care Excellence, 2023)
Perspective	NHS/PSS	NHS/PSS	NICE reference case (National Institute of Health and Care Excellence, 2023)
Treatment waning effect	Included; 36, 48, and 60 months	No treatment waning in base-case. Scenarios assuming loss of treatment effect at end of trial and a gradual loss of treatment effect after the trial period were explored.	Given the shape of the Kaplan-Meier curves in the observed trial data from ASTRUM-005, there is no indication for the loss of treatment effect within the trial period. Reduction in treatment effect was explored in scenario analysis to investigate the impact of different treatment waning assumptions beyond the end of the trial period and to ensure a plausible long-term scenario is captured in the model.
Source of utilities	IMpower133 trial, EQ-5D from patient-level data	ASTRUM-005 trial, patient-level data	The pivotal trial collected EQ-5D, which is in line with the NICE reference case (National Institute of Health and Care Excellence, 2023).
Source of costs	Unit costs derived from NHS reference costs (NHS England, 2023) and eMIT (Department of Health and Social Care, 2024)	Chemotherapy acquisition costs are derived from eMIT (Department of Health and Social Care, 2024), with the cost of atezolizumab sourced from the BNF (British National Formulary). Healthcare resource use costs are	The selected sources are widely accepted sources for economic models. Costs and resource use applied in the model were aligned with the NICE appraisal for ES-SCLC (TA638). Healthcare resource use frequency was validated by clinicians.

		derived from NHS reference costs and the PSSRU (Jones, 2023).	

***Abbreviations**: BNF, British national formulary; eMIT, electronic market information tool; ES-SCLC, extensive-stage small cell lung cancer; QALYs, quality-adjusted life years; NICE, National Centre for Health and Care Excellence; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit.*

3.2.3 Intervention technology and comparators

The intervention of interest in the model is serplulimab, with 4.5 mg/kg administered every 3 weeks until treatment discontinuation, based on the TTOT curve from ASTRUM-005 (Shanghai Henlius Biotech, 2024). In the first 4 rounds of administration (Weeks 0, 3, 6, and 9), serplulimab is administered in combination with carboplatin plus etoposide (Cheng et al. 2022). All patients receive 100mg/m^2 of etoposide on Days 1, 2, and 3, and carboplatin within the area under curve (AUC) of 5mg/mL (up to 750mg) on Day 1 of each cycle for up to 4 cycles via intravenous infusion. The TTOT curves were used to accurately reflect that some patients were eligible to continue receiving treatment after disease progression at the discretion of the investigators if prespecified criteria were met. For patients in the PD state and who are off treatment, the costs of subsequent second-line treatment were applied. The subsequent therapies included in the model are consistent with those included in TA638, and are informed by UK clinical opinion.

In line with the final scope, the relevant comparators for serplulimab are platinum-based combination chemotherapy, atezolizumab with carboplatin and etoposide (for patients with ECOG PS of 0 or 1), and durvalumab with carboplatin and etoposide. Based on TA638, ASTRUM-005, and clinical feedback for this assessment, platinum-based chemotherapy in all arms of the model was carboplatin and etoposide, as this best reflects NHS standard of care for patients with ES-SCLC. Durvalumab was not included in the assessment as described earlier, as final guidance has not been issued by NICE at the time of submission (expected 19th February 2025) and is not currently recommended for use in the NHS.

The comparison of serplulimab with atezolizumab is informed by a MAIC (see Section 2.8), as direct head-to-head data was not available for this comparison. Published data from the IMpower133 trial, which compared atezolizumab plus carboplatin and etoposide with carboplatin and etoposide (placebo arm), was used (Horn et al., 2018). HRs were obtained to inform the comparison of atezolizumab

and serplulimab for OS and PFS. Full details of the methodology of the MAIC are provided in Section 2.8.

Atezolizumab with carboplatin and etoposide is modelled in line with the dosing schedule of IMpower133, which is aligned to the EMA marketing authorisation (European Medicines Agency, 2024a) and TA638. Atezolizumab is given at a fixed dose of 1,200mg on Day 1 of every 3-week cycle until loss of clinical benefit or unacceptable toxicity. Carboplatin and etoposide are administered using the same dose and frequency as the serplulimab arm (AUC 5mg/mL on Day 1 of each 3-week cycle for 4 cycles of carboplatin; 100mg/m² on Days 1, 2, and 3 of each 3-weekly cycle for 4 cycles of etoposide).

Relative dose intensity (RDI) is applied to all arms of the model based on individual patient-level data for serplulimab, carboplatin, and etoposide, and the reported RDI in TA638 for atezolizumab.

3.3 Clinical parameters and variables

3.3.1 Baseline characteristics

Baseline characteristics from the ASTRUM-005 trial were used to determine the starting age of patients included in the cost-effectiveness model. The median age in the ASTRUM-005 trial was 62 years at screening in the ITT population (Cheng et al., 2022a, Cheng et al., 2022b).

The proportion of female patients (17.8%) was also used to inform general population mortality rates. Mean weight (68.4 kg) and height (167 cm) were used to calculate dosing of weight or body surface area (BSA)-based treatment regimens (Cheng et al., 2022a, Cheng et al., 2022b).

3.3.2 Time-to-event outcomes

Long-term time-to event outcomes (PFS, OS, and TTOT) were extrapolated using IPD from ASTRUM-005 for the serplulimab and placebo (carboplatin-etoposide) arms. For the atezolizumab arm, PFS, OS, and TTOT extrapolations were generated by applying HRs derived from the MAIC, discussed in Section 2.8, to the selected serplulimab extrapolation. To allow for a comparison of the extrapolated

atezolizumab outcomes based on the MAIC to the IMpower133 trial data, Kaplan-Meier curves from IMpower133 were digitised for the atezolizumab arm (Horn et al., 2018) using the software DigitizeIt version 2.5. Pseudo-IPD was reconstructed using the IPDfromKM software from trialdesign.org. This software uses the Liu et al. methodology, which is based on the Guyot et al. algorithm (Guyot et al., 2012, Liu et al., 2021a). This algorithm assumes a constant rate of censoring over time when simulating IPD.

Parametric survival models were fitted to the time-to-event data for PFS, OS, and TTOT in each study arm of ASTRUM-005, using several parametric distributions as recommended in NICE Decision Support Unit (DSU) Technical Support Document 14 (TSD14) (Latimer, 2013): Exponential, Weibull, Gamma, Log-normal, Log-logistic, Gompertz, and Generalised Gamma. Selection of the most relevant extrapolations was performed using proportional hazard plots and inspection of visual fit, as well as statistical fit using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Clinical expert opinion was also used to ensure the selected curves were in line with long-term expectations of survival and progression (Appendix M). The carboplatin-etoposide arm was also compared with real-world evidence to test the external validity of the selected curves. Further detail of the external validity of the carboplatin-etoposide curve is provided in Section 3.12.

3.3.3 Extrapolation of PFS

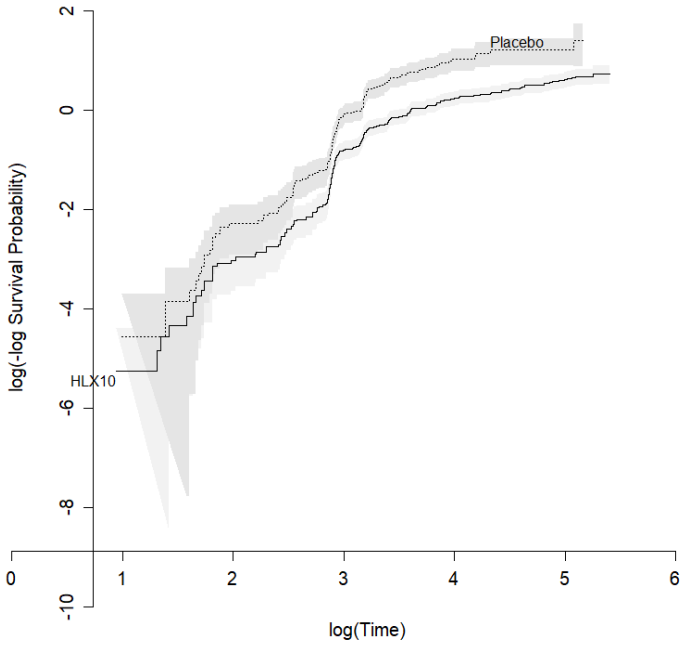
The Kaplan-Meier curve of PFS (assessed by IRRC according to RECIST 1.1) over time for the ITT population in ASTRUM-005 is shown in **Error! Reference source not found.**. As of the 7th May 2024, [redacted] of patients had progressed disease or died ([redacted]/585). In the serplulimab arm, [redacted]/389) of patients had progressed disease or died, compared to [redacted]/196) in the placebo arm. Median PFS in the serplulimab arm was 5.82 months, compared to 4.34 months in the placebo arm.

Assessment of proportional hazards

A diagnostic plot of the log-cumulative hazard for PFS against log-time for the ASTRUM-005 arms was assessed to test the proportional hazards assumption, as presented in Figure 15. Generally, the two log-cumulative hazard curves appear to have similar shapes without diverging or crossing each other. This indicates that the

proportional hazards assumption is not violated, that is, the HRs between the groups does not change over time. However, as outlined in NICE DSU TSD14, it is not necessary to rely upon the assumption of proportional hazards when patient-level data are available. (Latimer, 2013) Therefore, it was deemed most appropriate to fit separate parametric models to each treatment arm, as this approach involves fewer assumptions.

Figure 15: PFS log-cumulative hazard plot from ASTRUM-005



***Abbreviations**: HLX10, serplulimab.*

Visual and statistical goodness of fit of the parametric functions

Parametric distributions were assessed for their goodness of fit to the data using the AIC and BIC, with low values of AIC and BIC indicating a better statistical fit of the parametric model to the trial data. According to these criteria, the Gen. Gamma model provided the best statistical fit for the serplulimab arm, with the Log-logistic model providing the best for the placebo arm, as presented in Table 30.

Table 30: Ranking of PFS parametric fits based on AIC and BIC

Parametric model	Serplulimab				Placebo			
	AIC	Rank	BIC	Rank	AIC	Rank	BIC	Rank
Exponential	2704.7	6	2708.6	5	1415.1	6	1418.4	6
Weibull	2706.3	7	2714.3	7	1395.3	5	1401.9	5
Gamma	2704.5	5	2712.4	6	1369.9	4	1376.4	4
Log-normal	2615.7	3	2623.6	3	1334.1	2	1340.6	2
Log-logistic	2609.3	2	2617.3	2	**1309.1**	**1**	**1315.6**	**1**
Gen. Gamma	**2596.7**	**1**	**2608.5**	**1**	1335.3	3	1345.2	3

Gompertz	2669.8	4	2677.8	4	1416.7	7	1423.2	7

Abbreviations: *AIC, Akaike information criterion; BIC, Bayesian information criterion.*

The different parametric models for PFS in the serplulimab and placebo arms, superimposed on the respective KM curves, are presented in **Error! Reference s ource not found.** and **Error! Reference source not found.**, respectively. For the serplulimab arm, there is notable variation between the different model fits based on visual inspection. For example, the log-logistic fit provides a closer fit to the earlier part of the trial before underestimating PFS at later timepoints, whereas the Gompertz provides a closer fit to the later timepoints and overestimates survival in the earlier portion. Given the relative completeness of the PFS data in the placebo arm, less variation was observed between the different model fits. Clinical experts judged the log-logistic distribution to be the most plausible model for PFS extrapolation in both treatment arms (Appendix M). Furthermore, it is recommended in the guidance provided in NICE DSU TSD14 to fit the same type of model to each treatment arm, unless there is strong justification for using a different type of model based on clinical expert judgement, biological plausibility, and robust statistical analysis. (Latimer, 2013) Therefore, it was deemed most appropriate to apply the Log-logistic parametric extrapolation to both arms in the model.

[redacted]

Abbreviations: *KM, Kaplan-Meier.*

[redacted]

Abbreviations: *KM, Kaplan-Meier.*

Model base-case

The selected Log-logistic extrapolations of PFS for the serplulimab and carboplatin-etoposide (placebo) arms in the model base-case are presented in **Error! Reference s ource not found.**. Each of the alternative parametric models described previously can be selected in the model, and the impact of the different extrapolations on the results are explored in scenario analyses.

[redacted]

Plausibility of extrapolation

Whilst the ASTRUM-005 PFS data is relatively complete, there is uncertainty around the appropriateness of the extrapolated portion of the curve beyond the observed trial data. Clinical experts judged the log-logistic model to provide the most plausible extrapolations of PFS (Appendix M).

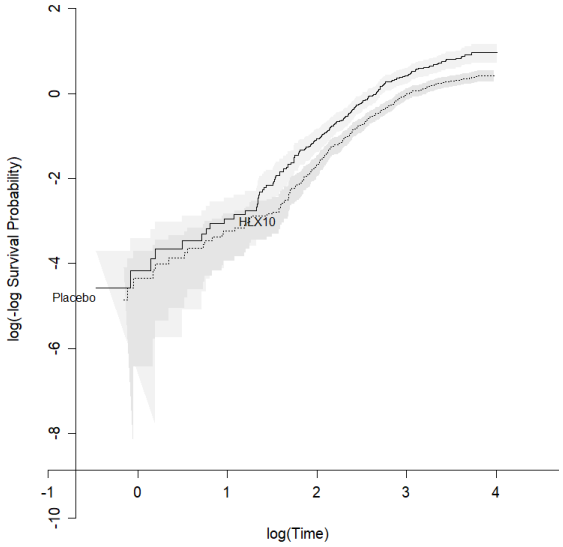
3.3.4 Extrapolation of OS

The Kaplan-Meier curve of OS over time for the ITT population in ASTRUM-005 is shown in Figure 7. As of the 7th May 2024, [redacted] of patients died ([redacted]/585) after a median duration of follow-up of 42.4 months. In the serplulimab arm, [redacted] ([redacted]/389) of patients died compared to [redacted]/196) of patients in the placebo arm.

Assessment of proportional hazards

As for PFS, a diagnostic plot of the log-cumulative hazard for OS against log-time for the ASTRUM-005 arms was assessed to test the proportional hazards assumption, as presented in Figure 16. Generally, the two log-cumulative hazard curves appear to have similar shapes without diverging or crossing each other, indicating that the proportional hazards assumption is not violated. It was deemed most appropriate to fit separate parametric models to each treatment arm as this approach involves fewer assumptions.

Figure 16: OS log-cumulative hazard plot from ASTRUM-005



Abbreviations: *HLX10, serplulimab.*

Visual and statistical goodness of fit of the parametric functions

As for PFS, parametric distributions were assessed for their goodness of fit to the data using the AIC and BIC, with low values of AIC and BIC indicating a better statistical fit of the parametric curve to the trial data. According to these criteria, the log-logistic curve provided the best statistical fit, as presented in Table 31.

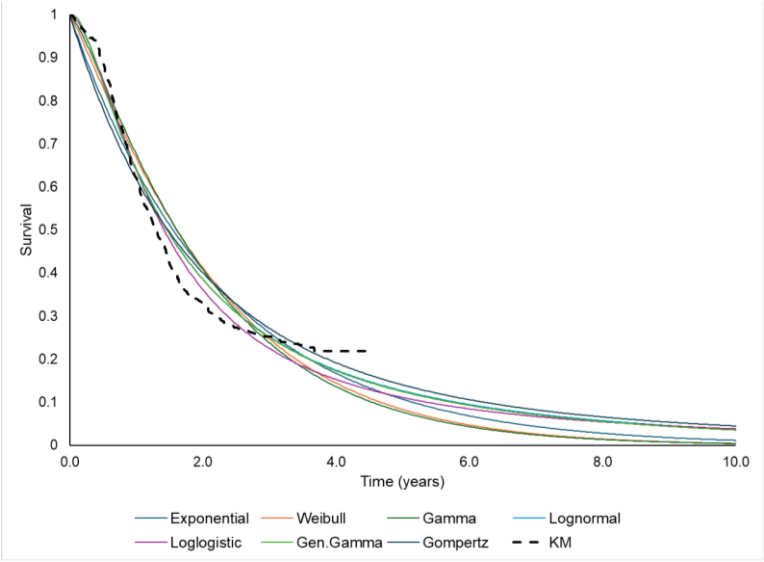
Table 31: Ranking of OS parametric fits based on AIC and BIC

Parametric model	Serplulimab				Placebo			
	AIC	Rank	BIC	Rank	AIC	Rank	BIC	Rank
Exponential	3226.8	7	3230.8	5	1739.3	6	1742.6	6
Weibull	3223.2	5	3231.1	6	1726.7	5	1733.2	5
Gamma	3216.2	4	3224.1	4	1718.8	4	1725.4	4
Log-normal	3187.1	2	3195.0	2	1711.1	3	1717.7	2
Log-logistic	**3176.5**	**1**	**3184.4**	**1**	**1699.6**	**1**	**1706.2**	**1**
Gen. Gamma	3189.0	3	3200.9	3	1711.1	2	1720.9	3
Gompertz	3225.7	6	3233.6	7	1740.7	7	1747.3	7

Abbreviations: *AIC, Akaike information criterion; BIC, Bayesian information criterion.*

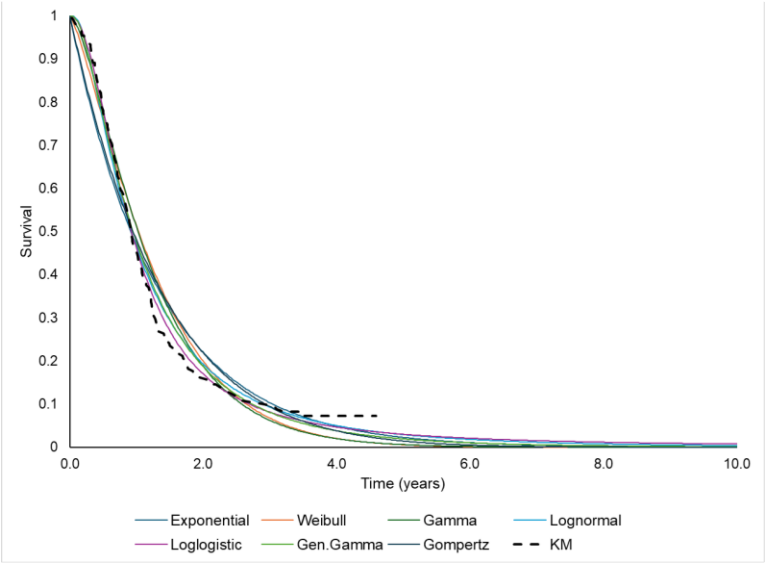
The different parametric models for OS in the serplulimab and placebo arms superimposed on the respective KM curves are presented in Figure 17 and Figure 18, respectively. Consistent with the assessment of statistical fit, the log-logistic model provided the best fit to the trial data based on visual inspection. Given the consistency between the two treatment arms, and the non-violation of the proportional hazards assumption, the log-logistic parametric extrapolation was applied to both arms in the model. The plausibility of the log-logistic model for the extrapolation of OS was validated by clinical experts (Appendix M).

Figure 17: OS parametric models for the serplulimab arm



Abbreviations: *KM, Kaplan-Meier.*

Figure 18: OS parametric models for the placebo arm

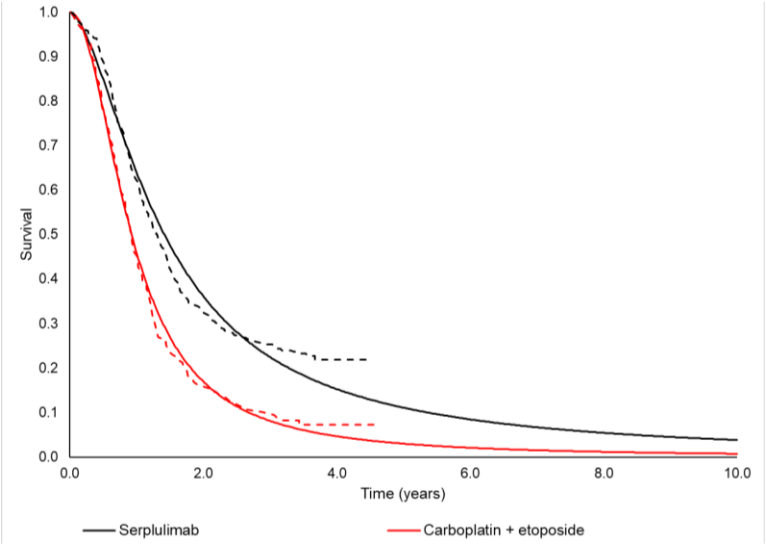


Abbreviations: *KM, Kaplan-Meier.*

Model base-case

The selected log-logistic OS extrapolations for the serplulimab and carboplatin-etoposide (placebo) arms in the model base-case are presented in Figure 19. As for PFS, each of the alternative OS parametric models described previously can be selected in the model, and the impact of the different extrapolations on the results are explored in scenario analyses.

Figure 19: Base-case OS extrapolations



Plausibility of extrapolation beyond trial

Whilst the ASTRUM-005 OS data is relatively complete, there is uncertainty around the appropriateness of the extrapolated portion of the curve beyond the observed trial data. Validation of the clinical plausibility of the log-logistic model for the extrapolations of OS was based on expert clinical opinion (Appendix M).

3.3.5 Extrapolation of TTOT

The Kaplan-Meier curve for TTOT for the ITT population in ASTRUM-005 is shown in **Error! Reference source not found.**. TTOT was defined based on the actual d uration of treatment exposure (weeks) in each treatment arm as $\frac{end\ of\ treatment\ date - date\ of\ randomisation + 1}{7}$. The median TTOT in the serplulimab arm was [redacted] weeks, compared to [redacted] weeks for the placebo arm.

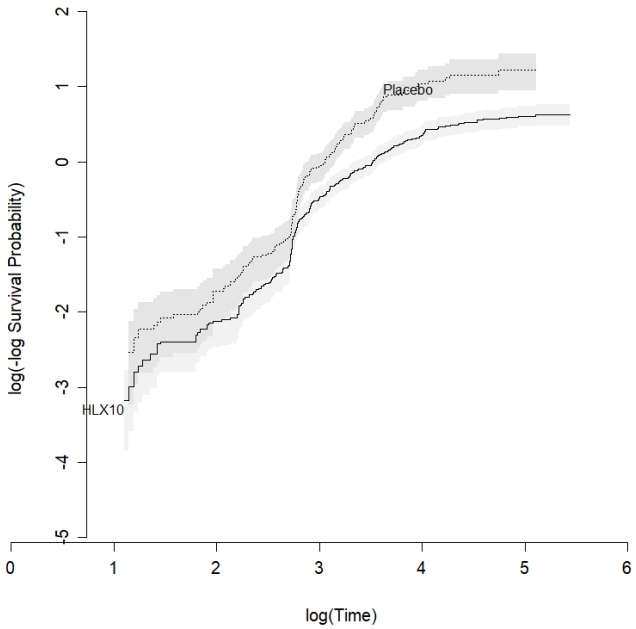
[redacted]

Abbreviations: *HLX10, serplulimab.*

Assessment of proportional hazards

For PFS and OS, a diagnostic plot of the log-cumulative hazard for TTOT against log-time for the ASTRUM-005 arms was assessed to test the proportional hazards assumption, as presented in Figure 20. Consistent with PFS and OS, the two log-cumulative hazard curves appear to have similar shapes without diverging or crossing each other, indicating that the proportional hazards assumption is not violated. However, as previously discussed, guidance from NICE DSU TSD14 states that it is not necessary to rely upon the assumption of proportional hazards when patient-level data are available (Latimer, 2013). Therefore, it was deemed most appropriate to fit separate parametric models to each treatment arm, as this approach involves fewer assumptions.

Figure 20: TTOT log-cumulative hazard plot from ASTRUM-005



Abbreviations: *HLX10, serplulimab.*

Visual and statistical goodness of fit of the parametric functions

As for PFS and OS, parametric distributions were assessed for their goodness of fit to the data using the AIC and BIC, with low values of AIC and BIC indicating a better statistical fit of the parametric curve to the trial data. According to these criteria, the Gompertz curve provided the best statistical fit, as presented in Table 32.

Table 32: Ranking of TTOT parametric fits based on AIC and BIC

Parametric model	Serplulimab				Placebo			
	AIC	Rank	BIC	Rank	AIC	Rank	BIC	Rank
Exponential	3097.9	7	3101.8	7	1536.9	3	1540.1	3
Weibull	3063.8	5	3071.7	5	1538.5	5	1545.0	5
Gamma	3080.4	6	3088.4	6	1537.8	4	1544.3	4
Log-normal	3043.8	4	3051.7	4	1591.5	7	1598.0	7
Log-logistic	2995.0	2	3002.9	2	1534.8	2	1541.3	2
Gen. Gamma	3035.9	3	3047.8	3	1539.0	6	1548.8	6
Gompertz	**2981.7**	**1**	**2989.6**	**1**	**1533.6**	**1**	**1540.1**	**1**

Abbreviations: *AIC, Akaike information criterion; BIC, Bayesian information criterion.*

The different parametric models for TTOT in the serplulimab and placebo arms superimposed on the respective KM curves are presented in **Error! Reference s ource not found.** and **Error! Reference source not found.**, respectively. Whilst the Gompertz model provided the best statistical fit to the trial data, this model provided an implausible long-term extrapolation beyond the end of the trial in the serplulimab arm based on visual inspection. As such, the log-logistic model which had the

second-best statistical fit, was judged to be the most appropriate model selection. As previously discussed, it is recommended in the guidance provided in NICE DSU TSD14 to fit the same type of model to each treatment arm; therefore, it was deemed most appropriate to apply the log-logistic extrapolation to both arms in the model (Latimer, 2013).

[redacted]

Abbreviations: *KM, Kaplan-Meier.*

[redacted]

Abbreviations: *KM, Kaplan-Meier.*

Model base-case

The selected log-logistic TTOT extrapolations for the serplulimab and carboplatin-etoposide (placebo) arms in the model base-case are presented in **Error! Reference s ource not found.**. For PFS and OS, each of the alternative parametric models described previously can be selected in the model, and the impact of the different extrapolations on the results are explored in scenario analyses.

[redacted]

3.3.6 PFS, OS, and TTOT extrapolations for atezolizumab

For the atezolizumab arm, PFS, OS, and TTOT extrapolations were generated by applying HRs derived from the MAIC to the cycle probabilities in the selected serplulimab extrapolation. Full details of the methodology of the MAIC are provided in Section 2.8. This approach was deemed most appropriate as it does not rely on the assumption that there is no difference between the trials in the distribution of effect-modifying variables when assessing the relative efficacy of serplulimab and atezolizumab, because any differences are adjusted for as part of the MAIC. The model also contains an option to extrapolate time-to-event outcomes in the atezolizumab arm using parametric curves derived from reconstructed pseudo-IPD, as discussed in Section 3.3.2. However, this approach was not selected in the base-case as the relative efficacy between the two treatment arms would be confounded by differences in the distribution of effect-modifying variables between ASTRUM-005 and IMpower133.

PFS

In the matched analysis from the MAIC, treatment with serplulimab was estimated to result in improved PFS in comparison with atezolizumab, with an estimated HR of [redacted]. In the model, this HR is applied to the cycle probabilities in the selected extrapolation for the serplulimab arm to generate the atezolizumab extrapolation. The selected base-case log-logistic extrapolation for the serplulimab arm and the corresponding HR-derived extrapolation for the atezolizumab arm are presented in **Error! Reference source not found.**. **Error! Reference source not found.** also shows that the selected PFS extrapolation for atezolizumab overestimates PFS compared to the Kaplan-Meier based on pseudo-IPD from the atezolizumab arm in IMpower133, resulting in a conservative assessment of the relative efficacy of serplulimab against atezolizumab in the model.

[redacted]

OS

In the matched analysis from the MAIC, treatment with serplulimab was estimated to result in improved OS in comparison with atezolizumab, with an estimated HR of [redacted]. As for PFS, this HR is applied to the cycle probabilities in the selected extrapolation for the serplulimab arm to generate the atezolizumab extrapolation. The selected base-case log-logistic extrapolation for the serplulimab arm and the corresponding HR-derived extrapolation for the atezolizumab arm are presented in **Error! Reference source not found.**. This figure also shows that the a tezolizumab extrapolation fits closely to the Kaplan-Meier based on pseudo-IPD from the atezolizumab arm in IMpower133, suggesting face validity of the atezolizumab extrapolation.

[redacted]

TTOT

The TTOT extrapolation for the atezolizumab arm was derived by applying the reciprocal of the OS HR from the MAIC to the selected TTOT extrapolation for serplulimab. The OS HR was judged to be more appropriate than the PFS because patients could remain on treatment beyond evidence of disease progression in

IMpower133, until loss of clinical benefit if certain criteria were met, as described in TA638 (National Institute of Health and Care Excellence, 2020). The selected base-case log-logistic extrapolation for the serplulimab arm and the corresponding HR-derived extrapolation for the atezolizumab arm are presented in **Error! Reference s ource not found.**. Pseudo-IPD could not be reconstructed to compare against the Kaplan-Meier based on the atezolizumab arm from IMpower133 because information on number at risk was not reported in TA638. Overall, patients spend longer on treatment with serplulimab compared to atezolizumab, consistent with the improved OS with serplulimab compared to atezolizumab.

[redacted]

3.3.7 Conclusion of base-case extrapolations

For the serplulimab and carboplatin-etoposide (placebo) arms, the base-case extrapolations of time-to-event data in the model are derived from independent models fitted to each of the arms in the ASTRUM-005 trial. A summary of the base-case selected extrapolations selected is provided in Table 33. For the atezolizumab arm, extrapolations of PFS, OS, and TTOT were generated by applying HRs from the MAIC to the selected extrapolation in the serplulimab arm. These were visually assessed against the Kaplan-Meier curves based on pseudo-IPD from the atezolizumab arm in IMpower133, which demonstrated that PFS in the atezolizumab is likely overestimated in the model, leading to a conservative estimate of the relative efficacy of serplulimab compared to atezolizumab. The clinical outcomes of the selected base-case extrapolations are detailed further in Appendix K.

It is important to note that there is uncertainty in the long-term extrapolations beyond the end of the trial including the duration of the treatment effect of serplulimab. As such, the model features the option to include treatment waning in the serplulimab arm to wane to match the cycle probabilities in either the atezolizumab or the placebo arm. Given the shape of the Kaplan-Meier curves in the observed trial data from ASTRUM-005, there is no indication for the loss of treatment effect within the trial period. Importantly, this contrasts with what was observed in the trial data from IMpower133 presented in TA638, as the Kaplan-Meier curves began to converge toward the end of the trial, indicating reduction of treatment effect. Furthermore,

ASTRUM-005 had a considerably longer follow-up compared to IMpower133, which provides a greater time for any potential loss of treatment effect to be observed. Therefore, in the base-case, no loss of treatment effect in the serplulimab arm is assumed; however, the impact of different assumptions regarding the duration of treatment effect is explored in scenario analysis.

Table 33: Base-case selected extrapolations

Endpoint	Treatment	Lowest AIC	Lowest BIC	Best visual fit	Selected fit	Rationale for selected fit
OS	Serplulimab	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Best statistical and visual fit, validated with clinical experts (Appendix M)
	Carboplatin-etoposide	Log-logistic	Log-logistic	Log-logistic	Log-logistic	
PFS	Serplulimab	Gen. Gamma	Gen. Gamma	Log-logistic	Log-logistic	NICE DSU TSD14 guidance (Latimer, 2013). Clinical experts' opinion (Appendix M)
	Carboplatin-etoposide	Log-logistic	Log-logistic	Log-logistic	Log-logistic	
TTOT	Serplulimab	Gompertz	Gompertz	Log-logistic	Log-logistic	Log-logistic 2nd best statistical fit and best visual fit. NICE DSU TSD14 guidance (Latimer, 2013)
	Carboplatin-etoposide	Gompertz	Gompertz	Log-logistic	Log-logistic	

Abbreviations: *OS, overall survival; NICE DSU TSD, National Institute of Health and Care Excellence Decision Support Unit Technical Support Document; PFS, progression-free survival; TTOT, time to off treatment.*

3.3.8 Population subgroups

ASTRUM-005 included a non-Asian prespecified subgroup, which was included in the economic model for completeness. A summary comparison of baseline characteristics and outcomes is provided in Table 34. Non-Asian patients had slightly lower median survival and PFS compared with the ITT population. More current smokers were also recorded in the non-Asian subgroup compared with the ITT, which may also explain the difference in outcomes. However, consultation with clinical experts confirmed that the ITT population was more generalisable to the NHS and is therefore suitable for decision-making. Furthermore, the population modelled is not a key driver of results. Nevertheless, to explore the efficacy and results in non-Asian patients, the model includes this subgroup, with time-to-event data, utilities, and AEs sourced from the ASTRUM-005 subgroup data. Further detail on the inputs and results of the non-Asian subgroup is provided in Section 3.10.

Table 34: Comparison of baseline characteristics and outcomes for the ITT and non-Asian subgroup of ASTRUM-005

Characteristic or endpoint	ITT	Non-Asian subgroup
Baseline median age	62.0	62.0
Proportion male	82.2%	87%
Proportion of non-smokers	19.8%	8.7%
Proportion of current smokers	25.5%	46.7%
Median OS (serplulimab)	15.77 months	15.64 months
Median PFS (serplulimab)	5.82 months	[redacted]
Median OS (placebo)	11.10 months	11.20 months
Median PFS (placebo)	4.34 months	[redacted]

***Abbreviations**: ITT, intention to treat; OS, overall survival; PFS, progression-free survival.*

3.3.9 Adverse events

Treatment-related Grade 3-5 AEs or serious AEs with an occurrence of more than 2% in either arm in ASTRUM-005, or those reported in TA638 (National Institute of Health and Care Excellence, 2020), were included in the model. The frequencies of AEs were obtained from the ASTRUM-005 trial. Data from the 13th June 2022 data cut were used. These frequencies are not suitable for use in the economic model because each patient can only contribute to the numerator once in the duration of the study, i.e. if a patient had 2 events of anaemia during the trial, they would count as 1 when reporting frequencies, as opposed to 2 if calculating the rate. Therefore, for use in the economic model, event probabilities were calculated by determining the ratio of the number of AE occurrences to the number of patient weeks at risk. Total follow-up was 23,367 (n=389) and 9,595 (n=196) in the serplulimab and placebo arms, respectively (see Table 35).

Table 35: Adverse events in ASTRUM-005, ITT population

Adverse event	Serplulimab with carboplatin and etoposide			Carboplatin and etoposide			Probability difference
	Count	Events	Weekly probability	Count	Events	Weekly probability	
Neutrophil count decreased	[redacted]						
White blood cell count decreased	[redacted]						
Neutropenia	[redacted]						
Platelet count decreased	[redacted]						
Anaemia	[redacted]						
Leukopenia	[redacted]						
Hyponatraemia	[redacted]						
Thrombocytopenia	[redacted]						
Lymphocyte count decreased	[redacted]						
Pneumonia	[redacted]						

Hypertriglyceridemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: ITT, intention to treat.*
***Source**: ASTRUM-005 Clinical Study Report (Shanghai Henlius Biotech, 2024)*

When compared to the probability of events reported in TA638 (National Institute of Health and Care Excellence, 2020), weekly probabilities were substantially higher in the ASTRUM-005 trial when compared to the IMpower133 trial in both arms, suggesting potential differences in patient populations. To account for the potential differences, AE probabilities in the atezolizumab arm in the model were calculated by applying the difference in probability of an AE in the atezolizumab arm vs. carboplatin-etoposide from IMpower133 to the AE probabilities in the carboplatin-etoposide arm from ASTRUM-005. Results from the non-Asian subgroup analysis were more comparable to those reported in TA638. As a result, a conservative base-case is applied using the AEs from the ITT, and an alternative assumption is explored in scenario analysis using probabilities from the non-Asian subgroup (see Table 36).

Table 36: Comparison of AE probabilities for IMpower133 and ASTRUM-055

Adverse event	IMpower133			ASTRUM-005					
	Atezolizumab (TA638)			Total			"non-Asian" subgroup		
	A+C+E	C+E	Difference	S+C+E	C+E	Difference	S+C+E	C+E	Difference
Anaemia	0.0026	0.0022	0.0004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	0.0004	0.0002	0.0002	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	NR			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	0.0005	0.0011	-0.0006	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	NR			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertriglyceridemia	NR			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	NR			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	NR			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	NR			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reaction	0.0004	0.0003	0.0001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	0.0013	0.0009	0.0004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	NR			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	0.0060	0.0058	0.0002	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	0.0042	0.0047	-0.0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pancytopenia	0.0001	0.0003	-0.0002	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	0.0009	0.0009	0.0000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	0.0003	0.0001	0.0002	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	0.0018	0.0015	0.0003	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	0.0003	0.0003	0.0000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	0.0007	0.0010	-0.0003	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	NR			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: A+C+E, atezolizumab + carboplatin + etoposide; AE, adverse event; C+E, carboplatin + etoposide; NR, not reported; S+C+E, serplulimab + carboplatin + etoposide.*

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality of life data from clinical trials

The ASTRUM-005 trial included the Euro Quality of Life 5 Dimensions 5-Level Version (EQ-5D-5L) questionnaire, which was completed by patients at each scheduled study visit. In total, 585 patients completed the EQ-5D-5L at baseline. 3,378 EQ-5D-DL measurements from were collected within the ASTRUM-005 study.

Mapped EQ-5D index mean and change from baseline values were summarised at each visit by treatment group and overall population in ASTRUM-005. The mean, median, standard deviation, min-max, and interquartile range were all reported.

3.4.2 Mapping

Utility values used for this analysis were derived according to NICE guidelines. As NICE does not recommend using the EQ-5D-5L value set directly, the EQ-5D-5L was mapped onto the EQ-5D-3L value set using the mapping function developed by the DSU (Hernández-Alava and Pudney, 2017), using the 'EEPRU dataset' (Hernández-Alava et al., 2023).

3.4.3 Health-related quality of life studies

An SLR was conducted to identify and collect evidence on economic evaluations, healthcare resource utilisation (HCRU), associated costs, and quality of life related to treatments for adults with untreated ES-SCLC. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix I. The SLR was conducted in accordance with guidelines provided by the Cochrane collaboration, the CRD and NICE requirements, with methodology and results being reported as per PRISMA guidelines. Full details of the SLR search strategy, study selection process, results, and narrative synthesis are presented in Appendix I.

Electronic searches were conducted across key biomedical databases on May 7, 2024. 694 records were identified, of which 190 were duplicates and 448 were excluded following title/ abstract screening. All remaining 55 references were retrieved for full publication screening; however, 29 articles failed to meet the PICOS inclusion criteria and were excluded.

26 publications identified through database searching were included in the review, with 7 additional articles being identified through supplementary searches for published and unpublished economic and quality of life literature. Of these, 5 identified publications provided relevant information on the quality of life of adult patients with ES-SCLC. The PRISMA flow diagram representing the study identification and selection process is presented in Figure 13.

3.4.4 Adverse reactions

Adverse event disutility values were obtained from the atezolizumab NICE appraisal (TA638) (National Institute of Health and Care Excellence, 2020) and the literature. Two alternative approaches were considered for the inclusion of the impact of AEs on HRQoL:

- Additional utility decrements for AEs are required, as the base-case health state utility values may underestimate the disutility associated with AEs.
- No additional disutility decrements for AEs are required, as the disutility is captured by the base-case health state utility values through the patient-reported EQ-5D in ASTRUM-005.

In line with the Committee's preferences in the previous NICE appraisal for ES-SCLC (TA638), the base-case analysis takes the former assumption and considers AE-related disutilities. In scenario analysis, the impact of excluding additional AE-related disutilities due to potential double counting was assessed. To calculate AE disutilities, the published disutility associated with each AE was multiplied by the weekly probability and average duration reported in ASTRUM-005 (Table 37 and Table 38). The weekly probability of each AE was specific for each treatment as reported in Section 3.3.9. Disutilities due to AEs were applied while on treatment in the PFS and PD states. A scenario analysis is included for the non-Asian subgroup in Section 3.10, with AE probabilities derived from the non-Asian subgroup in the serplulimab and placebo arms. Several publications were identified to model utility loss in ES-SCLC:

- Nafees et al, 2008: health state utilities for NSCLC (Nafees et al., 2008)

- Nafees et al, 2016: health state utilities in NSCLC: An international study (Nafees et al., 2017)

- Doyle et al, 2008: health state utility scores in advanced NSCLC (Doyle et al., 2008)

Table 37. Disutility values for adverse events

Adverse event	Disutility	Original source
Anaemia	-0.07346	Assumed equal to fatigue in Nafees et al, 2008* (Nafees et al., 2008)
Diarrhoea	-0.0468	Nafees et al, 2008* (Nafees et al., 2008)
Fatigue	-0.07346	Nafees et al. 2008 (Nafees et al., 2008)
Febrile neutropenia	-0.09002	Nafees et al, 2008* (Nafees et al., 2008)
Hyperglycaemia	-0.03	Assumed the same as hypertension
Hypertension	-0.03	Nafees et al. 2016 (Nafees et al., 2017)
Hypertriglyceridaemia	-0.03	Assumed the same as hypertension
Hypocalcaemia	-0.03	Assumed the same as hypertension
Hypokalaemia	-0.03	Assumed the same as hypertension
Hyponatraemia	-0.085	NICE TA428 disutility: KEYNOTE-10
Infusion-related reaction	-0.05	Doyle et al, 2008* (Doyle et al., 2008)
Leukopenia	-0.08973	Assumed equal to neutropenia*
Lymphocyte count decreased	0	Assumption*
Neutropenia	-0.08973	Nafees et al, 2008* (Nafees et al., 2008)
Neutrophil count decreased	0	Assumption*
Pancytopenia	-0.08973	Assumed equal to neutropenia*
Platelet count decreased	-0.05	Assumption based on nintedanib NICE appraisal (TA347)*
Pneumonia	-0.008	Marti et al, 2013* (Martí et al., 2013)
Thrombocytopenia	-0.08973	Assumed equal to neutropenia*
Vomiting	-0.04802	Nafees et al. (2008)* (Nafees et al., 2008)
White blood cell count decreased	-0.05	Assumption based on nintedanib NICE appraisal (TA347)*

***Abbreviations**: NICE, National Centre for Health and Care Excellence.*
**Based on values reported in the clarification questions of TA638 (National Institute of Health and Care Excellence, 2020).*

Table 38. Duration (weeks) of adverse events included in the cost-effectiveness model.

Adverse Event	N	Duration (weeks)	SE	Reference
Anaemia	[redacted]	[redacted]	[redacted]	ASTRUM-005
Diarrhoea	[redacted]	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	[redacted]	
Febrile neutropenia	[redacted]	[redacted]	[redacted]	
Hyperglycaemia	[redacted]	[redacted]	[redacted]	
Hypertension	[redacted]	[redacted]	[redacted]	
Hypertriglyceridaemia	[redacted]	[redacted]	[redacted]	
Hypocalcaemia	[redacted]	[redacted]	[redacted]	
Hypokalaemia	[redacted]	[redacted]	[redacted]	
Hyponatraemia	[redacted]	[redacted]	[redacted]	
Leukopenia	[redacted]	[redacted]	[redacted]	ASTRUM-005
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]	
Neutropenia	[redacted]	[redacted]	[redacted]	
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	
Pancytopenia	[redacted]	[redacted]	[redacted]	Assumed to be the same as leukopenia

Platelet count decreased	[redacted]	[redacted]	[redacted]	ASTRUM-005
Pneumonia	[redacted]	[redacted]	[redacted]	
Thrombocytopenia	[redacted]	[redacted]	[redacted]	
Vomiting	[redacted]	[redacted]	[redacted]	
White blood cell count decreased	[redacted]	[redacted]	[redacted]	

***Abbreviations**: SE, standard error.*

3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

HRQoL measures collected in the ASTRUM-005 trial were analysed to derive health state utility values in the economic model. Data from the 13th June 2022 data cut was used.

Based on previous appraisals in oncology and the Committee's conclusion in TA638 (National Institute of Health and Care Excellence, 2020) that the time to death approach should not be considered the standard approach in ES-SCLC, progression-based utilities were used in the base-case. This approach estimates patient utility based on their progression status instead of patients' proximity to death and is more widely accepted. Furthermore, the TTD approach introduces time-dependent confounding because post-baseline covariates (such as proximity to death) are influenced by the treatment itself. This creates potential confounding because the covariate is both a predictor and an outcome of interest.

In the base-case, utility values associated with disease progression state regardless of treatment status were used and are presented in Table 39. To include additional granularity in the estimation method, patients' treatment status was also included (i.e., on or off treatment), resulting in four distinct utility values in the base-case, as presented in Table 39. This approach was explored in scenario analysis. Results from the on/off treatment analysis show that when patients are on treatment, they experience higher utilities in the PFS state versus the progressed state. When off treatment, they experience higher utilities in the progressed state versus the PFS state. This can be explained by a number of factors:

- Patients in the PFS state who are off treatment may still be experiencing long-term toxicities or residual side effects from treatment, and may feel anxious about disease progression without active treatment leading to lower utilities

- Patients who remain on treatment and progression-free may represent a subset of patients who tolerate the treatment well (i.e. better symptom

management, improved tumour control, and a sense of stability), leading to higher utilities.

- Progressed patients off treatment may have adjusted their expectations and focused on symptom management, improving their reported QoL.

For logical consistency, the utilities by disease progression state without on/off treatment status were used in the base-case.

Table 39: Estimated utility by disease progression state and on/off-treatment status using data from ASTRUM-005

Health state	Utility value (mean, 95% CI)
By disease progression and on/off-treatment status (base-case)	
On-treatment	
PFS	0.855 (0.843, 0.866)
Progressed disease	0.836 (0.813, 0.859)
Off-treatment	
PFS	0.757 (0.741, 0.773)
Progressed disease	0.786 (0.760. 0.812)
By disease progression state	
PFS	0.838 (0.826, 0.849)
Progressed disease	0.805 (0.785, 0.825)

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

An alternative scenario explored the use of the TTD approach to derive health state utility values. The TTD approach was estimated using the EQ-5D collected in ASTRUM-005 and is shown in Table 40. Four “proximity to death” sub-states were used to capture patients HRQoL as a proxy of time to death: ≤5 weeks before death, >5 to ≤15 weeks before death, >15 to ≤30 weeks before death, and >30 weeks before death. This approach was in line with the time categories used in TA638 (National Institute of Health and Care Excellence, 2020).

These sub-states were further stratified by on/off-treatment status. A mixed linear model was used to estimate utilities in each of these eight categories. Data from patients still alive at time of data cutoff were included in the >30 weeks before death category if they had over 30 weeks of follow-up after the EQ-5D questionnaire was completed. The model was adjusted for baseline EQ-5D values and “proximity of death”. Health state utility values were computed using the least square means method. Analyses were performed in RStudio, using the ‘nlme’ and ‘emmeans’ packages for conducting mixed linear models and computing least square means, respectively.

When using the TTD approach to estimate the utility at each cycle, the sum product of the percentage of patients alive at a given cycle who transition to the death state at ≤5, >15 to ≤30, and >30 weeks after that cycle with the estimated utility based on the proximity to death state was calculated.

Table 40: Estimated utility using time to death and on/off-treatment status using data from ASTRUM-005

Health state	Model-based estimate	n	Descriptive statistics
On-treatment			
0-≤5 weeks	0.849 (0.785, 0.913)	20	0.680 (0.543, 0.817)
>5-≤15 weeks	0.825 (0.799, 0.852)	113	0.778 (0.737, 0.818)
>15-≤30 weeks	0.836 (0.819, 0.854)	322	0.809 (0.789, 0.829)
>30 weeks	0.862 (0.851, 0.873)	2,098	0.859 (0.852, 0.866)
Off-treatment			
0-≤5 weeks	0.464 (0.361, 0.567)	18	0.432 (0.250, 0.613)
>5-≤15 weeks	0.697 (0.640, 0.753)	68	0.673 (0.596, 0.749)
>15-≤30 weeks	0.765 (0.718, 0.812)	94	0.770 (0.724, 0.817)
>30 weeks	0.817 (0.785, 0.850)	216	0.828 (0.804, 0.852)

The trial-reported values for PFS and PD, on-treatment, result in utility values that are near the general population. The potential overestimation of EQ-5D in oncology trials has been studied in the literature and can be attributed to the adaptation of patients to the disease as well as the inability of EQ-5D domains to fully capture the AEs associated with chemotherapy and its insensitivity to dimensions such as fatigue, cognitive functioning or social well-being. This leads to higher than expected utilities (Lang et al., 2010, Llewellyn-Thomas et al., 1993, Pickard et al., 2007).

A scenario analysis is also provided for the non-Asian subgroup, with utility values estimated in this subgroup presented in Section 3.10.

A summary of the utilities applied in the model base case is provided in Table 41.

Table 41: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	95% confidence interval	Reference in submission (section and page number)	Justification
PFS – on-treatment	0.855	0.843, 0.866	Table 39	Based on the Committee's preferred assumptions in TA638. The TTD approach should not be considered the standard approach in ES-
PFS – off-treatment	0.757	0.741, 0.773		
PD – on-treatment	0.836	0.813, 0.859		
PD – off-treatment	0.786	0.760, 0.812		
PFS	0.838	0.826, 0.849		
PD	0.805	0.785, 0.825		
Anaemia	-0.07346	Assumed +/-10%	Table 37	
Diarrhoea	-0.0468	Assumed +/-10%		

Fatigue	-0.07346	Assumed +/-10%		SCLC. The Committee also preferred for AE disutilities to be modelled in addition to the health state utilities.
Febrile neutropenia	-0.09002	Assumed +/-10%		
Hyperglycaemia	-0.03	Assumed +/-10%		
Hypertension	-0.03	Assumed +/-10%		
Hypertriglyceridaemia	-0.03	Assumed +/-10%		
Hypocalcaemia	-0.03	Assumed +/-10%		
Hypokalaemia	-0.03	Assumed +/-10%		
Hyponatraemia	-0.085	Assumed +/-10%		
Infusion-related reaction	-0.05	Assumed +/-10%		
Leukopenia	-0.08973	Assumed +/-10%		
Lymphocyte count decreased	0	Assumed +/-10%		
Neutropenia	-0.08973	Assumed +/-10%		
Neutrophil count decreased	0	Assumed +/-10%		
Pancytopenia	-0.08973	Assumed +/-10%		
Platelet count decreased	-0.05	Assumed +/-10%		
Pneumonia	-0.008	Assumed +/-10%		
Thrombocytopenia	-0.08973	Assumed +/-10%		
Vomiting	-0.04802	Assumed +/-10%		
White blood cell count decreased	-0.05	Assumed +/-10%		

Abbreviations*: AE, adverse event; ES-SCLC; extensive-stage small cell lunger cancer; PD, progressed disease; PFS, progression-free survival; TTD, time to death.*

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify and collect evidence on economic evaluations, healthcare resource utilisation (HCRU), associated costs and quality of life related to treatments for adults with untreated ES-SCLC, by ESMO treatment guidelines. The SLR was conducted in accordance with guidelines provided by the Cochrane collaboration and the CRD, as well as NICE requirements, with methodology and results being reported as per PRISMA guidelines. Full details of the SLR search strategy, study selection process, results, and narrative synthesis are presented in Appendix I.

Electronic searches were conducted across key biomedical databases on 7th May 2024. 694 records were identified, of which 190 were duplicates and 448 were excluded following title/ abstract screening. All remaining 55 references were retrieved for full publication screening; however, 29 articles failed to meet the PICOS inclusion criteria and were excluded. 26 publications identified through database searching were included in the review, with 7 additional articles being identified

through supplementary searches for published and unpublished economic and quality of life literature. Of these, one real-world population-based study provided relevant information on healthcare resource utilisation associated with the treatment patterns and clinical outcomes of patients with ES-SCLC. The PRISMA flow diagram representing the study identification and selection process is presented in Figure 13. Further detail of the healthcare and resource use SLR is provided in Appendix I.

3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug dosing, time on treatment, and discontinuation for serplulimab and carboplatin and etoposide are estimated from the ASTRUM-005 trial. In the base-case, vial sharing is assumed for the administration of chemotherapy drugs (i.e., no wastage), consistent with previous oncology appraisals including TA638 (National Institute of Health and Care Excellence, 2020). For serplulimab, vial sharing was not assumed in the base-case, as clinical opinion confirmed that vials are not expected to be shared in hospitals across the NHS. Further detail of the clinical opinion is provided in Appendix M. Atezolizumab is given at a fixed dose. The impact of the vial sharing assumptions are explored in scenario analyses.

The drug acquisition costs applied in the model are summarised in Table 42, including the cost of first-line treatments in each of the model arms and the cost of subsequent therapies. Carboplatin, etoposide, cyclophosphamide, doxorubicin, and vincristine are available as generics to the NHS; therefore, unit costs were sourced from the electronic market information tool (eMIT). The list prices for atezolizumab and topotecan were sourced from the BNF (British National Formulary).

Table 42: Drug acquisition costs.

Drug	Cost per vial	Standard deviation	Source
Serplulimab 10mL/100mg (list price)	£1,321.83*	NA	Accord, data on file
Serplulimab 10mL/100mg (PAS price)	[redacted]	NA	
Atezolizumab 20mL/1,200mg (list price)	£3,807.69	NA	BNF, January 2025
Carboplatin 5mL/50mg	£6.71	£4.97	eMIT 2024
Carboplatin 60mL/600mg	£38.93	£38.35	eMIT 2024
Etoposide 5mL/100mg	£5.07	£2.04	eMIT 2024
Etoposide 25mL/500mg	£13.93	£10.66	eMIT 2024
Cyclophosphamide 1g powder for solution	£13.11	£0.68	eMIT 2024

Doxorubicin 25mL/50mg	£10.06	£37.02	eMIT 2024
Vincristine 2mL/2mg	£11.00	£9.53	eMIT 2024
Topotecan 1mg capsules	£360.00	NA	BNF, January 2025

Note: **Proposed list price.*
Abbreviations*: BNF, British National Formulary; eMIT, electronic market information tool; NA, not applicable; PAS, patient access scheme.*
Sources*: (Accord Data on File, 2024a, British National Formulary, 2025)*

Relative dose intensity (RDI) is applied to account for missed doses for serplulimab in ASTRUM-005 and for atezolizumab in IMpower133 (using information from TA638 (National Institute of Health and Care Excellence, 2020)). For carboplatin and etoposide, RDI was also estimated using information from ASTRUM-005. A summary of the RDI for each drug is provided in Table 43.

Table 43: Relative dose intensity reported in the ASTRUM-005 and IMpower 133 studies

Drug	Regimen	RDI	SE	Source
Serplulimab	Serplulimab plus carboplatin and etoposide	[redacted]	[redacted]	ASTRUM-005 CSR
Atezolizumab	Atezolizumab plus carboplatin and etoposide	92.10%	0.70%	TA638
Carboplatin	Carboplatin and etoposide with or without serplulimab	[redacted]	[redacted]	ASTRUM-005 CSR
Etoposide				

Abbreviations*: CSR, clinical study report; RDI: relative dose intensity; SE: standard deviation.*
Sources*: (Shanghai Henlius Biotech, 2024, National Institute of Health and Care Excellence, 2020)*

For serplulimab, weight-based dosing (4.5mg/kg) was applied to a distribution of weights informed by the ASTRUM-005 trial (mean: 68.395kg; standard deviation: 15.1149kg) to calculate the number of packs required per treatment cycle. Considering wastage, the average number of packs per treatment cycle was calculated to be 3.58 (see Table 44). The cost per treatment cycle was calculated by multiplying the pack the cost by the average number of packs per treatment cycle.

Table 44: Average number of packs per treatment cycle for serplulimab (weight-based dosing)

Weight (kg)	Cumulative distribution	Proportion in each band (non-cumulative)	Number of vials	Distribution of vials
0.00				
22.22	0.00	0.00	1	0.00
44.44	0.06	0.06	2	0.11
66.67	0.45	0.40	3	1.19
88.89	0.91	0.46	4	1.83
111.11	1.00	0.09	5	0.43
133.33	1.00	0.00	6	0.01
155.56	1.00	0.00	7	0.00
Total (average number of packs per treatment cycle)				**3.58**

Abbreviations*: kg, kilogram.*

For all chemotherapy drugs included in the model, including carboplatin-etoposide, the cost per administration was calculated using the mean BSA (1.77m²) of the participants in the ASTRUM-005 trial. This was calculated using the Dubois formula, where W represents the mean weight of the population in kg (68.395kg) and H represents the mean height of the population in cm (167.27cm): $BSA = 0.007184 \times (W^{0.425}) \times (H^{0.725})$. For carboplatin, the dosing of which is based on AUC, an average dose of 300mg/m^2 was assumed, which represents an average population with slightly impaired renal function. Atezolizumab is provided as a fixed dose (1200mg).

The dosing schedule and dose per administration of all drugs included in the cost-effectiveness model is summarised in Table 45. The drug costs of the combination regimens were assumed to be equal to the sum of individual drug's costs included in the combination regimen. The drug cost per treatment cycle for the different treatment regimens in the cost-effectiveness model are summarised in Table 46. The cost per treatment cycle is calculated using pack price, the average number of packs per cycle and RDI.

Table 45: Dosing schedule and dose per administration

Drug	Dose per administration	Administration frequency
Serplulimab	4.5 mg/kg	Q3W
Atezolizumab	1,200 mg	Q3W
Carboplatin	5mg/mL/min (AUC) 300mg/m^2 assumed	Q3W
Etoposide	100 mg/m^2/day	Q3W (administered on 3 days in each cycle)
Cyclophosphamide	1000mg/m^2	Q3W
Doxorubicin	50mg/m^2	Q3W
Vincristine	1.4mg/m^2	Q3W
Topotecan	2.3mg/m^2/day for 5 days	Q3W (administered on 5 days in each cycle)

***Abbreviations**: AUC, area under curve; Q3W, once every 3 weeks;*

Table 46: Drug cost per treatment cycle for treatment regimens used in the cost-effectiveness model

Regimen	Cost per treatment cycle
Serplulimab plus carboplatin-etoposide	Serplulimab: £4,354.21 (list) Serplulimab: [redacted] (PAS) Carboplatin: £29.57 Etoposide: £17.71 **Total (list): £4,401.48** **Total (PAS): [redacted]**
Atezolizumab plus carboplatin-etoposide	Atezolizumab: £3,506.88 Carboplatin: £29.57 Etoposide: £17.71 **Total: £3,554.16**
Carboplatin-etoposide	Carboplatin: £29.57 Etoposide: £17.71 **Total: £47.28**
Topotecan	**Total: £733.21**
Cyclophosphamide plus doxorubicin plus vincristine (CAV)	Cyclophosphamide: £23.22 Doxorubicin: £17.82 Vincristine: £13.64 **Total: £54.67**

***Abbreviations**: PAS, Patient access scheme.*

3.5.2 Subsequent treatment costs

To capture the full cost of treatment appropriately, subsequent treatment costs were included in the model and applied to all patients who were progressed or off-treatment. The subsequent therapies included in the model are informed by clinical expert advice elicited to support the atezolizumab appraisal, TA638 (National Institute of Health and Care Excellence, 2020): according to UK practising oncologists, approximately 10-20% patients move to second-line treatment once their disease has relapsed, with 80-90% receiving palliative care or surveillance only. In UK clinical practice patients are treated by either a re-challenge with their first-line chemotherapy, treated with topotecan, or treated with cyclophosphamide, doxorubicin and vincristine (CAV). Furthermore, the consensus amongst the experts was that a third of patients would be attributed to each of these three predominant second-line therapies. Therefore, in the model base-case it is assumed that 85% of patients receive second-line therapy, with 5% receiving a re-challenge with their first-line chemotherapy (carboplatin-etoposide), 5% receiving oral topotecan, and 5% receiving CAV. These second-line therapies are also aligned with the treatment algorithm for SCLC in patients with recurrent SCLC (i.e. second-line therapy and beyond) outlined in the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of SCLC. The proportion of patients receiving each subsequent therapy was assumed to be equivalent in the different treatment arms in the model.

3.5.3 Administration costs

The drug administration costs used in the model are summarised in Table 47. The administration cost for the first administration (i.e., Day 1 of the treatment cycle for all combination regimens) was costed as a complex chemotherapy day case procedure (SB13Z of the NHS reference costs). For the subsequent elements of etoposide treatment (i.e., Day 2 and 3 of each treatment cycle), the cost of delivering subsequent elements of a chemotherapy cycle as a day case procedure was applied (SB15Z of the NHS reference costs). Since the infusion of serplulimab or atezolizumab alone requires less time, costs relating to a simple infusion were used for patients receiving monotherapy (SB12Z of the NHS reference costs (NHS England, 2023)).

Table 47: Drug administration costs

Drug	Type of administration	NHS reference code	Cost per administration
First administration of treatment cycle for all combination regiments	Deliver more Complex Parenteral Chemotherapy at first attendance – daycase.	SB13Z	£518.82
Subsequent elements of etoposide treatment, i.e. Day 2 and 3 of each treatment cycle	Deliver subsequent elements of a chemotherapy cycle – daycase.	SB15Z	£413.69
Serplulimab/ atezolizumab monotherapy administration	Deliver simple parenteral chemotherapy at first attendance – outpatient.	SB12Z	£217.22

***Reference**: (NHS England, 2023)*

3.5.4 Health state unit costs and resource use

Resource use data was sourced from the previous NICE appraisal for ES-SCLC, TA638. It considered different treatment options and disease stages, including carboplatin-etoposide treatment, atezolizumab plus carboplatin-etoposide treatment, surveillance only, and atezolizumab monotherapy (Table 48). This data was obtained from a survey of clinicians and represents the expected average resource use of a patient considering treatment and disease stage (National Institute of Health and Care Excellence, 2020). The resource use for serplulimab was assumed to be equivalent to atezolizumab and this assumption was validated with clinical experts. As the reported resource use costs already considers the average duration of treatment, the costs were divided over the estimated time frame reported in Table 48 and applied for the duration of the time frame. The weekly surveillance cost was calculated and applied to patients receiving surveillance or subsequent second-line therapy until death. The unit costs associated with each resource are presented in Table 49.

Table 48: Resource use for ES-SCLC treatment and disease stages, per patient

Resource	Receiving carboplatin-etoposide treatment (first 4 cycles)		Receiving serplulimab/atezolizumab plus carboplatin-etoposide treatment (first 4 cycles)		Receiving surveillance/subsequent 2L therapy		Receiving serplulimab/atezolizumab monotherapy (after first 4 chemo cycles)	
	Number of appointments (mean ± SD)	% of patients requiring appointments (mean ± SD)	Number of appointments (mean ± SD)	% of patients requiring appointments (mean ± SD)	Number of appointments (mean ± SD)	% of patients requiring appointments (mean ± SD)	Number of appointments (mean ± SD)	% of patients requiring appointments (mean ± SD)
Estimated time frame	4 cycles		4 cycles		3-4 months		4-5 months	
Outpatient visit	5.0±1.5	100±0	5.0±1.5	100±0	3.6±2.1	86±19	5.0±2.1	100±0
GP visit – surgery	1.9±1.3	71±39	1.9±1.3	71±39	2.3±1.4	69±38	1.5±1.3	71±39
GP visit – home	0.6±1.5	68±43	0.7±0.8	68±43	1.6±1.3	66±40	1.2±1.3	68±43
Cancer nurse visit	1.6±1.4	67±37	1.6±1.4	75±32	2.1±1.3	54±34	2.0±.0.5	61±40
Community nurse visit	1.6±1.5	64±37	1.7±1.5	68±31	1.5±1.4	47±39	1.1±1.1	61±40
ECG	0.3±0.5	64±48	0.5±0.5	66±45	0.1±0.4	50±50	0.2±0.4	51±48
Chest X-ray	2.0±1.9	78±32	2.0±1.9	75±30	2.4±1.3	74±21	2.8±1.7	71±32
CT scan	1.6±0.5	96±9	1.6±0.5	89±20	1.6±1.0	69±28	1.9±1.1	86±20
MRI scan	0.4±0.5	48±45	0.4±0.5	61±48	0.3±0.5	49±48	0.4±0.8	51±48
Blood test	4.0±0	100±0	4.4±0	35±0	6±0	80±0	2.2±3.11	100±0

***Abbreviations**: CT, computerised tomography; ECG, electrocardiogram; GP, general practitioner; SD, standard deviation.*

Table 49: Unit costs for both PFS and PD health states

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£148.19	Per visit	National schedule of NHS costs 2022/23 - Total Outpatient Attendances - Service code 800, Clinical Oncology consultant led
GP surgery visit	£49.00	Per visit	PSSRU 2023, pg 64, general practitioner, Per surgery consultation lasting 10 minutes
GP home visit	£93.28	Per visit	TA638: 2018 cost inflated to 2023 cost (TA638 reported: PSSRU 2016, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel - inflated to 2017/18)
Cancer nurse visit	£48.00	Per visit	Assumed to be 66.7% of Community Nurse (PSSRU 2023, band 8a cost per working hour, 66.7%)
Community nurse visit	£72.00	Per visit	PSSRU 2023, pg 56, unit costs for community-based scientific and professional staff, band 8a cost per working hour
ECG	£370.94	Per visit	National schedule of NHS costs 2022/23, complex ECG (EY50Z)
Chest X-ray	£154.13	Per case	National schedule of NHS costs 2022/23, diagnostic imaging (RD24Z two areas, with contrast)
CT scan	£154.13	Per case	National schedule of NHS costs 2022/23, diagnostic imaging (RD24Z two areas, with contrast)
MRI scan	£303.07	Per scan	National schedule of NHS costs 2022/23, diagnostic imaging (RD05Z, scan of two or three areas with contrast)
Blood test	£2.75	Per scan	National schedule of NHS costs 2022/23 (DAPS05, haematology)

***Abbreviations**: CT, computerised tomography; ECG, electrocardiogram; GP, general practitioner; HRG, healthcare resource group; PD, progressed disease; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit.*
***Sources**: (NHS England, 2023, Personal Social Services Research Unit, 2022, National Institute of Health and Care Excellence, 2020)*

The calculated average cost for a patient in each treatment and disease stage was:

- On carboplatin-etoposide treatment = £1,594.27 expected to represent 4 cycles of treatment
- On serplulimab/atezolizumab plus carboplatin-etoposide treatment = £1,651.00 expected to represent 4 cycles of treatment
- On serplulimab/atezolizumab monotherapy = £1,652.85 expected to represent 4-5 months' treatment
- On surveillance/receiving subsequent 2L therapy = £85.13 per week applied until death

The cost of PCI was also included in the model in line with the assumptions used in TA638. 90% of patients were assumed to receive PCI every 3 weeks for a maximum of 5 doses. A specific cost for PCI is not available in the NHS reference costs;

therefore, the sum of the NHS reference costs for preparation and delivery of radiotherapy was used (HRG codes: SC47Z = £463.46 and SC22Z = £252.65; total cost = £716.11). The cost of PCI is applied for the PFS state only.

3.5.5 Cost of terminal care

Terminal care costs specific to SCLC were used in the model (Oliver et al., 2001). The mean cost of palliative care reported was £3,495 in 1998 prices. This was inflated to 2024 prices using the PSSRU inflation index for Hospital and Community Health Services, giving a cost of £7,440.60. As 2023/24 inflation indices were not yet available at the time of submission, the average rate of inflation over the previous three years was assumed.

3.5.6 Adverse reaction unit costs and resource use

As described previously (Section 3.3.9), the weekly probabilities for treatment-related Grade 3-5 AEs or serious AEs, with an occurrence of 2% or more in either arm of the ASTRUM-005 or IMpower133 studies were extracted directly from the ASTRUM-005 trial data and atezolizumab appraisal (TA638) respectively. The associated AE costs are applied for the duration of time in which a patient is on treatment. To calculate the costs associated with AEs in the model, the weekly probability is multiplied by the cost of each AE (Table 50).

Table 50: Unit cost per AE used in the model

Adverse Event	Cost	Reference
Anaemia	£3,380.51	Atezolizumab appraisal TA638 inflated to 2024 using NHSCII pay and prices
Diarrhoea	£199.83	National Schedule of NHS costs 2022/2023 Summary OP attendances, currency code WF01B, service code 106, Non-Admitted Face-to-Face Attendance, First, consultant led, Upper Gastrointestinal Surgery Service
Fatigue	£928.25	National Schedule of NHS costs 2022/23. Weighted average of total HRGs SA04G-L
Febrile neutropenia	£8,727.35	Atezolizumab appraisal TA638 inflated to 2024 using NHSCII pay and prices
Hyperglycaemia	£226.54	Assumed same as ‘neutrophil count decreased’
Hypertension	£759.36	National Schedule of NHS costs 2022/23. Total HRGs EB04Z
Hypertriglyceridaemia	£226.54	Assumed same as ‘neutrophil count decreased’
Hypocalcaemia	£226.54	Assumed same as ‘neutrophil count decreased’
Hypokalaemia	£226.54	Assumed same as ‘neutrophil count decreased’
Hyponatraemia	£226.54	Assumed same as ‘neutrophil count decreased’
Leukopenia	£463.61	Atezolizumab appraisal TA638 inflated to 2024 using NHSCII pay and prices
Lymphocyte count decreased	£226.54	Assumed same as ‘neutrophil count decreased’

Neutropenia	£739.06	Atezolizumab appraisal TA638 inflated to 2024 using NHSCII pay and prices (original source: Brown 2013)
Neutrophil count decreased	£226.54	Atezolizumab appraisal TA638 inflated to 2024 using NHSCII pay and prices
Pancytopenia	£739.06	Assumed same as 'neutropenia'
Platelet count decreased	£226.54	Assumed same as 'neutrophil count decreased'
Pneumonia	£3,423.55	Atezolizumab appraisal TA638 inflated to 2024 using NHSCII pay and prices
Thrombocytopenia	£150.61	Atezolizumab appraisal TA638 inflated to 2024 using NHSCII pay and prices
Vomiting	£199.83	Assumed same as 'diarrhoea'
White blood cell count decreased	£226.54	Assumed same as 'neutrophil count decreased'

***Abbreviations**: HRG, healthcare resource group; NHSCII, NHS cost inflation index; OP, outpatient; TA, technology appraisal*
***Sources**: (NHS England, 2023, Personal Social Services Research Unit, 2022, National Institute of Health and Care Excellence, 2020)*

3.5.7 Miscellaneous unit costs and resource use

No miscellaneous costs are included in the cost-effectiveness analysis beyond those discussed in Sections 3.5.1 – 3.5.6.

3.6 Severity

ES-SCLC is a severe condition with a median life expectancy of 9–10 months on platinum-based chemotherapy, and serplulimab qualifies for a severity weight of 1.2 (Wlodarczyk et al., 2018, Zhang et al., 2022, Dingemans et al., 2021). The summary feature of the QALY shortfall analysis is provided in Table 51. Given the time of submission of atezolizumab (2019), the submission did not include a severity modifier, although the manufacturer (and ERG) considered atezolizumab to meet end-of-life criteria. Based on the total QALYs accumulated in the atezolizumab arm of 1.52, discounted at 3.5%, this represents an absolute shortfall of 10.41 QALYs given the QALYs otherwise accrued in the general population (11.91).

Table 51: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	17.8% female	Section 3.3.1
Starting age	62.0	

***Abbreviations**: QALY, quality-adjusted life year.*

3.7 Summary of base-case analysis inputs and assumptions

3.7.1 Summary of base-case analysis inputs

A summary of the base-case analysis inputs is provided in Table 52.

Table 52: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General model parameters			
Time horizon	Lifetime	NA	Section 3.2.2
Discount rate – costs and outcomes	3.5%	NA	
Population parameters			
Age	62.0	Not varied	Section 3.3.1
Body weight	68.4kg	SD: 15.12	
Height	167.27cm	SD: 8.435	
% female	17.8%	Not varied	
Utilities – base-case			
Progression-free	0.838	95% CI (0.826, 0.849)	Section 3.4.5
Progressed disease	0.805	95% CI (0.785, 0.825)	
Disutilities AEs			
Anaemia	-0.07346	Assumed +/- 10%	Table 37
Diarrhoea	-0.0468		
Fatigue	-0.07346		
Febrile neutropenia	-0.09002		
Hyperglycaemia	-0.03		
Hypertension	-0.03		
Hypertriglyceridaemia	-0.03		
Hypocalcaemia	-0.03		
Hypokalaemia	-0.03		
Hyponatraemia	-0.085		
Infusion-related reaction	-0.05		
Leukopenia	-0.08973		
Lymphocyte count decreased	0		
Neutropenia	-0.08973		
Neutrophil count decreased	0		
Pancytopenia	-0.08973		
Platelet count decreased	-0.05		
Pneumonia	-0.008		
Thrombocytopenia	-0.08973		
Vomiting	-0.04802		
White blood cell count decreased	-0.05		
Drug aquisition costs (mean, SD)			
Serplulimab 10mL/100mg (list price)	£1,321.83	NA	Section 3.5.1
Serplulimab 10mL/100mg (PAS price)	[redacted]	NA	
Atezolizumab 20mL/1,200mg (list price)	£3,807.69	NA	
Carboplatin 5mL/50mg	£6.71	£4.97	
Carboplatin 60mL/600mg	£38.93	£38.35	
Etoposide 5mL/100mg	£5.07	£2.04	
Etoposide 25mL/500mg	£13.93	£10.66	
Cyclophosphamide 1g powder for solution	£13.11	£0.68	
Doxorubicin 25mL/50mg	£10.06	£37.02	
Vincristine 2mL/2mg	£11.00	£9.53	
Topotecan 1mg capsules	£360.00	NA	
Relative dose intensity (mean, SE)			
Serplulimab	[redacted]	[redacted]	Section 3.5.1
Atezolizumab			
Carboplatin	85.77%	0.66%	
Etoposide	[redacted]	[redacted]	

Administration costs			
First administration of treatment cycle for all combination regiments	£518.82	Assumed +/- 25%	Section 3.5.1
Subsequent elements of etoposide treatment, i.e. Day 2 and 3 of each treatment cycle	£413.69		
Serplulimab/atezolizumab monotherapy administration	£217.22		
Resource use costs (mean, SD)			
Outpatient visit, placebo arm, number of visits	5.0	1.5	Section 3.5.4
GP visit – surgery, placebo arm, number of visits	1.9	1.3	
GP visit – home, placebo arm, number of visits	0.6	1.5	
Cancer nurse visit, placebo arm, number of visits	1.6	1.4	
Community nurse visit, placebo arm, number of visits	1.6	1.5	
ECG, placebo arm, number of visits	0.3	0.5	
Chest X-ray, placebo arm, number of visits	2.0	1.9	
CT scan, placebo arm, number of visits	1.6	0.5	
MRI scan, placebo arm, number of visits	0.4	0.5	
Blood test, placebo arm, number of visits	4.0	0	
Outpatient visit, placebo arm, % patients	100	0	
GP visit – surgery, placebo arm, % patients	71	39	
GP visit – home, placebo arm, % patients	68	43	
Cancer nurse visit, placebo arm, % patients	67	37	
Community nurse visit, placebo arm, % patients	64	37	
ECG, placebo arm, % patients	64	48	
Chest X-ray, placebo arm, % patients	78	32	
CT scan, placebo arm, % patients	96	9	
MRI scan, placebo arm, % patients	48	45	
Blood test, placebo arm, % patients	100	0	
Outpatient visit, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	5.0	1.5	
GP visit – surgery, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	1.9	1.3	
GP visit – home, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	0.7	0.8	
Cancer nurse visit, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	1.6	1.4	
Community nurse visit, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	1.7	1.5	
ECG, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	0.5	0.5	
Chest X-ray, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	2.0	1.9	
CT scan, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	1.6	0.5	
MRI scan, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	0.4	0.5	
Blood test, serplulimab/ atezolizumab arm, number of visits (first 4 cycles)	4.4	0	
Outpatient visit, serplulimab/ atezolizumab arm, % patients (first 4 cycles)	100	0	
GP visit – surgery, serplulimab/ atezolizumab arm, % patients (first 4 cycles)	71	39	
GP visit – home, serplulimab/ atezolizumab arm, % patients (first 4 cycles)	68	43	
Cancer nurse visit, serplulimab/ atezolizumab arm, % patients (first 4 cycles)	75	32	
Community nurse visit, serplulimab/ atezolizumab arm, % patients (first 4 cycles)	68	31	
ECG, serplulimab/ atezolizumab arm, % patients (first 4 cycles)	66	45	
Chest X-ray, serplulimab/ atezolizumab arm, % patients (first 4 cycles)	75	30	
CT scan, serplulimab/ atezolizumab arm, % patients (firs 4 cycles)	89	20	

MRI scan, serplulimab/ atezolizumab arm, % patients (first 4 cycles)	61	48	
Blood test, serplulimab/ atezolizumab arm, % patients (first 4 cycles)	35	0	
Outpatient visit, subsequent 2L, number of visits	3.6	2.1	
GP visit – surgery, subsequent 2L, number of visits	2.3	1.4	
GP visit – home, subsequent 2L, number of visits	1.6	1.3	
Cancer nurse visit, subsequent 2L, number of visits	2.1	1.3	
Community nurse visit, subsequent 2L, number of visits	1.5	1.4	
ECG, subsequent 2L, number of visits	0.1	0.4	
Chest X-ray, subsequent 2L, number of visits	2.4	1.3	
CT scan, subsequent 2L, number of visits	1.6	1.0	
MRI scan, subsequent 2L, number of visits	0.3	0.5	
Blood test, subsequent 2L, number of visits	6	0	
Outpatient visit, subsequent 2L, % patients	86	19	
GP visit – surgery, subsequent 2L, % patients	69	38	
GP visit – home, subsequent 2L, % patients	66	40	
Cancer nurse visit, subsequent 2L, % patients	54	34	
Community nurse visit, subsequent 2L, % patients	47	39	
ECG, subsequent 2L, % patients	50	50	
Chest X-ray, subsequent 2L, % patients	74	21	
CT scan, subsequent 2L, % patients	69	28	
MRI scan, subsequent 2L, % patients	49	48	
Blood test, subsequent 2L, % patients	80	0	
Outpatient visit, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	5.0	2.1	
GP visit – surgery, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	1.5	1.3	
GP visit – home, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	1.2	1.3	
Cancer nurse visit, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	2.0	0.5	
Community nurse visit, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	1.1	1.1	
ECG, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	0.2	0.4	
Chest X-ray, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	2.8	1.7	
CT scan, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	1.9	1.1	
MRI scan, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	0.4	0.8	
Blood test, serplulimab/ atezolizumab arm, number of visits (after first 4 cycles)	2.2	3.11	
Outpatient visit, serplulimab/ atezolizumab arm, % patients (after first 4 cycles)	100	0	
GP visit – surgery, serplulimab/ atezolizumab arm, % patients (after first 4 cycles)	71	39	
GP visit – home, serplulimab/ atezolizumab arm, % patients (after first 4 cycles)	68	43	
Cancer nurse visit, serplulimab/ atezolizumab arm, % patients (after first 4 cycles)	61	40	
Community nurse visit, serplulimab/ atezolizumab arm, % patients (after first 4 cycles)	61	40	
ECG, serplulimab/ atezolizumab arm, % patients (after first 4 cycles)	51	48	
Chest X-ray, serplulimab/ atezolizumab arm, % patients (after first 4 cycles)	71	32	
CT scan, serplulimab/ atezolizumab arm, % patients (firs 4 cycles)	86	20	
MRI scan, serplulimab/ atezolizumab arm, % patients (after first 4 cycles)	51	48	

Blood test, serplulimab/ atezolizumab arm, % patients (after first 4 cycles)	100	0	
Unit costs for healthcare resource use			
Outpatient follow-up visit	£ 148.19	+/- 25%	Section 3.5.4
GP surgery visit	£49.00		
GP home visit	£93.28		
Cancer nurse visit	£48.00		
Community nurse visit	£72.00		
ECG	£370.94		
Chest X-ray	£154.13		
CT scan	£154.13		
MRI scan	£303.07		
Blood test	£2.75		
Palliative care costs			
Cost of terminal care	£7,440.60	+/- 25%	Section 3.5.4
Adverse event costs			
Anaemia	£3,380.51	+/- 10%	Section 3.5.6
Diarrhoea	£199.83		
Fatigue	£928.25		
Febrile neutropenia	£8,727.35		
Hyperglycaemia	£226.54		
Hypertension	£759.36		
Hypertriglyceridaemia	£226.54		
Hypocalcaemia	£226.54		
Hypokalaemia	£226.54		
Hyponatraemia	£226.54		
Leukopenia	£463.61		
Lymphocyte count decreased	£226.54		
Neutropenia	£739.06		
Neutrophil count decreased	£226.54		
Pancytopenia	£739.06		
Platelet count decreased	£226.54		
Pneumonia	£3,423.55		
Thrombocytopenia	£150.61		
Vomiting	£199.83		
White blood cell count decreased	£226.54		

***Abbreviations**: 2L, second-line; AEs, adverse events; BSA, body surface area; CT, computerised tomography; ECG, electrocardiogram; GP, general practitioner; MRI, magnetic resonance imaging; NA, not available; PAS, patient access scheme; PF, progression-free; PD, progressed disease; SD, standard deviation; SE, standard error.*

3.1.1. Assumptions

Key assumptions included in the model are summarised in Table 53.

Table 53: List of key assumptions applied in the model

Parameter	Assumption	Justification
Time horizon	The time horizon corresponds to 20 years (lifetime).	The mean age of patients in the model is 62 years. The time horizon allows for most patients to die before the end of the time horizon. This time horizon is sufficiently long to fully capture the differences in costs and outcomes for serplulimab vs atezolizumab and SoC. It is also consistent with TA638.
Subsequent therapies	Subsequent therapies are modelled in line with UK clinical practice with patients receiving re-challenge with first-line chemotherapy, oral topotecan, or cyclophosphamide/doxorubicin/vincristine.	The range of subsequent therapies are reflective of those seen in clinical practice in England, as reported in TA638.

Comparators	Carboplatin-etoposide is the relevant SoC treatment for ES-SCLC. Atezolizumab is another appropriate comparator in this indication. Durvalumab is not currently recommended by NICE for use in the NHS and is therefore excluded from this appraisal.	This assumption is based on the NICE scope and TA638. Clinical opinion also confirmed that carboplatin-etoposide is an appropriate comparator in this indication.
Relevance of ITT population	The ITT population is modelled in the base-case.	The ITT population is generalisable to the NHS based on expert opinion and a comparison of baseline characteristics of the ITT and non-Asian subgroup. The non-Asian population is presented in subgroup analysis.
Duration of treatment effect	Treatment waning is not applied in the base.	Given the shape of the Kaplan-Meier curves in the observed trial data from ASTRUM-005, there is no indication for the loss of treatment effect within the trial period. However, given the uncertainty around the duration of treatment effect beyond the end of the trial, the impact of different assumptions regarding the duration of treatment effect is explored in scenario analysis.
Long-term extrapolation of OS and PFS for serplulimab	Log-logistic	These are based on a combination of visual inspection and best statistical fit, and clinical expert opinion, as described in Section 3.3.
Long-term extrapolation of OS and PFS for carboplatin-etoposide	Log-logistic	
Long-term extrapolation of OS and PFS for atezolizumab	Generated by applying HRs from the MAIC to the selected serplulimab extrapolation	To appropriately adjust for differences between ASTRUM-005 and IMpower133 in the distribution of effect-modifying variables when assessing the relative efficacy of serplulimab and atezolizumab. These extrapolations result in a conservative comparison against atezolizumab.
HRQoL	HRQoL is modelled using progression status.	This is in line with the Committee's preference in TA638 and accurately reflects the disease trajectory of ES-SCLC, as confirmed by clinical experts.
Safety	Grade 3 to 5 treatment-related AEs experienced by ≥2% of patients in ASTRUM-005 are included.	The 2% threshold is a conservative approach and captures AEs that are relevant to treatment with serplulimab, atezolizumab and carboplatin-etoposide.

***Abbreviations**: AEs, adverse events; ES-SCLC, extensive-stage small cell lung cancer; HRQoL, health-related quality of life; ITT, intention to treat; NICE, National Institute for Health and Care Excellence; SoC, standard of care.*

3.8 Base-case results

Base-case results for serplulimab compared with atezolizumab and carboplatin-etoposide are presented below.

3.8.1 Base-case incremental cost-effectiveness analysis results

Base-case results for serplulimab compared with atezolizumab and carboplatin-etoposide at list price are reported in Table 54, Table 55, and Table 56. Details of the PAS price results are provided in Appendix N. In the pairwise analysis, at PAS price,

serplulimab dominates atezolizumab, yielding a lower total cost and greater total QALYs. At list price, the ICER for serplulimab compared with atezolizumab is £41,447, and £64,799 compared with carboplatin-etoposide.

Table 54: Base-case results, pairwise (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	£79,427	2.47	2.10				
Atezolizumab	£54,671	1.74	1.50	£24,756	0.74	0.60	£41,447
Carboplatin-etoposide	£21,561	1.38	1.21	£57,866	1.09	0.89	£64,799

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

Table 55: Base-case results, full incremental analysis (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Serplulimab	£79,427	2.10			
Atezolizumab	£54,671	1.50	£24,756	0.60	£41,447
Carboplatin-etoposide	£21,561	1.21	£33,110	0.30	£111,968

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

Table 56: Net health benefit (list price)

Technologies	NHB at £20,000	NHB at £30,000
Serplulimab vs atezolizumab	-£12,810	-£6,837
Serplulimab vs carboplatin-etoposide	-£40,006	-£31,076

***Abbreviations**: NHB, net health benefit.*

3.9 Exploring uncertainty

Uncertainty in the model is explored by means of deterministic, probabilistic, and scenario analyses. Probabilistic sensitivity analysis was deemed to accurately demonstrate the range of uncertainty present in the model, and the reliability of the base-case results. Probabilistic results were relatively congruent with the deterministic results. For the comparison against atezolizumab, the ICER in the probabilistic analysis was £42,259 at list price, and [redacted] For the comparison against carboplatin-etoposide, the ICER in the probabilistic analysis was £65,995 at list price, and [redacted] at PAS price.

3.9.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with key model inputs. PSA results for 1,000 iterations are

presented in Table 57 and Table 59 for serplulimab vs atezolizumab and carboplatin-etoposide respectively. The mean incremental costs and QALYs of serplulimab compared with atezolizumab and carboplatin-etoposide were calculated to estimate the probabilistic ICER. Details of the PAS price results are provided in Appendix N.

For the comparison against atezolizumab, the probabilistic results were comparable with the deterministic results. At list price, the incremental QALYs and costs in the probabilistic analysis were 0.52 and £21,963, respectively, compared to compared to 0.60 and £24,756 in the deterministic analysis. At the PAS price, the incremental QALYs and costs in the probabilistic analysis were 0.55 and [redacted], respectively, compared to 0.60 and [redacted] in the deterministic analysis. A scatter plot showing the total number of simulations at list price is presented in Figure 21. The probabilistic analysis resulted in an ICER of £42,259, with a [redacted]. Cost effectiveness-acceptability curves vs. atezolizumab at list price are presented in Figure 23. The probability of cost-effectiveness vs. atezolizumab at list price and PAS price, at different willingness-to-pay thresholds, is presented in Table 58.

For the comparison against carboplatin-etoposide, the probabilistic results were also comparable with the deterministic results. At list price, the incremental QALYs and costs in the probabilistic analysis were 0.89 and £58,753, respectively, compared to 0.89 and £57,866 in the deterministic analysis. At the PAS price, the incremental QALYs and costs in the probabilistic analysis were 0.89 and [redacted], respectively, compared to 0.89 and [redacted] in the deterministic analysis. A scatter plot showing the total number of simulations at list price are presented in Figure 22. The probabilistic analysis resulted in an ICER of £65,995 at list price, and an ICER of [redacted] at PAS price. The cost effectiveness-acceptability curves vs. carboplatin-etoposide at list price is presented in Figure 24. The probability of cost-effectiveness vs. carboplatin-etoposide at list price at different willingness-to-pay thresholds is presented in Table 60.

Table 57: Probabilistic results vs. atezolizumab (list price)

	Serplulimab	Atezolizumab	Incremental	ICER
Total costs (£)	£81,354	£59,390	£21,963	£42,259
Total QALYs	2.10	1.58	0.52	

Abbreviations: *LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio;*

Table 58: Probability of cost-effectiveness vs. atezolizumab at different willingness to pay thresholds

WTP threshold (£/QALY)	Probability of cost-effectiveness (%)	
	List price	PAS price
30,000	15.0	[redacted]
50,000	70.7	[redacted]
100,000	90.0	[redacted]
150,000	91.2	[redacted]
200,000	91.8	[redacted]

Abbreviations: *PAS, patient access scheme; QALY: quality-adjusted life year; WTP, willingness-to-pay*

Table 59: Probabilistic results vs. carboplatin-etoposide (list price)

	Serplulimab	Carboplatin-etoposide	Incremental	ICER
Total costs (£)	£81,354	£22,601	£58,753	£65,995
Total QALYs	2.10	1.21	0.89	

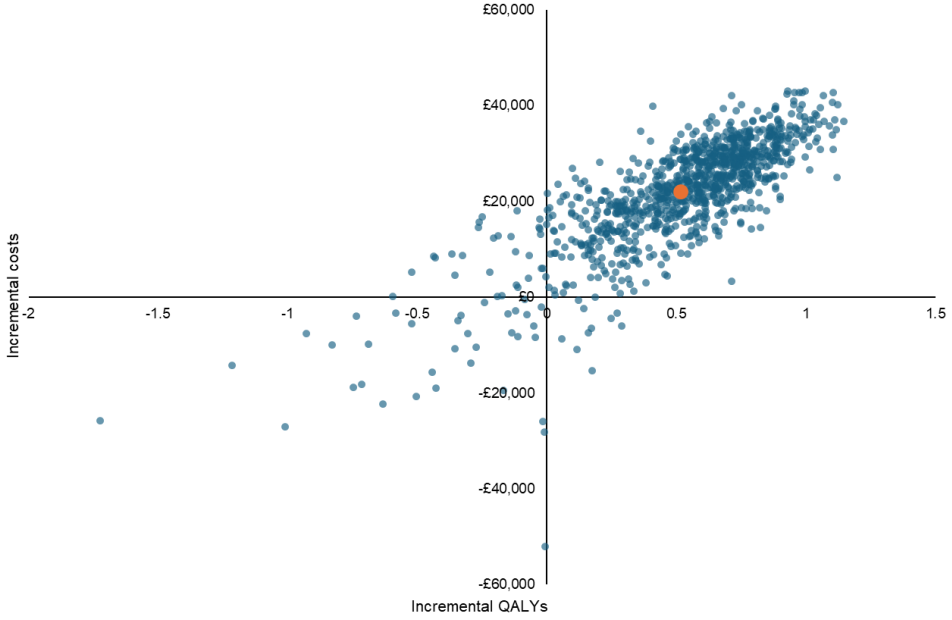
Abbreviations: *LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio;*

Table 60: Probability of cost-effectiveness vs. carboplatin-etoposide at different willingness to pay thresholds

WTP threshold (£/QALY)	Probability of cost-effectiveness (%)	
	List price	PAS price
30,000	0.0	[redacted]
50,000	2.7	[redacted]
100,000	97.5	[redacted]
150,000	100.0	[redacted]
200,000	100.0	[redacted]

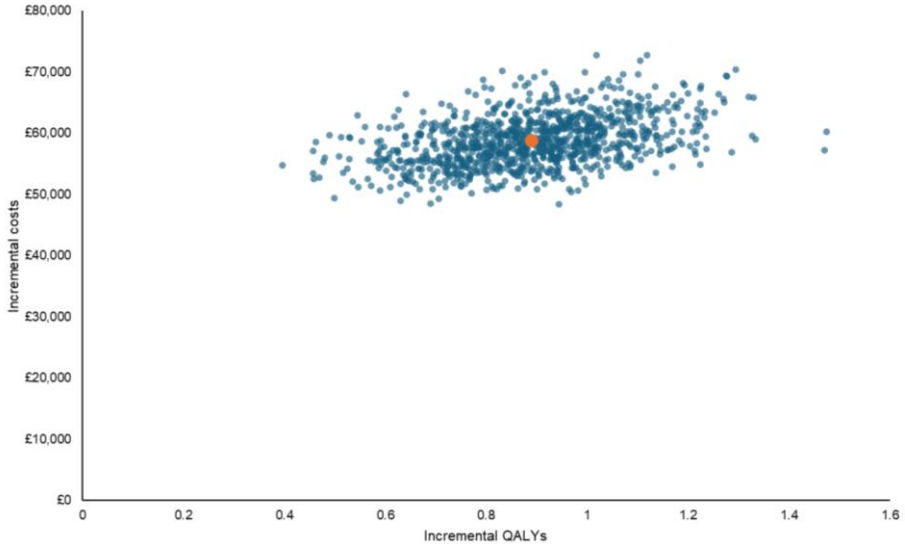
Abbreviations: *PAS, patient access scheme; QALY: quality-adjusted life year; WTP, willingness-to-pay*

Figure 21: Cost-effectiveness plane from PSA (1,000 simulations) – comparator atezolizumab (list price)



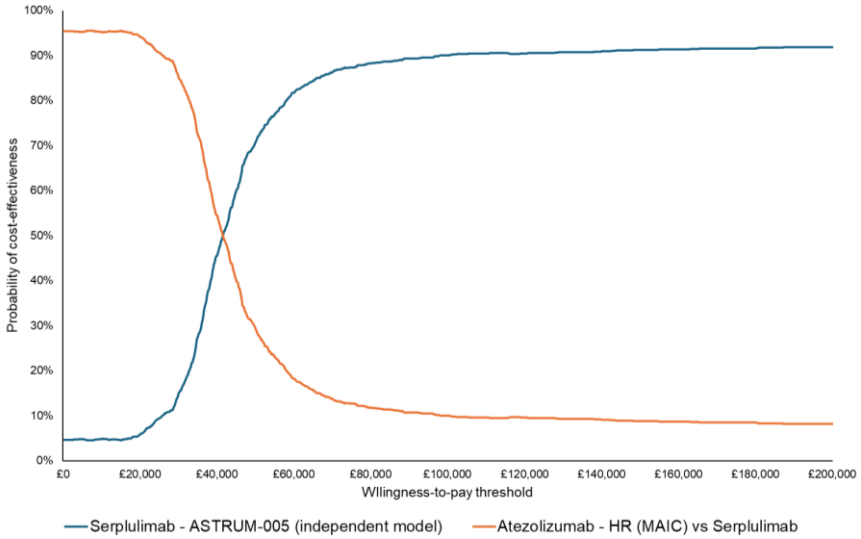
Abbreviations*: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.*

Figure 22: Cost-effectiveness plane from PSA (1,000 simulations) – comparator carboplatin-etoposide (list price)



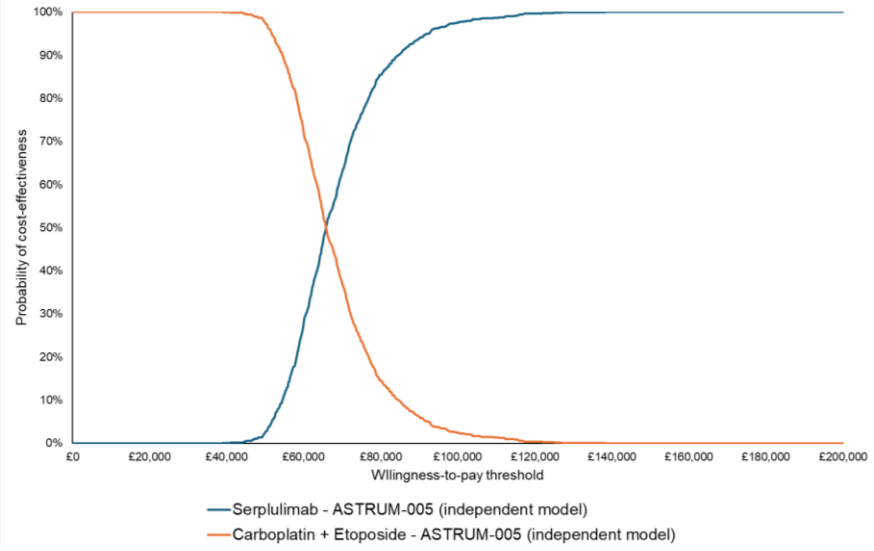
***Abbreviations**: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.*

Figure 23: Cost-effectiveness acceptability curve – comparator atezolizumab (list price)



***Abbreviations**: HR, hazard ratio; MAIC, matched-adjusted indirect comparison*

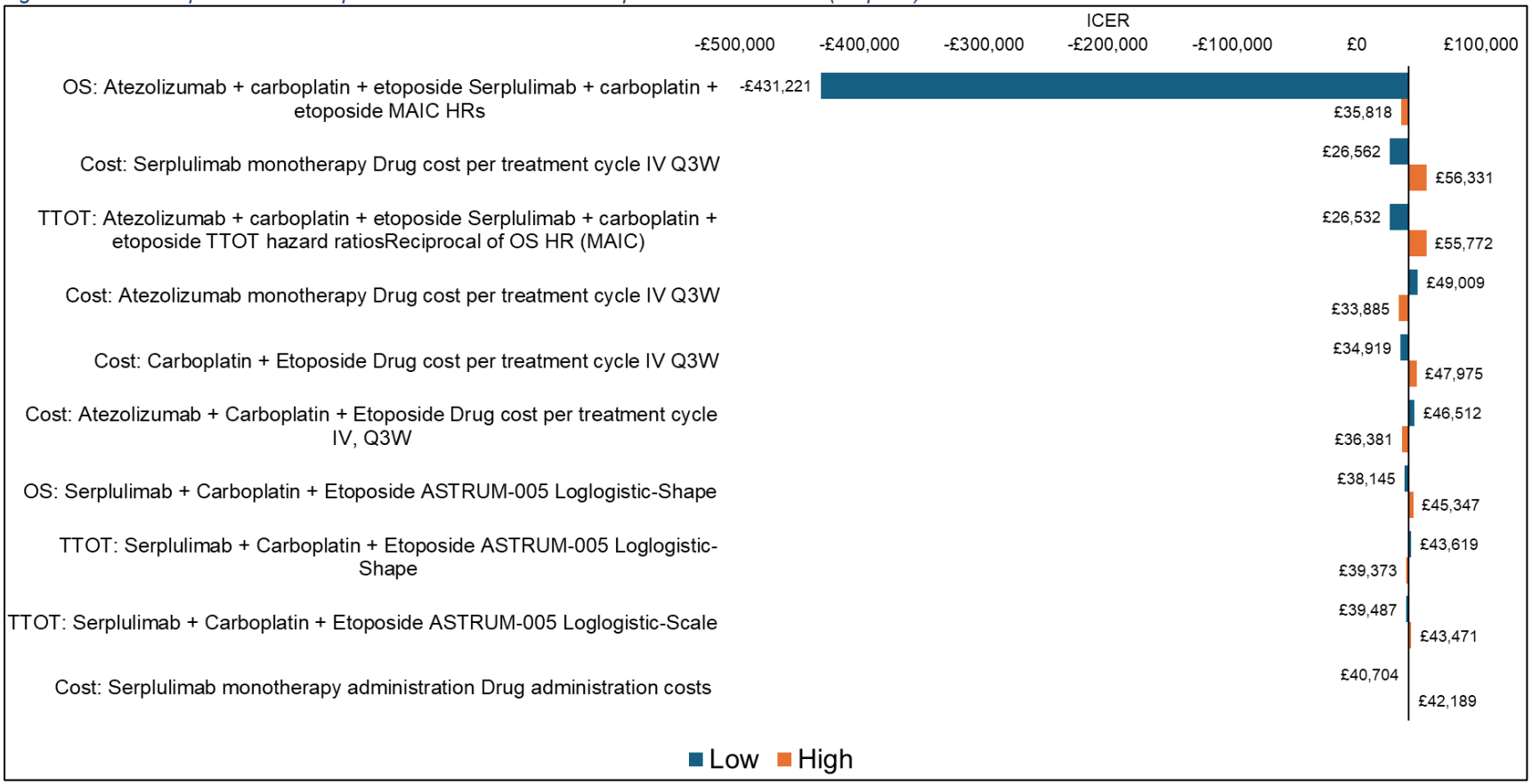
Figure 24: Cost-effectiveness acceptability curve – comparator carboplatin-etoposide (list price)



3.9.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were performed to explore the effect of uncertainty associated with varying individual model inputs. The inputs with the greatest impact on the ICER against atezolizumab and carboplatin-etoposide are presented in descending order as a tornado plot in Figure 25 and Figure 26, respectively. For the comparison against atezolizumab, the ICER was most sensitive to changes in the HR derived from the MAIC (atezolizumab vs serplulimab, HR = [redacted]) used to inform the OS extrapolation in the atezolizumab arm, particularly when the HR was varied to the lower confidence interval value ([redacted]). Otherwise, the ICER was relatively insensitive to variations in the model inputs with treatment costs and time on treatment parameters having the largest impact. For the comparison against carboplatin-etoposide, the ICER was relatively insensitive to variations in the model inputs with variations in the coefficients of the log-logistic model for OS having the largest impact on the ICER, followed by treatment costs and time on treatment parameters.

Figure 25: Tornado plot of sensitive parameters in the DSA – comparator atezolizumab (list price)



Abbreviations: *HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenous; MAIC, matched-adjusted indirect comparison; OS, overall survival; Q3W; every 3 weeks; TTOT, time to off treatment*

Figure 26: Tornado plot of sensitive parameters in the DSA – comparator carboplatin-etoposide (list price)

Abbreviations: *HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenous; MAIC, matched-adjusted indirect comparison; OS, overall survival; Q3W; every 3 weeks; TTOT, time to off treatment*

3.9.3 Scenario analysis

Different scenarios were performed on the base-case to assess the impact of key assumptions in the model on the results. The scenarios presented include different parametric models for OS, PFS, and TTOT extrapolation, alternative utility derivation methods, different sources for AEs, and scenarios around the long-term treatment effect of serplulimab. A description of the scenarios and the results (incremental QALYs, costs, and ICER) against each comparator, at serplulimab list price, are presented in Table 61 and Table 62. Notably, the scenarios using different models for OS and PFS extrapolation had little impact on the cost-effectiveness. Furthermore, the scenarios that were less cost-effective were deemed to be either inappropriate e.g., the time to death approach for applying utilities or shorter time horizons, or overly conservative. Serplulimab [redacted]

Table 61: Summary of scenario analysis – comparator atezolizumab (list price)

Scenario	Description	Value	Incremental QALYs	Incremental costs	ICER (£/QALY gained)
Base-case			0.60	£24,756	£41,447
OS parametric model	Scenarios using alternative parametric models are presented.	Exponential	0.49	£24,244	£49,402
		Weibull	0.43	£23,792	£55,156
		Gamma	0.42	£23,673	£56,477
		Log-normal	0.60	£25,179	£41,774
		Gompertz	0.66	£25,696	£38,696
		Gen. Gamma	0.59	£25,094	£42,282
PFS parametric model	Scenarios using alternative parametric models are presented.	Exponential	0.60	£24,759	£41,577
		Weibull	0.60	£24,764	£41,560
		Gamma	0.59	£24,748	£41,613
		Log-normal	0.60	£24,732	£41,400
		Gompertz	0.61	£24,765	£40,710
		Gen. Gamma	0.60	£24,712	£40,944
TTOT parametric model	Scenarios using alternative parametric models are presented.	Exponential	0.60	£24,116	£39,932
		Weibull	0.60	£25,185	£42,068
		Gamma	0.60	£24,988	£41,619
		Log-normal	0.60	£26,843	£45,099
		Gompertz	0.59	£29,282	£49,661
		Gen. Gamma	0.60	£25,559	£42,785
Data source for atezolizumab extrapolation	Scenarios with alternative approaches are presented.	HR from MAIC (before matching)	0.51	£22,436	£43,829
		Independent model fitted to pseudo-IPD from IMpower133	0.67	£24,910	£37,167
Time horizon (years)	Scenarios with shorter time horizons are presented.	5	0.36	£22,517	£62,907
		10	0.50	£24,054	£47,737
		15	0.57	£24,556	£43,428
Utility derivation method	Scenarios using the time to death approach and progression status by treatment status are presented. Scenarios using the time to death approach and	Time to death	0.44	£24,756	£55,970
		Progression status by on/off treatment	0.58	£24,756	£43,045

	progression status by treatment status are presented.				
Adverse events	Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented.	Exclude AE disutilities	0.60	£24,756	£41,566
		Non-Asian AEs	0.59	£24,767	£41,915
Treatment waning	Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented.	Immediate loss of treatment effect at 5 years	0.51	£24,072	£47,338
		Gradual loss of treatment effect from 5-10 years	0.55	£24,422	£44,304
Vial sharing assumed for serplulimab	A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	0.60	£17,633	£29,521

Abbreviations: *AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; MAIC, matched-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTOT, time to off treatment*

Table 62: Summary of scenario analysis – comparator carboplatin-etoposide (list price)

Scenario	Description	Value	Incremental QALYs	Incremental costs	ICER (£/QALY gained)
Base-case			0.89	£57,866	£64,799
OS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.79	£56,537	£71,322
		Weibull	0.75	£56,999	£75,624
		Gamma	0.75	£57,306	£76,896
		Log-normal	0.95	£58,838	£61,679
		Gompertz	1.10	£58,261	£53,107
		Gen. Gamma	0.98	£59,019	£59,975
PFS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.89	£58,161	£65,073
		Weibull	0.89	£57,939	£64,777
		Gamma	0.89	£57,891	£64,776
		Log-normal	0.90	£57,929	£64,707
		Gompertz	0.91	£57,995	£63,565
		Gen. Gamma	0.90	£57,916	£64,066
TTOT parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.88	£61,830	£70,077
		Weibull	0.89	£59,743	£67,454
		Gamma	0.88	£60,668	£68,602
		Log-normal	0.89	£61,310	£69,133
		Gompertz	0.88	£62,512	£71,112
		Gen. Gamma	0.89	£59,813	£67,533
Time horizon (years)	Scenarios with shorter time horizons are presented.	5	0.59	£55,164	£92,854
		10	0.78	£57,060	£72,768
		15	0.86	£57,642	£67,266
Utility derivation method	Scenarios using the time to death approach and progression status by treatment status are presented.	Time to death	0.66	£57,866	£87,366
		Progression status by on/off treatment	0.85	£57,866	£67,851
Adverse events	Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented.	Exclude AE disutilities	0.91	£57,866	£63,834
		Non-Asian AEs	0.90	£57,885	£64,593
Treatment waning	Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented.	Immediate loss of treatment effect at 5 years	0.81	£57,205	£70,887
		Gradual loss of treatment effect from 5-10 years	0.85	£57,562	£67,653

Vial sharing assumed for serplulimab	A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	0.89	£50,742	£56,822

Abbreviations: *AE, adverse event; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTOT, time to off treatment*

3.10 Subgroup analysis

Data on the non-Asian population were collected as part of ASTRUM-005 and applied in the economic model. The model uses data on survival (OS and PFS), TTOT, AEs, and utilities to derive cost-effectiveness results in this cohort. Topline results from the analysis are presented below. The results are relatively congruent with the base-case analysis using the ITT cohort of ASTRUM-005. In the non-Asian population, serplulimab yielded slightly increased total costs, primarily due to increased acquisition costs because of differences in weight and BSA. There are small differences in the QALYs accumulated in the non-Asian population (2.03 vs 2.10 in the ITT) because of slight differences in the survival recorded in ASTRUM-005, and therefore the shape of the extrapolations. The ICER compared with carboplatin-etoposide is slightly higher in the non-Asian cohort (at PAS price: [redacted] vs [redacted] in the ITT, and at list price: £65,814 vs £64,799 in the ITT). This is also the case for the comparison with atezolizumab – at PAS price, the ICER for serplulimab compared with atezolizumab is [redacted] compared with a dominant ICER in the ITT, and at list price, the ICER is £57,310 vs £41,447 in the ITT. Further detail is provided in Appendix E.

3.11 Benefits not captured in the QALY calculation

The health utility gain from serplulimab for ES-SCLC may not be fully captured in the QALY calculation included in the economic modelling.

Firstly, the EQ-5D may not fully capture the disease burden of ES-SCLC, as is the case in other areas of oncology; studies suggest this measure can inadequately reflect the total quality of life impact in these patients (notably fatigue and cognitive function or social well-being) (Lang et al., 2010, Llewellyn-Thomas et al., 1993, Pickard et al., 2007). ES-SCLC patients often experience symptoms beyond physical pain or functional limitations such as high psychological distress, which may not be adequately represented in the QALY calculation.

Additionally, there are caregiver implications, as families often provide support despite a median OS of 15.8 months, and while the caregiver burden is lower

relative to chronic conditions, it remains a notable factor. A study by Feliciano et al. on the family-centred concerns of lung cancer revealed that caregivers experience a wide range of barriers involving psychological, emotional, and technical aspects, while helping their affected person (Feliciano et al., 2020). Their responsibilities occupy a significant portion of their time, and they often live with the patient (Bebb et al., 2023). Moreover, ES-SCLC poses productivity losses that are not addressed in utility-based measures, potentially affecting societal economic costs. These broader impacts suggest health benefits that exceed those reflected in the QALY calculation from the model.

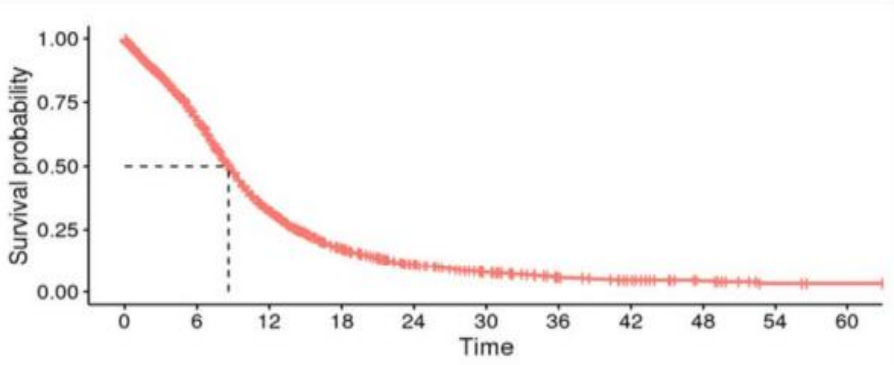
3.12 Validation

3.12.1 Validation of cost-effectiveness analysis

Real-world data from the Flatiron Health Database for ES-SCLC was sourced from TA638 to test the external validity of the comparator arm of ASTRUM-005, which is used to model the comparative efficacy of serplulimab vs carboplatin-etoposide.

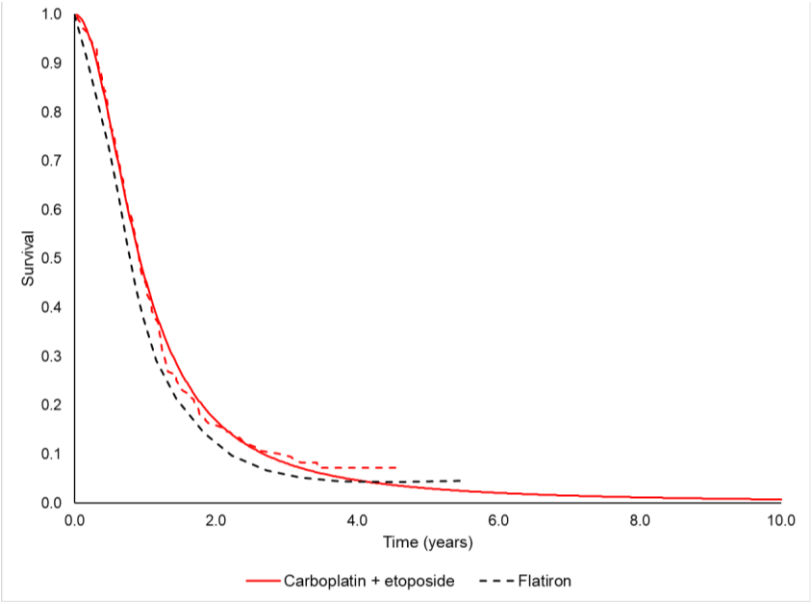
The Flatiron Health database is a US-based, observational, longitudinal database containing electronic health record data from over 265 cancer clinics (~800 sites of care), including more than 2 million active US cancer patients available for analysis (National Institute of Health and Care Excellence, 2020). Figure 27 shows the long-term survival of patients with ES-SCLC as shown in TA638, which restricted patients to ECOG 0-1. These data were collected as part of the submission development for atezolizumab, which was published in 2019, and were deemed recent enough to use for comparison with ASTRUM-005. The cohort presented is consistent with the population in ASTRUM-005, which included patients with ECOG 0 or 1, only. Patients in Flatiron were treated with either cisplatin-etoposide or carboplatin-etoposide. The extrapolations from ASTRUM-005 in Figure 28 demonstrate that the ASTRUM-005 data is broadly reflective of real-world data for ES-SCLC patients treated with platinum-based chemotherapy, as the shape of the curves are very similar. Notably, the curve for the placebo arm in ASTRUM-005 sits higher than the Flatiron curve, indicating that OS is slightly overestimated in the ASTRUM-005 placebo arm compared to real-world OS. This suggests that the data used in the economic model are conservative in estimating the treatment benefit of serplulimab compared with carboplatin-etoposide.

Figure 27: Flatiron Health database, long-term survival for ES-SCLC patients with ECOG 0-1, treated with platinum-etoposide regimen



***Abbreviations**: ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small cell lung cancer.*

Figure 28: Long-term survival from Flatiron and placebo arm extrapolations from ASTRUM-005



3.13 Interpretation and conclusions of economic evidence

ES-SCLC is a fatal condition with a high unmet need and a life expectancy of 9–10 months with current standard of care options, which include atezolizumab with carboplatin-etoposide and carboplatin-etoposide. Serplulimab demonstrated a significant benefit in OS and PFS compared to placebo (carboplatin-etoposide) in the ASTRUM-005 trial, in which the placebo arm had similar outcomes to the real-world database Flatiron. This provides evidence of the external validity and applicability of the trial data to patients with ES-SCLC eligible for serplulimab in England. Given the severity of ES-SCLC, serplulimab is eligible for a severity weight of 1.2.

Results from the MAIC confirm the treatment benefit of serplulimab, with HRs of [redacted] and [redacted] for serplulimab vs atezolizumab for PFS and OS, respectively.

Serplulimab is a highly effective treatment in ES-SCLC, resulting in a LYG of 1.09 compared with carboplatin-etoposide, and 0.74 compared with atezolizumab. This represents a significant improvement in the current standard of care for patients in ES-SCLC, whose life expectancy is extremely limited. In the base-case, greater QALYs are also accumulated with serplulimab compared with atezolizumab (2.10 vs 1.50, respectively). At the serplulimab PAS price [redacted], serplulimab dominates atezolizumab (list price), whereby more QALYs are accumulated at a lower total cost. Serplulimab is therefore an effective use of NHS resources for treating ES-SCLC. The ICER compared with carboplatin-etoposide is [redacted]. Greater QALYs are also accumulated compared with carboplatin-etoposide (2.10 vs 1.21, respectively). At list price, the ICER for serplulimab compared with atezolizumab is £41,447 and £64,799 compared with carboplatin-etoposide.

In the non-Asian cohort, serplulimab is cost-effective at £20,000 compared with atezolizumab at PAS price (ICER = [redacted]) and has a similar ICER to the ITT cohort compared with carboplatin-etoposide (ICER = [redacted]). At list price, the ICERs are very similar to the ITT £57,310 and £65,814 compared with atezolizumab and carboplatin-etoposide, respectively). A similar number of total QALYs are accumulated in the non-Asian cohort and ITT cohort (2.03 vs 2.10, respectively).

The key drivers of cost-effectiveness in the analyses are the HR derived from the MAIC in the comparison with atezolizumab and the coefficients of the OS model for the comparison against carboplatin-etoposide. The model is relatively insensitive to variations in parameter inputs. The probability of cost-effectiveness vs. atezolizumab is 15.0% and [redacted], at list price and PAS price, respectively, at a WTP threshold of £30k/QALY. At the same WTP threshold, the probability of cost-effectiveness vs, carboplatin-etoposide is 0.0% and [redacted], at list price and PAS price, respectively.

The key strengths of the analysis are;

- The availability of patient-level data from a large, randomised controlled trial (ASTRUM-005), providing a reliable source of outcomes and baseline characteristics to tailor the analysis to the target population in the NHS

- Validated methods and NICE preferences published in the atezolizumab appraisal, as well as the availability of real-world evidence curves for long-term survival in ES-SCLC treated with platinum-based chemotherapy

- Evidence from clinical experts who confirmed the validity of the long-term extrapolation for time-to-event curves, producing a robust base-case
- Data from a large real-world evidence platform (Flatiron) which confirmed the external validity of the placebo curve of ASTRUM-005.

The key limitations of the analysis are:

- The relative overestimation of OS and PFS in the atezolizumab arm, using the curve derived by applying the HR from the MAIC or using parametric curves derived from reconstructed pseudo-IPD, in the absence of spline models. However, this leads to conservative treatment benefits for serplulimab, underestimating its long-term efficacy. As a result, the true benefit of serplulimab is likely to be greater in NHS clinical practice.
- The inability to fully capture quality of life of patients with ES-SCLC using EQ-5D-5L, which is well-documented to be limiting when assessing wider aspects of quality of life in cancer patients (Lang et al., 2010, Llewellyn-Thomas et al., 1993, Pickard et al., 2007). The EORTC scores collected in ASTRUM-005 provide additional qualitative evidence into how patients are affected by their disease.
- The uncertainty associated with the long-term extrapolation of survival beyond the duration of the ASTRUM-005 trial. However, the long-term survival assumptions were validated with clinical experts. Furthermore, uncertainties around the duration of treatment effect beyond the duration of the ASTRUM-005 trial were tested in scenario analysis which demonstrated a limited impact on the results.

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Appendices

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

1.1 SmPC

Please see document ‘Appendix C – SmPC’

1.2 UK public assessment report

Currently serplulimab is awaiting the UK public assessment report. This will become available during the assessment (estimated March 2025) and will be shared with NICE accordingly.

Appendix D: Identification, selection and synthesis of clinical evidence

1.1 Identification and selection of relevant studies

Included in ‘Appendix D, H, I, J – SLR Results’

1.2 Participant flow in the relevant randomised control trials

Included in ‘Appendix D, H, I, J – SLR Results’

1.3 Critical appraisal for each study

Included in ‘Appendix D, H, I, J – SLR Results’

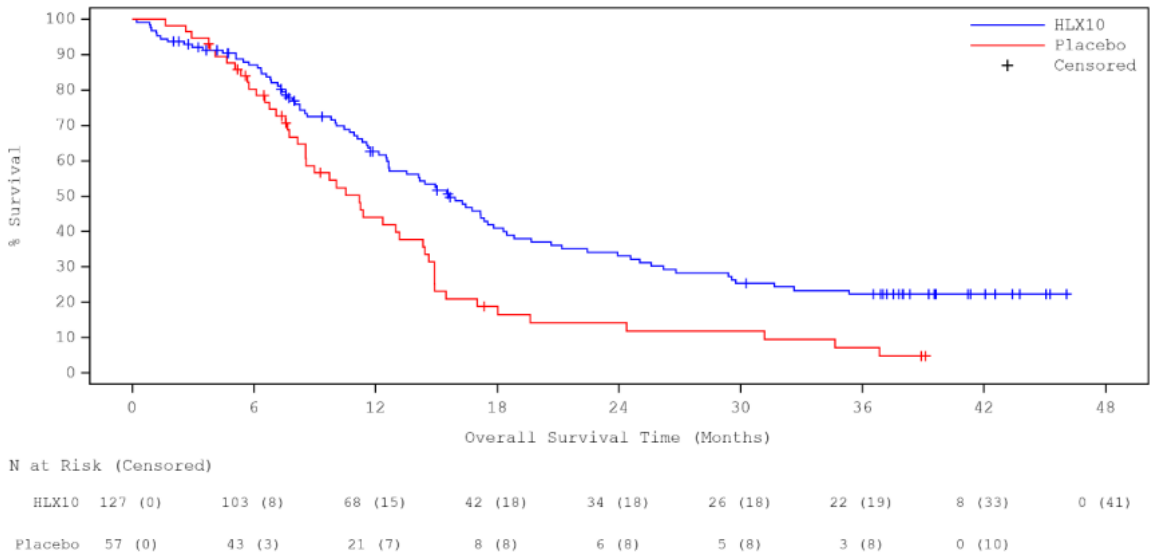
Appendix E: Subgroup analysis

This appendix provides OS and PFS results for the non-Asian subgroup of ASTRUM-005. Further information on subgroup analysis is also provided in Figure 11. Results from the non-Asian cohort were consistent with results from the ITT population. The ITT population is the population of interest for the submission, as clinical experts during the Delphi panel stated that the ITT is reflective of the population expected to be treated in the NHS.

OS

In the non-Asian population, the Kaplan-Meier curve of OS over time is shown in Figure 29. The analysis of OS is presented in Table 63. As of May 7th 2024, the median duration of follow-up in the non-Asian population was 38.34 months. The median (95% CI) OS was 15.64 (12.649, 17.807) months in the serplulimab group and 11.20 (8.542, 14.324) months in the placebo group. The stratified HR (95% CI) was 0.50 (0.337, 0.738) with $p < 0.001$. Treatment with serplulimab reduced the risk of death by 50% and prolonged the median OS by 4.44 months. The 12-month OS rate was 62.6% and 44.0% in the serplulimab and placebo groups, respectively; the 24-month OS rate was 33.1% and 14.1%; the 36-month OS rate was 22.3% and 7.1%. The OS benefit observed with the addition of serplulimab in the non-Asian population was consistent with that in the ITT population.

Figure 29: Overall survival in the non-Asian population (data cutoff: 7th May 2024)



***Note**: HLX10 is serplulimab's previous name.*
***Source**: ASTRUM-005 CSR Figure 62 (Shanghai Henlius Biotech, 2024)*

Table 63: Primary efficacy analysis: OS (non-Asian)

	Serplulimab group (N=127)	Placebo group (N=57)
Events (deaths)[a], n (%)	86 (67.7)	47 (82.5)
Median OS (95% CI)[b], mo	15.64 (12.649, 17.807)	11.20 (8.542, 14.324)
Stratified [b] Hazard Ratio (95% CI) [c]; p-Value [d]	0.50 (0.337, 0.738) < 0.001	
1-yr OS rate (95% CI)[e]	0.626 (0.531, 0.707)	0.440 (0.301, 0.570)
2-yr OS rate (95% CI) [e]	0.331 (0.244, 0.420)	0.141 (0.060, 0.256)
3-yr OS rate (95% CI) [e]	0.223 (0.149, 0.306)	0.071 (0.019, 0.170)
45-month-OS rate (95% CI) [e]	0.223 (0.149, 0.306)	NA (NA, NA)

Notes: *a The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS. b Stratification factor: PD-L1 expression level (TPS < 1%, TPS ≥ 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years). c The hazard ratio and its 95% CI were estimated by stratified/unstratified) Cox proportional hazards model. Efron's method was used to handle ties. d The comparison of OS between the two arms was performed by a two-sided stratified/unstratified log-rank test. e The standard error of the survival rate was calculated using Greenwood's formula. The OS for patient 11031004 is censored since the month and day of death date is missing*
Abbreviations*: CI, confidence interval: ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death ligand- 1; TPS, tumor proportion score.*
Source: *ASTRUM-005 CSR Table 62 (Shanghai Henlius Biotech, 2024)*

PFS

Analysis of PFS assessed by IRRC according to RECIST 1.1 for non-Asian patients is presented in Table 64 and illustrated in **Error! Reference source not found.**.

The median (95% CI) PFS assessed by IRRC according to RECIST 1.1 was [redacted] months in the serplulimab group and [redacted] months in the placebo group. The stratified HR (95% CI) was [redacted]. Treatment with serplulimab reduced the risk of progressive disease or death by [redacted] in non-Asian patients.

[redacted]

Note: *HLX10 is serplulimab's previous name*.
Abbreviations: *IRRC, Independent Radiology Review Committee; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors*
Source: *ASTRUM-005 CSR Figure 68 (Shanghai Henlius Biotech, 2024)*

Table 64: Secondary outcomes assessed by the independent radiology review committee – non-Asian population

	Serplulimab group (N=127)	Placebo group (N=57)
PFS events, n (%)[a]	[redacted]	[redacted]
Median PFS (95% CI), mo	[redacted]	[redacted]
Stratified HR (95% CI); p-value	[redacted]	
1-yr PFS rate (95% CI)	[redacted]	[redacted]
Confirmed ORR, n (%) [95% CI]	[redacted]	[redacted]
Median DoR (95% CI), mo	[redacted]	[redacted]
Stratified HR (95% CI); p-value	[redacted]	

Notes*: [a] PFS assessed per Response Evaluation Criteria in Solid Tumours version 1.1*
Abbreviations*: CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio;*

mo, month; NE, not evaluated; PD, progressive disease; PR, partial response; ORR, objective response rate; PFS, progression-free survival.
Source: *ASTRUM-005 CSR, Supplementary Table 14.2.2.3.1na (p472) (Shanghai Henlius Biotech, 2024)*

Cost-effectiveness results

Cost-effectiveness results for the non-Asian population can be found below, including PAS and list price results.

Table 65: Base-case results, pairwise (PAS price) – non-Asian

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	[redacted]	2.57	2.03				
Atezolizumab	£55,754	1.76	1.43	[redacted]	0.81	0.60	[redacted]
Carboplatin-etoposide	£20,553	1.17	0.97	[redacted]	1.40	1.05	[redacted]

Abbreviations: *ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life; PAS, patient access scheme.*

Table 66: Base-case results, full incremental analysis (PAS price) – non-Asian

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Serplulimab	[redacted]	2.03			
Atezolizumab	£55,754	1.43	[redacted]	0.60	[redacted]
Carboplatin-etoposide	£20,553	0.97	[redacted]	0.46	[redacted]

Abbreviations: *ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; PAS, patient access scheme.*

Table 67: Net health benefit (PAS price) – non-Asian

Technologies	NHB at £20,000	NHB at £30,000
Serplulimab vs atezolizumab	[redacted]	[redacted]
Serplulimab vs carboplatin-etoposide	[redacted]	[redacted]

Abbreviations: *NHB, net health benefit; PAS, patient access scheme.*

Table 68: Base-case results, pairwise (list price) – non-Asian

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	£89,915	2.57	2.03				
Atezolizumab	£55,754	1.76	1.43	£34,160	0.81	0.60	£57,310
Carboplatin-etoposide	£20,553	1.17	0.97	£69,362	1.40	1.05	£65,814

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

Table 69: Base-case results, full incremental analysis (list price) – non-Asian

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Serplulimab	£89,915	2.03			
Atezolizumab	£55,754	1.43	£34,160	0.60	£57,310

Carboplatin-etoposide	£20,553	0.97	£35,201	0.46	£76,885

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

Table 70: Net health benefit (list price) – non-Asian

Technologies	NHB at £20,000	NHB at £30,000
Serplulimab vs atezolizumab	-£22,239	-£16,279
Serplulimab vs carboplatin-etoposide	-£48,284	-£37,745

***Abbreviations**: NHB, net health benefit.*

Appendix F: Adverse reactions

There are no other studies available that have data reporting on additional adverse reactions. Therefore, the only AEs of consideration are those reported in the ASTRUM-005 study.

Appendix G: Additional ASTRUM-005 adverse events information

Table 71: TEAEs occuring in ≥5% of all subjects

System Organ Class preferred term	Serplulimab group (n=389)	Placebo group (n=196)	Total (N=585)
Any TEAE with incidence ≥5%, n (%)	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders, n (%)	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]
Blood lactate dehydrogenase increased	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]	[redacted]
Blood cholesterol increased	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders, n (%)	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]	[redacted]
Hypertriglyceridaemia	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]
Hypercholesterolaemia	[redacted]	[redacted]	[redacted]
Hyperuricaemia	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]
Hypoproteinaemia	[redacted]	[redacted]	[redacted]
Hypochloraemia	[redacted]	[redacted]	[redacted]

System Organ Class preferred term	Serplulimab group (n=389)	Placebo group (n=196)	Total (N=585)
Hyperlipidaemia	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders, n (%)	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions, n (%)	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders, n (%)	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]	[redacted]
Productive cough	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders, n (%)	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Infections and infestations, n (%)	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Endocrine disorders, n (%)	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]
Nervous system disorders, n (%)	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Psychiatric disorders, n (%)	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Renal and urinary disorders, n (%)	[redacted]	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]	[redacted]
Vascular disorders, n (%)	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Cardiac disorders, n (%)	[redacted]	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders, n (%)	[redacted]	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]	[redacted]

Abbreviations*: TEAE, treatment-emergent adverse event*
Source*: ASTRUM-005 CSR Table 85 (Shanghai Henlius Biotech, 2024)*

Table 72: Summary of common TEAEs (incidence ≥5%) related to serplulimab/placebo by system organ class and preferred term

System Organ Class preferred term	Serplulimab group (n=389)	Placebo group (n=196)	Total (N=585)
Any TEAE with incidence ≥ 5% and related to serplulimab/placebo, n (%)	[redacted]	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]

System Organ Class preferred term	Serplulimab group (n=389)	Placebo group (n=196)	Total (N=585)
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]
Blood lactate dehydrogenase increased	[redacted]	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders, n (%)	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders, n (%)	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders, n (%)	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Endocrine disorders, n (%)	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions, n (%)	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]

Abbreviations*: TEAE, Treatment-emergent adverse events*
Source*: ASTRUM-005 CSR Table 88 (Shanghai Henlius Biotech, 2024)*

Table 73: Summary of TEAEs leading to death by system organ class and preferred term

System Organ Class preferred term	Serplulimab group (n=389)	Placebo group (n=196)	Total (N=585)
TEAEs leading to death, n (%)	[redacted]	[redacted]	[redacted]
TEAEs Leading to death [a], n (%)	[redacted]	[redacted]	[redacted]
TEAEs Leading to death [b], n (%)	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions, n (%)	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Infections and infestations, n (%)	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Intracranial infection	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]

System Organ Class preferred term	Serplulimab group (n=389)	Placebo group (n=196)	Total (N=585)
Respiratory, thoracic, and mediastinal disorders, n (%)	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]
Immune-mediated lung disease	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Cardiac disorders, n (%)	[redacted]	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]	[redacted]
Cardiopulmonary failure	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]
Nervous system disorders, n (%)	[redacted]	[redacted]	[redacted]
Diabetic hyperosmolar coma	[redacted]	[redacted]	[redacted]
Immune-mediated encephalitis	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders, n (%)	[redacted]	[redacted]	[redacted]
Intestinal obstruction	[redacted]	[redacted]	[redacted]

Abbreviations: *TEAE, treatment-emergent adverse event*
Source: *ASTRUM-005 CSR Table 96 (Shanghai Henlius Biotech, 2024)*

Table 74: TEAEs related to serplulimab/placebo leading to death (safety set)

Sex/Age/Race	Treatment group	Preferred term	Action taken	Relatedness
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *M, male; NA, not applicable; TEAE, Treatment-emergent adverse events*
Source: *ASTRUM-005 CSR Table 97 (Shanghai Henlius Biotech, 2024)*

Table 75: Summary of SAEs related to serplulimab/placebo by system organ class and preferred term (safety set)

System Organ Class preferred term	Serplulimab group (n=389)	Placebo group (n=196)	Total (N=585)
Any serious TEAE related to serplulimab/placebo, n (%)	[redacted]	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Blood ketone body increased	[redacted]	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders, n (%)	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]
Diabetic ketoacidosis	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders, n (%)	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]

Leukopenia	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Infections and infestations, n (%)	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Encephalitis herpes	[redacted]	[redacted]	[redacted]
Febrile infection	[redacted]	[redacted]	[redacted]
Lip infection	[redacted]	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions, n (%)	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]
Nervous system disorders, n (%)	[redacted]	[redacted]	[redacted]
Immune-mediated encephalitis	[redacted]	[redacted]	[redacted]
Cognitive disorder	[redacted]	[redacted]	[redacted]
Lacunar infarction	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]
Neurotoxicity	[redacted]	[redacted]	[redacted]
Peripheral sensorimotor neuropathy	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders, n (%)	[redacted]	[redacted]	[redacted]
Immune-mediated lung disease	[redacted]	[redacted]	[redacted]
Pneumothorax	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders, n (%)	[redacted]	[redacted]	[redacted]
Drug-induced liver injury	[redacted]	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]	[redacted]
Immune-mediated hepatitis	[redacted]	[redacted]	[redacted]
Hepatic failure	[redacted]	[redacted]	[redacted]
Jaundice	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders, n (%)	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]	[redacted]
Immune-mediated pancreatitis	[redacted]	[redacted]	[redacted]
Intestinal obstruction	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Cardiac disorders, n (%)	[redacted]	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]
Cardiac failure acute	[redacted]	[redacted]	[redacted]
Immune system disorders, n (%)	[redacted]	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	[redacted]	[redacted]	[redacted]
Endocrine disorders, n (%)	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]
Eye disorders, n (%)	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]
Psychiatric disorders, n (%)	[redacted]	[redacted]	[redacted]
Panic disorder	[redacted]	[redacted]	[redacted]
Renal and urinary disorders, n (%)	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Vascular disorders, n (%)	[redacted]	[redacted]	[redacted]
Aortic arteriosclerosis	[redacted]	[redacted]	[redacted]

***Abbreviations**: SAE, serious adverse event; TEAE, treatment-emergent adverse events.*
***Source**: ASTRUM-005 CSR Table 98 (Shanghai Henlius Biotech, 2024)*

Table 76: Summary of TEAEs related to serplulimab/placebo leading to discontinuation of serplulimab/placebo by system organ class and preferred term (safety set)

System Organ Class preferred term	Serplulimab group (N=389)	Placebo group (N=196)	Total (N=585)
Any TEAE related to serplulimab/placebo leading to discontinuation of serplulimab/placebo, n (%)	[redacted]	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Cortisol decreased	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Troponin increased	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders, n (%)	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Gastric ulcer	[redacted]	[redacted]	[redacted]
Immune-mediated pancreatitis	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Nervous system disorders, n (%)	[redacted]	[redacted]	[redacted]
Cognitive disorder	[redacted]	[redacted]	[redacted]
Immune-mediated encephalitis	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]
Peripheral sensorimotor neuropathy	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]	[redacted]
Dermatitis bullous	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions, n (%)	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders, n (%)	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]
Diabetic ketoacidosis	[redacted]	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders, n (%)	[redacted]	[redacted]	[redacted]
Immune-mediated lung disease	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders, n (%)	[redacted]	[redacted]	[redacted]
Cardiac disorders, n (%)	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]
Endocrine disorders, n (%)	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]
Eye disorders, n (%)	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders, n (%)	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Infections and infestations, n (%)	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]

Abbreviations: *TEAE, treatment-emergent adverse event*
Source: *ASTRUM-005 CSR Table 101 (Shanghai Henlius Biotech, 2024)*

Table 77: Summary of treatment-emergent infusion reactions by system organ class and preferred term (safety set)

System Organ Class preferred term	Serplulimab group (N=389)	Placebo group (N=196)	Total (N=585)
Any TEAE that was an infusion reaction, n (%)	[redacted]	[redacted]	[redacted]

System Organ Class preferred term	Serplulimab group (N=389)	Placebo group (N=196)	Total (N=585)
Immune system disorders, n (%)			
Anaphylactic reaction			
Drug hypersensitivity			
Hypersensitivity			
Injury, poisoning, and procedural complications, n (%)			
Infusion-related reaction			

***Abbreviations**: TEAE, treatment-emergent adverse event*
***Source**: ASTRUM-005 CSR Table 104 (Shanghai Henlius Biotech, 2024)*

Table 78: Summary of immune-related TEAEs by system organ class and preferred term (safety set)

System Organ Class preferred term	Serplulimab group (N=389)	Placebo group (N=196)	Total (N=585)
Any immune-related TEAE, n (%)			
Endocrine disorders, n (%)			
Hypothyroidism			
Hyperthyroidism			
Thyroid disorder			
Adrenal insufficiency			
Hypophysitis			
Central hypothyroidism			
Investigations, n (%)			
Alanine aminotransferase increased			
Aspartate aminotransferase increased			
Gamma-glutamyl transferase increased			
Platelet count decreased			
White blood cell count decreased			
Neutrophil count decreased			
Blood lactate dehydrogenase increased			
Blood alkaline phosphatase increased			
Blood creatine phosphokinase increased			
Myoglobin blood increased			
Blood thyroid stimulating hormone decreased			
Blood thyroid stimulating hormone increased			
Troponin increased			
Blood bilirubin increased			
Thyroxine free decreased			
Skin and subcutaneous tissue disorders, n (%)			
Rash			
Rash maculo-papular			
Pruritus			
Eczema			
Psoriasis			
General disorders and administration site conditions, n (%)			
Malaise			
Asthenia			
Fatigue			
Pyrexia			
Metabolism and nutrition disorders, n (%)			
Hyperglycaemia			
Decreased appetite			
Diabetic ketoacidosis			

System Organ Class preferred term	Serplulimab group (N=389)	Placebo group (N=196)	Total (N=585)
Hyperlipidaemia	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders, n (%)			
Anaemia	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders, n (%)			
Diarrhoea	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders, n (%)			
Immune-mediated lung disease	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]
Nervous system disorders, n (%)			
Dizziness	[redacted]	[redacted]	[redacted]
Immune-mediated encephalitis	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]
Cardiac disorders, n (%)			
Arrhythmia	[redacted]	[redacted]	[redacted]
Sinus bradycardia	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders, n (%)			
Arthralgia	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders, n (%)			
Hepatic function abnormal	[redacted]	[redacted]	[redacted]
Drug-induced liver injury	[redacted]	[redacted]	[redacted]
Infections and infestations, n (%)			
Pneumonia	[redacted]	[redacted]	[redacted]

Abbreviations*: TEAE, treatment-emergent adverse event.*
Source*: ASTRUM-005 CSR Table 105 (Shanghai Henlius Biotech, 2024)*

Appendix H: Published cost-effectiveness studies

Included in 'Appendix D, H, I, J – SLR Results'

Appendix I: Health-related quality-of-life studies

Included in 'Appendix D, H, I, J – SLR Results'

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

Included in 'Appendix D, H, I, J – SLR Results'

Appendix K: Clinical outcomes and disaggregated results from the model

Clinical outcomes from the model

The economic model predicts median OS and PFS that are consistent with the results from the clinical trials. For serplulimab, median OS and PFS are slightly overestimated in the model compared with the results in ASTRUM-005 and IMpower133. Results for carboplatin-etoposide are consistent with those from ASTRUM-005 (see Table 79 and Table 80). The percentages of patients reaching landmark survival times for OS and PFS based on the selected base-case extrapolations are presented in Table 81 and Table 82, respectively, alongside the predicted survival based on the KM curves from ASTRUM-005, and the digitised KM curve for atezolizumab. Notably, the percentage survival at each timepoint with the selected curves in the model is consistent with the KM curves from ASTRUM-005. The largest discrepancy is in PFS in the atezolizumab arm, which is overestimated in the model, resulting in a conversative estimate of the relative efficacy of serplulimab compared to atezolizumab.

Table 79: Outcomes predicted by the economic model

	Serplulimab	Atezolizumab	Carboplatin-etoposide
Median OS	16.90	13.45	11.15
Median PFS	7.70	5.86	4.48

Abbreviations: *OS, overall survival; PFS, progression-free survival.*

Table 80: Outcomes reported in clinical trials

	Serplulimab	Atezolizumab	Carboplatin-etoposide
Median OS	15.8	10.3	11.1
Median PFS	5.75	5.1	5.03

Abbreviations: *OS, overall survival; PFS, progression-free survival.*
Source*: (Shanghai Henlius Biotech, 2024, Horn et al., 2018).*

Table 81: Landmark survival times – OS

Year	Serplulimab		Atezolizumab		Carboplatin-etoposide	
	Modelled	KM	Modelled	KM	Modelled	KM
Year 1	64.08%	61.92%	55.19%	51.57%	46.10%	44.87%
Year 2	36.24%	32.46%	25.78%	21.50%	17.03%	15.79%
Year 3	22.55%	25.26%	13.68%	-	8.18%	9.51%
Year 5	11.14%	-	5.34%	-	3.02%	-
Year 10	3.84%	-	1.29%	-	0.74%	-
Year 20	1.26%	-	0.29%	-	0.18%	-

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

Table 82: Landmark survival times – PFS

	Serplulimab	Atezolizumab	Carboplatin-etoposide

	Modelled	KM	Modelled	KM	Modelled	KM
Year 1	31.68%	[redacted]	20.11%	12.57%	5.69%	[redacted]
Year 2	12.53%	[redacted]	5.52%	-	0.82%	[redacted]
Year 3	6.72%	[redacted]	2.32%	-	0.26%	[redacted]
Year 5	2.95%	-	0.74%	-	0.06%	-
Year 10	0.93%	-	0.15%	-	0.01%	-
Year 20	0.29%	-	0.03%	-	0.00%	-

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

Disaggregated results of the base-case incremental cost-effectiveness analysis

Disaggregated results for QALYs and costs are presented in Table 83 to Table 86 for serplulimab compared with atezolizumab and carboplatin-etoposide. Most of the costs accrued in the serplulimab arm are associated with the acquisition of serplulimab, followed by resource use. This is the case for atezolizumab too. In the carboplatin-etoposide arm, most of the cost is associated with resource use. Patients spend a similar amount of time in the progression-free arm in the comparison vs atezolizumab and carboplatin-etoposide, with slightly more time spent in progressed disease in the latter. In all arms, patients spend more time in the progressed state vs the progression-free state. The health state occupancy over the entire time horizon for the three modelled treatment arms is presented in Figure 30 to Figure 32. The discounted cumulative QALYs in each of the modelled treatment arms is presented in Figure 33.

Table 83: Summary of QALY gain (discounted) by health state – atezolizumab

Health state	QALY serplulimab	QALY comparator atezolizumab	Increment	Absolute increment	% absolute increment
Progression-free	0.90	0.60	0.30	0.30	60%
Progressed	0.92	0.73	0.20	0.20	40%
Total	1.82	1.32	0.50	0.50	100%

***Abbreviations**: QALY, quality-adjusted life-year.*

Table 84: Summary of QALY gain (discounted) by health state – carboplatin-etoposide

Health state	QALY serplulimab	QALY carboplatin-etoposide	Increment	Absolute increment	% absolute increment
Progression-free	0.90	0.60	0.51	0.51	68%
Progressed	0.92	0.73	0.24	0.24	32%
Total	1.82	1.32	0.76	0.76	100%

***Abbreviations**: QALY, quality-adjusted life-year.*

Table 85: Summary of predicted resource use by category of cost (list price) – atezolizumab

Item	Cost serplulimab	Cost atezolizumab	Increment	Absolute increment	% absolute increment
Drug acquisition costs	£52,422	£31,107	£21,316	£21,316	86%
Administration costs	£7,305	£5,923	£1,382	£1,382	6%
Resource use costs	£18,667	£16,646	£2,021	£2,021	8%
Adverse event costs	£1,033	£996	£38	£38	0%
Total	£79,427	£54,671	£24,756	£24,756	100%

Table 86: Summary of predicted resource use by category of cost (list price) – carboplatin-etoposide

Item	Cost serplulimab	Cost carboplatin-etoposide	Increment	Absolute increment	% absolute increment
Drug acquisition costs	£52,422	£918	£51,505	£51,505	89%
Administration costs	£7,305	£4,556	£2,749	£2,749	4.8%
Resource use costs	£18,667	£15,229	£3,437	£3,437	5.9%
Adverse event costs	£1,033	£858	£175	£175	0.3%
Total	£79,427	£21,561	£57,866	£57,866	100%

Figure 30: Health state occupancy – serplulimab

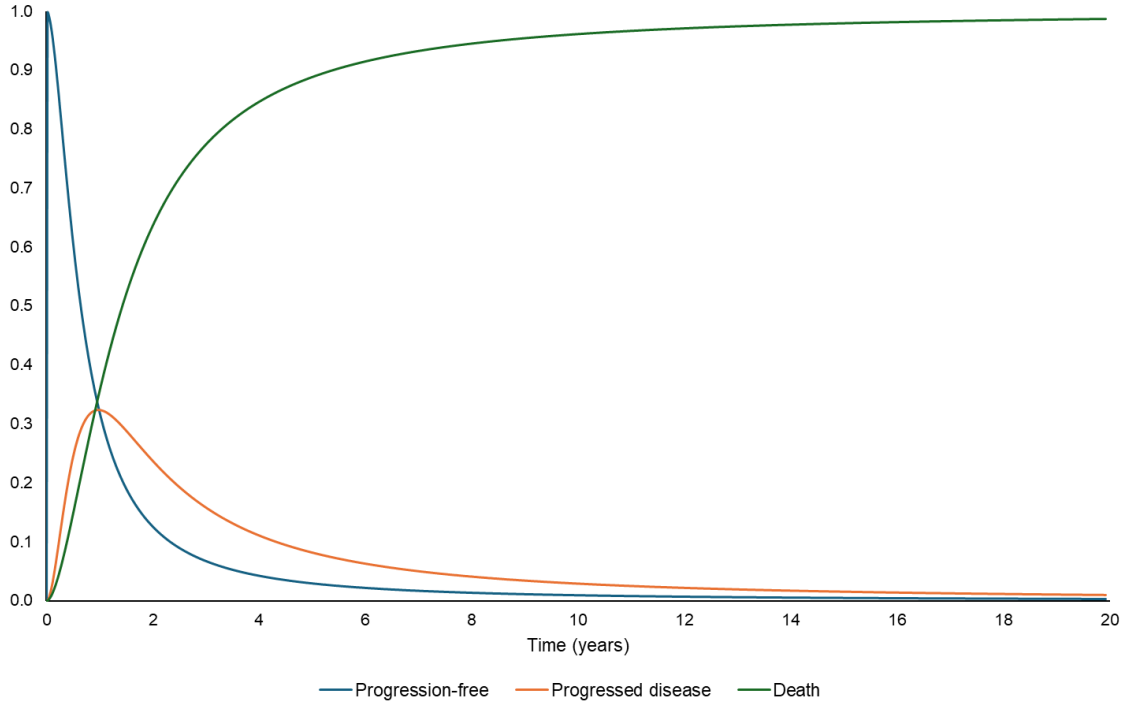


Figure 31: Health state occupancy – atezolizumab

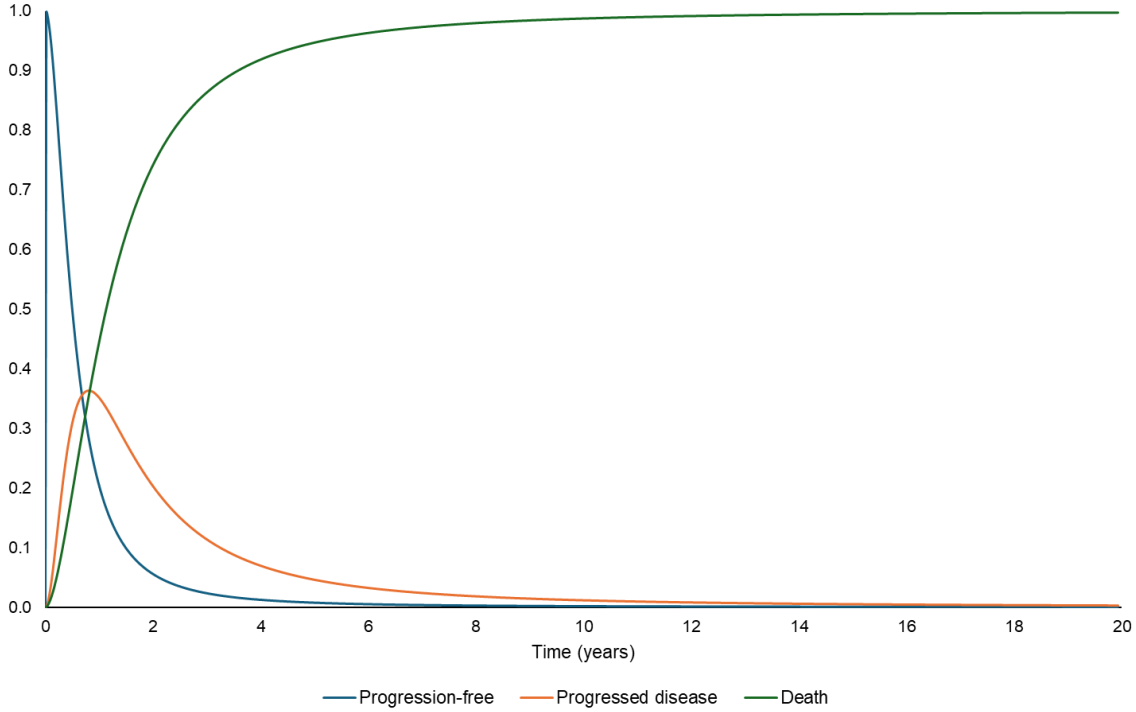


Figure 32: Health state occupancy – carboplatin-etoposide

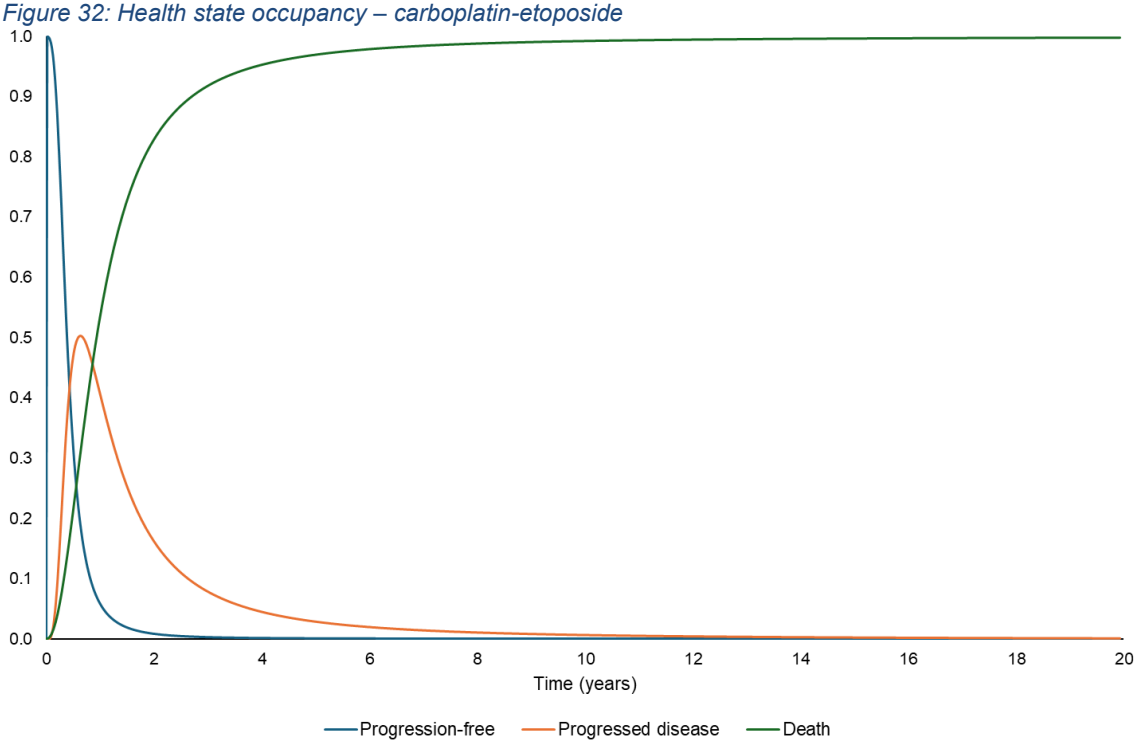
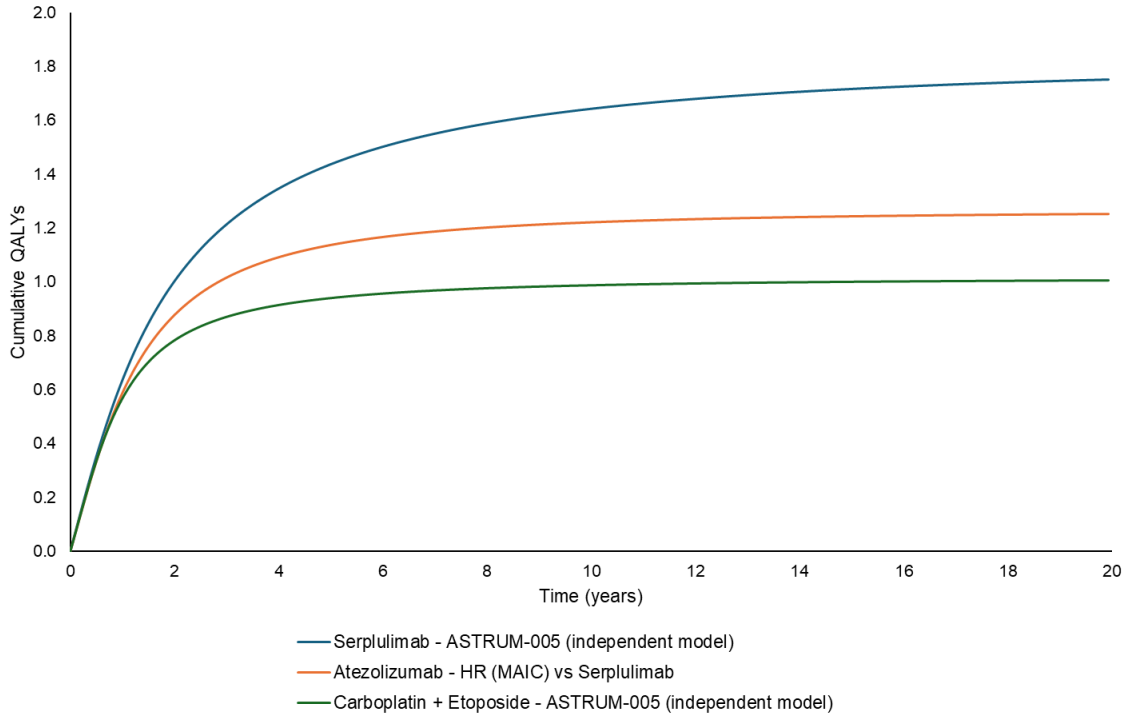


Figure 33: Cumulative QALYs (discounted)



***Abbreviations**: QALYs, quality adjusted life-years.*

Appendix L: Price details of treatments included in the submission

Price of intervention, comparators and subsequent treatments

A summary of the costs for the interventions included in the economic analysis are presented in Table 87.

Table 87: Details of all costs, including intervention, concomitant, comparator and subsequent medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source	PAS price (if known)	eMIT price/date searched for (if available)
Serplulimab	IV	100mg	10ml	£1,321.83	Accord, Data on File	[redacted]	-
Atezolizumab	IV	1200mg	20ml	£3,807.69	BNF	-	January 2025
		840mg	14ml	£2,665.38	BNF	-	
Carboplatin	IV	50mg	5ml	£6.71	eMIT	-	
		600mg	60ml	£38.93	eMIT	-	
Etoposide	IV	100mg	5ml	£5.07	eMIT	-	
		500mg	25ml	£13.93	eMIT	-	
Topotecan	Oral	1mg	10 capsules	£360.00	BNF	-	
Cyclophosphamide	IV	1000mg	NA	£13.11	eMIT	-	
Doxorubicin	IV	50mg	25ml	£10.06	eMIT	-	
Vincristine	IV	2mg	2ml	£11.00	eMIT	-	

***Abbreviations**: BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool; IV, intravenous; PAS, patient access scheme*

Appendix M: Expert elicitation

Details of the methodology for the Delphin panel is included below, and full results are available in the 'Appendix M – expert elicitation' report included in the submission pack. The panel focused on:

- The diagnosis and prevalence of ES-SCLC in the UK and Ireland
- The treatment and management of ES-SCLC in the UK and Ireland
- The applicability of ASTRUM-005 clinical trial data to the UK and Irish population
- The anticipated uptake and resource utilisation of serplulimab for first-line ES-SCLC in UK and Irish clinical practice
- The anticipated long-term treatment effect of PD-1/PD-L1 inhibitors for ES-SCLC

Participants were recruited to the study based on the following criteria:

- >5 years' experience in managing ES-SCLC patients
- Lung cancer-relevant key opinion leader (KOL) status, i.e. publications, conference presentation, working group membership
- Representation across the UK and Ireland

Round 1: online survey

- Throughout December 2024 and January 2025, a panel composed of 5 clinical experts were provided with a 1-hour virtual survey to complete. The online survey included a range of open-ended as well as closed qualitative and quantitative questions. For some questions data summaries and references were provided to support informed judgements from the panel. The results of the survey were analysed using thematic analysis and descriptive statistics where appropriate.
- The topics in the Round 1 survey included the prevalence of ES-SCLC in the UK and Ireland, present management of ES-SCLC, the applicability of clinical

trial data to the UK and Irish population, and the anticipated long-term treatment effect of PD-1/PD-L1 inhibitors for ES-SCLC.

Round 2: group consensus meeting

- Of the 5 clinicians who participated in the Round 1 online survey, 3 clinical experts took part in a group consensus meeting on the 30th of January 2025, to consider results from the individual interviews and seek further understanding.
- The Round 2 meeting was conducted by three researchers and lasted approximately 2 hours. This was split into two parts:
    - Discussion of anonymised and consolidated findings from Round 1: discussion points in the first part of the Round 2 meeting included the diagnosis, prevalence, treatment, and management of ES-SCLC in the UK and Ireland, as well as the applicability of clinical trial data to the UK and Irish population, the anticipated uptake and resource utilisation of serplulimab for first-line ES-SCLC in UK and Irish clinical practice, and the anticipated long-term treatment effect of PD-1/PD-L1 inhibitors for ES-SCLC.
    - Consensus-building: where consensus was reached in Round 1, findings were presented to the panellists, with opportunity to comment on the consensus opinion. Where consensus was not reached in Round 1, findings were presented to the panellists, with the facilitator opening a discussion to understand the rationale. After discussions, panellists then submitted their level of agreement on a 5-point Likert scale and anonymised results of the vote were presented. Depending on whether consensus was reached or not, the facilitator would provide time for further discussion, presenting of rationale, and opportunity to vote once again before moving on to further topics. The threshold for consensus was set at 70% agreement across all participants (equivalent to N=3/3 participants), as per standard modified Delphi practice (Kleynen et al., 2014, Santaguida et al., 2018, Schneider et al., 2017).

Appendix N: Results with PAS price

Results with the serplulimab PAS price are provided below. Base-case results are presented in Table 88 to Table 90. Probabilistic results are presented in Table 91, Table 92, and **Error! Reference source not found.** to **Error! Reference source not found.**. Scenario analysis results are presented in Table 93 and Table 94.

Table 88: Base-case results, pairwise (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	[redacted]	2.47	2.10				
Atezolizumab	£54,671	1.74	1.50	[redacted]	0.74	0.60	[redacted]
Carboplatin-etoposide	£21,561	1.38	1.21	[redacted]	1.09	0.89	[redacted]

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life; PAS, patient access scheme.*

Table 89: Base-case results, full incremental analysis (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	£54,671	1.50			
Serplulimab	[redacted]	*2.10*	[redacted]	*-0.60*	[redacted]
Carboplatin-etoposide	£21,561	1.21	[redacted]	0.89	[redacted]

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; PAS, patient access scheme.*

Table 90: Net health benefit (PAS price)

Technologies	NHB at £20,000	NHB at £30,000
Serplulimab vs atezolizumab	[redacted]	[redacted]
Serplulimab vs carboplatin-etoposide	[redacted]	[redacted]

***Abbreviations**: NHB, net health benefit; PAS, patient access scheme.*

Table 91: Probabilistic results vs. atezolizumab (PAS price)

	Serplulimab	Atezolizumab	Incremental	ICER
Total costs (£)	[redacted]	£58,299	[redacted]	[redacted]
Total QALYs	2.10	1.55	0.55	

***Abbreviations:** LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio;*

Table 92: Probabilistic results vs. carboplatin-etoposide (PAS price)

	Serplulimab	Carboplatin-etoposide	Incremental	ICER
Total costs (£)	[redacted]	£22,583	[redacted]	[redacted]
Total QALYs	2.10	1.21	0.89	

***Abbreviations:** LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio;*

[redacted]

***Abbreviations**: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.*

[redacted]

***Abbreviations**: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.*

[redacted]

[redacted]

Table 93: Summary of scenario analysis – comparator atezolizumab (PAS price)

Scenario	Description	Value	Incremental QALYs	Incremental costs	ICER (£/QALY gained)
Base-case			0.60	[redacted]	[redacted]
OS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.49	[redacted]	[redacted]
		Weibull	0.43	[redacted]	[redacted]
		Gamma	0.42	[redacted]	[redacted]
		Log-normal	0.60	[redacted]	[redacted]
		Gompertz	0.66	[redacted]	[redacted]
		Gen. Gamma	0.59	[redacted]	[redacted]
PFS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.60	[redacted]	[redacted]
		Weibull	0.60	[redacted]	[redacted]
		Gamma	0.59	[redacted]	[redacted]
		Log-normal	0.60	[redacted]	[redacted]
		Gompertz	0.61	[redacted]	[redacted]
		Gen. Gamma	0.60	[redacted]	[redacted]
TTOT parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.60	[redacted]	[redacted]
		Weibull	0.60	[redacted]	[redacted]
		Gamma	0.60	[redacted]	[redacted]
		Log-normal	0.60	[redacted]	[redacted]
		Gompertz	0.59	[redacted]	[redacted]
		Gen. Gamma	0.60	[redacted]	[redacted]
Data source for atezolizumab extrapolation	HR from the MAIC (after matching) applied to the selected serplulimab extrapolation in the base-case. Scenarios using the before-matching HR (more conservative) and using an independent model fitted to pseudo-IPD from IMpower133 (i.e., not HR-based) are presented.	HR from MAIC (before matching)	0.51	[redacted]	[redacted]
		Independent model fitted to pseudo-IPD from IMpower133	0.67	[redacted]	[redacted]
Time horizon (years)	A 20-year time horizon was selected in the base-case to reflect all important differences in costs and outcomes. Scenarios with shorter time	5	0.36	[redacted]	[redacted]
		10	0.50	[redacted]	[redacted]
		15	0.57	[redacted]	[redacted]

	horizons are presented.				
Utility derivation method	Utilities based on progression status were applied in the base-case, aligned with the Committee's stated preferences in TA638. Scenarios using the time to death approach and progression status by treatment status are presented.	Time to death	0.44	[redacted]	[redacted]
		Progression status by on/off treatment	0.58	[redacted]	[redacted]
Adverse events	AE rates from the ITT population were modelled in the base-case, with additional disutilities applied for AEs. Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities in case of double-counting are presented.	Exclude AE disutilities	0.60	[redacted]	[redacted]
		Non-Asian AEs	0.56	[redacted]	[redacted]
Treatment waning	No treatment waning is applied in the base-case, as there was no evidence for loss of treatment effect in the ASTRUM-005 trial. Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented. When treatment	Immediate loss of treatment effect at 5 years	0.51	[redacted]	[redacted]
		Gradual loss of treatment effect from 5-10 years	0.55	[redacted]	[redacted]

	waning is applied, the cycle probabilities in the serplulimab arm wane to the atezolizumab arm.				
Vial sharing assumed for serplulimab	No vial sharing is assumed in the base-case. A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	0.60	[redacted]	[redacted]

Abbreviations: *AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; MAIC, matched-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTOT, time to off treatment*

Table 94: Summary of scenario analysis – comparator carboplatin-etoposide (PAS price)

Scenario	Description	Value	Incremental QALYs	Incremental costs	ICER (£/QALY gained)
Base-case			0.89	[redacted]	[redacted]
OS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.79	[redacted]	[redacted]
		Weibull	0.75	[redacted]	[redacted]
		Gamma	0.75	[redacted]	[redacted]
		Log-normal	0.95	[redacted]	[redacted]
		Gompertz	1.10	[redacted]	[redacted]
		Gen. Gamma	0.98	[redacted]	[redacted]
PFS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.89	[redacted]	[redacted]
		Weibull	0.89	[redacted]	[redacted]
		Gamma	0.89	[redacted]	[redacted]
		Log-normal	0.90	[redacted]	[redacted]
		Gompertz	0.91	[redacted]	[redacted]
		Gen. Gamma	0.90	[redacted]	[redacted]
TTOT parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.88	[redacted]	[redacted]
		Weibull	0.89	[redacted]	[redacted]
		Gamma	0.88	[redacted]	[redacted]
		Log-normal	0.89	[redacted]	[redacted]
		Gompertz	0.88	[redacted]	[redacted]
		Gen. Gamma	0.89	[redacted]	[redacted]
Time horizon (years)	A 20-year time horizon was selected in the base-case to reflect all important differences in costs and outcomes. Scenarios with shorter time	5	0.59	[redacted]	[redacted]
		10	0.78	[redacted]	[redacted]
		15	0.86	[redacted]	[redacted]

	horizons are presented.				
Utility derivation method	Utilities based on progression status were applied in the base-case, aligned with the Committee's stated preferences in TA638. Scenarios using the time to death approach and progression status by treatment status are presented.	Time to death	0.66	[redacted]	[redacted]
		Progression status by on/off treatment	0.85	[redacted]	[redacted]
Adverse events	AE rates from the ITT population were modelled in the base-case, with additional disutilities applied for AEs. Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities in case of double-counting are presented.	Exclude AE disutilities	0.91	[redacted]	[redacted]
		Non-Asian AEs	0.84	[redacted]	[redacted]
Treatment waning	No treatment waning is applied in the base-case, as there was no evidence for loss of treatment effect in the ASTRUM-005 trial. Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented. When treatment	Immediate loss of treatment effect at 5 years	0.81	[redacted]	[redacted]
		Gradual loss of treatment effect from 5-10 years	0.85	[redacted]	[redacted]

	waning is applied, the cycle probabilities in the serplulimab arm wane to the carboplatin-etoposide arm.				
Vial sharing assumed for serplulimab	No vial sharing is assumed in the base-case. A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	0.89	[redacted]	[redacted]

Abbreviations: *AE, adverse event; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTOT, time to off treatment*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Serplulimab with carboplatin and etoposide for untreated extensive-stage small cell lung cancer [ID6346]

Summary of Information for Patients (SIP)

May 2025

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost-effectiveness.

File name	Version	Contains confidential information	Date
ID6346_Summary of information for patients	**FINAL**	**Yes**	**6th May 2025**

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

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

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

Generic name: Serplulimab Brand name: Hetronifly®

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

The patient population will match directly with serplulimab's approved use. Serplulimab is approved for adults with extensive-stage small cell lung cancer (ES-SCLC) that have not previously received treatment (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.

Marketing authorisation is a licence needed to sell a medicinal product on the market and sets out the conditions for use of a drug based on evidence of its safety and effectiveness. On 19 September 2024, the Committee for Medicinal Products for Human Use adopted a positive opinion, recommending the granting of a marketing authorisation for serplulimab. Serplulimab is currently awaiting marketing authorisation from the European Medicines Agency which oversees the approval process across Europe, and the Medicines and Healthcare products Regulatory Agency which oversees the approval process in the UK. Expected dates of approval are provided in Document B of the submission dossier (Table 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:

Accord Healthcare does not have any collaborations or conflicts of interest with any patient groups.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

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.
Lung cancer is one of the most common types of cancer globally and a leading cause of cancer-related deaths both worldwide and in England, accounting for the highest mortality rates of any cancer among both men and women (2-4). It occurs when cancer cells grow uncontrollably and cluster together to form a tumour affecting the healthy lung tissue around them (5). It can be characterised into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (6, 7). SCLC is the most aggressive form of lung cancer. It can be categorised into limited-stage (LS-SCLC) and extensive-stage (ES-SCLC). Limited disease is when the cancer has not spread beyond one lung and nearby lymph nodes, and extensive disease is when the cancer has spread beyond one lung and nearby lymph nodes. Lung cancer is one of the most common cancers in men and women – SCLC accounts for 13% to 17% of all lung cancers, and about 70% of these cases are extensive-stage at diagnosis. (8-12) The population we are interested in for this appraisal is ES-SCLC. The survival rate for ES-SCLC is low, with only 5% of patients surviving for five years in the UK. This type of cancer significantly impacts patients' quality of life, affecting their ability to perform daily activities, hobbies, and work. The symptoms also have a major impact on their physical, social, and emotional wellbeing, including mental health. (13-17) ES-SCLC is considered incurable; treatments are primarily aimed at providing relief (16). The standard treatment is a combination of chemotherapy drugs, which can extend life by about 9 to 10 months but have serious side effects (18-21). Other treatments like atezolizumab and durvalumab are options, although durvalumab is not yet approved for use in this condition in the NHS.

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?
The symptoms of SCLC vary depending on the tumour's location and size. Many of the symptoms such as cough and shortness of breath can be mistaken for common respiratory issues, leading to a delayed diagnosis. Doctors diagnose ES-SCLC by first taking a detailed medical history and performing a physical examination. They then use imaging tests like chest X-rays, CT scans, and MRIs to visualise the lungs and detect abnormalities. A bronchoscopy, which involves examining the inside of the lung, and taking a biopsy for histopathology (examining tissue under a microscope) are also common steps. Molecular testing (a method used to look at a person's DNA or RNA) is done to identify specific genetic mutations or markers, although currently, no predictive markers are available for ES-SCLC. There are no additional tests needed to determine whether people can be treated with serplulimab. (18)

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: o 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. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
ES-SCLC is considered incurable currently, treatments therefore focus on managing symptoms, extending overall survival and improving quality of life. The most common first treatment is a mix of chemotherapy drugs (platinum-based chemotherapy and etoposide), which can help patients live 9–10 months longer but often causes several side effects. Drugs like atezolizumab (Tecentriq) and durvalumab (Imfinzi) help the immune system attack cancer cells by targeting a protein called PD-L1. Atezolizumab is approved in the UK to be used with chemotherapy for patients in good physical condition. Durvalumab is not approved yet for use in the NHS for this type of cancer and is still being reviewed. Serplulimab in combination with platinum-based chemotherapy is an alternative to atezolizumab and durvalumab (both in combination with platinum-based chemotherapy) or an alternative to platinum-based chemotherapy on its own. After treatment with either serplulimab, atezolizumab or platinum-based chemotherapy, patients may expect to receive radiotherapy of the chest or brain to prevent the cancer from spreading, depending on how well they are. (22)

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.

In addition to the physical burden of ES-SCLC, patients' mental health is impacted substantially. The lack of treatment options and the inherently progressive nature of the disease leave patients feeling afraid of dying, and hoping to go into remission as a means of gaining more time (Bebb et al., 2023).

Looking to caregiver implications, a study by Feliciano et al. on the family-centred concerns of lung cancer revealed that caregivers experience a wide range of barriers involving psychological, emotional, and technical aspects, while helping their affected person (Feliciano et al., 2020). Their responsibilities occupy a significant portion of their time, and they often live with the patient (Bebb et al., 2023). Duties can be considered overwhelming, impacting their careers, family, and hobbies. Caregivers often express a desire for external support as they feel isolated while helping their family member (Bebb et al., 2023, Feliciano et al., 2020).

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.

Serplulimab is a type of immunotherapy (a treatment that helps your immune system fight cancer) used to treat ES-SCLC. It works by targeting a protein called PD-1 on the surface of immune cells. By blocking PD-1, serplulimab helps the immune system recognise and attack cancer cells more effectively. This can help slow down the cancer's growth and improve survival rates. It is used when ES-SCLC has not previously been treated by any other cancer treatments. (1)

Serplulimab plus chemotherapy has shown consistent benefits in improving overall survival, progression-free survival as well as benefits in other response markers versus placebo plus chemotherapy in the clinical trial. (23)

It is estimated that around 1,618 patients in England and Wales will be eligible for the treatment, serplulimab, in 2025. For more information on how serplulimab works and supporting evidence please see the Summary of Product Characteristics and Information for the Patient. (24)

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.

Serplulimab is used in combination with platinum-based chemotherapy (carboplatin and etoposide). These drugs kill cancer cell by damaging their DNA, which stops them from growing and dividing. When used together, serplulimab and platinum-based chemotherapy are complementary: the chemotherapy kills cancer cells directly, while serplulimab boosts the patient's immune system to keep attacking any remaining cancer cells. This combination can be more effective than either treatment alone. (1)

Platinum-based chemotherapy for ES-SCLC can cause several side effects. Common ones include nausea, vomiting, hair loss, fatigue, and a metallic taste in the mouth. It can also cause low blood cell counts, which increases the risk of infections, anaemia, and bleeding. Some people might experience kidney problems, nerve damage, and allergic reactions. (18, 20, 21)

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?

Serplulimab is given through an intravenous infusion in the hospital, lasting 30 to 90 minutes, and is administered once every 3 weeks. Platinum-based chemotherapy (carboplatin and etoposide), which is given in addition to serplulimab, is also given through an intravenous infusion. Etoposide is given on days 1, 2 and 3 of each 3-week cycle and carboplatin is given on the first day of each 3-week cycle. The dose of each drug is calculated using the patient's body weight. (24)

Platinum-based chemotherapy is given to patients for a maximum duration of four cycles, lasting 3 weeks each. Treatment with serplulimab is stopped when any of the following occur:

- The cancer progresses or gets worse
- The patient has severe side effects that cannot be tolerated
- The patient or the doctor decides to stop treatment
- The patient dies

Treatment with serplulimab means that patients have to go to the hospital every 3 weeks to receive their treatment. However, the frequency of administering serplulimab is similar to existing treatments such as atezolizumab.

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 safety and effectiveness of serplulimab was tested in a randomised, double-blind clinical trial (ASTRUM-005) meaning some participants received the treatment while others got a placebo (a non-active treatment). The trial took place in multiple regions (China, Georgia, Poland, Russia,

Turkey and the Ukraine), and was conducted from the 12th of September 2019 to the 7th of May 2024. (25, 26)

The ASTRUM-005 trial studied 585 patients with untreated ES-SCLC. Participants were either treated with serplulimab with platinum-based chemotherapy, or placebo with platinum-based chemotherapy. Patients had to be 18 years or older to enrol in ASTRUM-005 and had not received any prior treatment for their diseases. They had to have a good overall health score and an expected survival of at least 12 weeks. Patients were not eligible if they had another type of cancer in addition to ES-SCLC (recent or active), had severe heart problems or infections, or had any major surgeries or severe allergies. The trial investigated how long patients survived on either treatment, and whether each patient's cancer got worse or progressed. It also recorded patients' quality of life at various points throughout the study. (25, 26)

Serplulimab is currently being studied in a number of other trials, some of which are recruiting patients, which are studying the effect of serplulimab in combination with other types of treatments for ES-SCLC and other conditions.

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 ASTRUM-005 trial showed that adding serplulimab to chemotherapy significantly improved survival for patients with ES-SCLC. Patients treated with serplulimab lived about 15 months on average, compared to 11 months for those with a placebo. The combination also significantly reduced the risk of death or disease progression, with better survival rates at 4 years. Patients experienced a longer period before their disease progressed and had a higher overall response rate to the treatment, indicating a more long-term treatment effect. (25, 26)

Because serplulimab was not directly compared with atezolizumab in a clinical trial, but atezolizumab is used in the NHS for treating ES-SCLC, a statistical method was used to indirectly compare the treatment benefit of serplulimab and atezolizumab. The data on how well atezolizumab works was taken from the literature. This indirect comparison showed that serplulimab with platinum-based chemotherapy improved overall survival and progression-free survival compared to atezolizumab with platinum-based chemotherapy.

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.

The trial collected information on quality of life by asking patients to fill out questionnaires; using a number of instruments, including the EQ-5D-5L (5-level) and the European Organisation for Research and Treatment of Cancer quality of life instruments (EORTC) QLQ-C30 (which collects data on 30 different dimensions of a patient's quality of life, primarily functional and symptom

domains) and QLQ-LC13 (a lung cancer-specific questionnaire). The EQ-5D questionnaire is limited to five domains and provides a more general overview of patients' wellbeing, which are not specific to lung cancer. The EORTC questionnaires provide a more detailed insight into patients' quality of life during their treatment, which can help us understand how the treatment affected their cancer.

Results from the ASTRUM-005 trial showed that serplulimab combined with chemotherapy led to similar quality of life for patients with ES-SCLC. Patients reported improved physical and emotional wellbeing and experienced less pain in other parts of their body by Week 18. These improvements were similar to those seen with chemotherapy alone but showed a notable positive impact, especially in reducing pain. (25, 26)

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.

Based on the results of the clinical trial, serplulimab is considered well tolerated for patients treated for ES-SCLC:

- **Tolerability**: Serplulimab with platinum-based chemotherapy was well tolerated, with fewer overall side effects compared to placebo with platinum-based chemotherapy.
- **Drug-Related Side Effects**: There were more drug-related side effects in the serplulimab group compared to the placebo group.
- **Serious Side Effects**: The serplulimab group had a higher incidence of serious side effects, but the placebo group had a higher incidence of side effects leading to death.

Around 8% of patients in the serplulimab group and 7.7% in the placebo group had side effects that required stopping treatment. The number of patients who stopped treatment due to drug-related side effects was small, with 4.9% in the serplulimab group and 4.1% in the placebo group stopping. The most common side effects that led to stopping treatment were low levels of neutrophils (a type of white blood cell), low platelet (blood cells that stop bleeding) counts, anaemia (a lack of red blood cells to carry oxygen, causing tiredness and weakness), and overall low white blood cell counts. This suggests that serplulimab does not pose a significant risk of causing patients to discontinue treatment. (25, 26)

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.

Treatment with serplulimab offers several key benefits for patients with ES-SCLC compared to current treatments. Serplulimab is an immunotherapy, and it works by blocking the PD-1 protein, helping the immune system to better recognise and attack cancer cells, which is a novel approach to treatment. Combined with chemotherapy, serplulimab has shown significant improvements in overall survival and progression-free survival, with patients living longer and experiencing delayed

disease progression compared to chemotherapy alone. While the treatment is generally well tolerated, it does have a higher incidence of drug-related side effects, but these are manageable. Given as an infusion every 3 weeks, this schedule provides consistent treatment and regular check-ups, much like other treatments such as atezolizumab. Overall, serplulimab enhances the effectiveness of chemotherapy, improves survival outcomes, and maintains a manageable safety profile, making it a promising option for ES-SCLC patients. (25, 26)

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

While serplulimab offers a number of benefits for patients with ES-SCLC, there are some limitations to consider. One of the main challenges is the absence of direct trial data comparing serplulimab directly with other treatments such as atezolizumab, which means we rely on indirect comparisons to evaluate their relative effectiveness. Additionally, while serplulimab combined with chemotherapy improves overall survival and progression-free survival, it also presents a higher incidence of drug-related side effects. However, these side effects are generally manageable, and the treatment remains well tolerated overall. Despite these limitations, serplulimab is a novel and promising approach that improves the effectiveness of traditional chemotherapy and offers significant survival benefits for ES-SCLC patients. The manageable safety profile and consistent administration schedule make it an attractive option in the evolving landscape of cancer treatment.

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.

How the model reflects the condition

- The cost-effectiveness of serplulimab is assessed via an economic model which uses data from the ASTRUM-005 trial and atezolizumab trial to estimate the long-term costs and

benefits associated with treatment. The model uses data on overall, and progression-free survival to evaluate these. Data from ASTRUM-005 was available up to approximately 55 months, after which point, statistical methods were used to extrapolate survival (which means forecasting or predicting what survival may look like in the long-term, after the trial has ended). (25, 26)

Modelling how much a treatment extends life

- Treatment with serplulimab extends patients' lives compared with atezolizumab and platinum-based chemotherapy by delaying the progression of their cancer.

Modelling how much a treatment improves quality of life

- Treatment with serplulimab improves patients' quality of life by delaying the progression of their cancer and improving symptoms. Patients have a different quality of life score depending on whether they are on or off treatment.
- The quality of life scores used in the model were obtained using the EQ-5D-5L data collected in ASTRUM-005. As described earlier, the EQ-5D instrument collects information on five domains of how patients are feeling, but does not consider problems that are directly linked to lung cancer. As a result, the scores may not reflect certain aspects of the cancer, like fatigue, mental abilities or social happiness.

Modelling how the costs of treatment differ with the new treatment

- Serplulimab is associated with a cost of £1,321.83 per vial. The manufacturer has also proposed a confidential discount for serplulimab. There is an administration cost incurred by the NHS to deliver the infusion in the hospital, which costs between £217 and £519 per administration, depending on which treatment is given. This cost is similar to the cost of delivering platinum-based chemotherapy (carboplatin-etoposide) and atezolizumab.
- Patients who are given serplulimab have to attend a number of GP and hospital visits to monitor the progression of their cancer. The frequency of these visits is similar with platinum-based chemotherapy (carboplatin-etoposide) and atezolizumab.

Uncertainty

- The economic model was tested to determine whether certain aspects of the model that are less certain have a large impact on the cost-effectiveness of serplulimab. The model is sensitive to changing data on the relative efficacy of serplulimab and atezolizumab, which means that there was a larger effect on the cost-effectiveness of serplulimab when changing these data.
- To show that the long-term predictions of the economic model are consistent with clinical outcomes in the NHS, the model was compared with survival from a large group of patients with ES-SCLC in the US including more than 2 million cancer patients (the Flatiron Health database). The outcomes from the model and the Flatiron database were very similar, which means the model's predictions are reliable.

Additional factors

- Serplulimab is eligible for a severity modifier under the NICE appraisal process because ES-SCLC is a very severe condition. In the general population (healthy people in the UK), people who are the same age as those from the ASTRUM-005 trial can expect to accrue 11.92 quality-adjusted life years (QALYs), whereas those with ES-SCLC can only expect 1.52 QALYs because of their disease. As a result, serplulimab is eligible for a severity modifier of 1.2.
- The model doesn't directly capture any impact of ES-SCLC on carers or family members that are helping to look after a person with ES-SCLC, meaning that the potential health

and social benefits of serplulimab are probably higher than what is presented in the model.

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)

Serplulimab is an immunotherapy, helping the immune system to better recognise and attack cancer cells, which is a novel approach to treatment. Combined with chemotherapy, serplulimab has shown significant improvements in survival. Patients who took serplulimab in a clinical trial, compared with patients on placebo, lived longer and had fewer progression events (i.e. it took longer for patients' cancer to get worse). Patients who responded to surveys in the clinical trials also said that they generally had a better quality of life compared to patients taking the placebo drug. In addition to this, a statistical method shows that serplulimab also improves survival and delays progression in patients who take atezolizumab, which is an alternative to serplulimab in the NHS. On average, results from the model predict that patients can expect to live an additional 2.47 years when taking serplulimab, compared with 1.74 years with atezolizumab and 1.38 years with carboplatin-etoposide. (25, 26).

Serplulimab has also been designated an orphan medicine by EMA. This means that it was developed for use against a rare, life-threatening or chronically debilitating condition or, for economic reasons, it would be unlikely to have been developed without incentives. One of the criteria for orphan medicines is that the medicine must be significantly better than existing treatments.

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

The clinical experts did not identify any equality issues for accessing serplulimab.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

- Resources on the ASTRUM-005 trial:

    - Effect of First-Line Serplulimab vs Placebo Added to Chemotherapy on Survival in Patients With Extensive-Stage Small Cell Lung Cancer: The ASTRUM-005 Randomized Clinical Trial - PubMed
    - Serplulimab vs. placebo combined with chemotherapy as first-line treatment for extensive-stage small-cell lung cancer: Extended follow-up results and patient-reported outcomes from the international phase 3 ASTRUM-005 study. | Journal of Clinical Oncology
- NICE guideline for lung cancer:
    - Overview | Lung cancer: diagnosis and management | Guidance | NICE
- Summary of product characteristics for serplulimab
- Information on other trials with serplulimab

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 health technology assessments 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

Biomarker
A substance in your body that can be measured to give information about your health, like a signal for a disease.
CT scan
A detailed imaging test that uses X-rays to create pictures of the inside of your body.
ECOG performance status
A scale to measure how well a patient can perform everyday activities.
EQ-5D
A questionnaire that helps measure your overall health and quality of life.
EORTC QLQ-C30 and LC13
Questionnaires used to measure the quality of life in cancer patients, focusing on general wellbeing and lung cancer-specific symptoms.
ES-SCLC
Extensive-stage small cell lung cancer, a type of lung cancer that has spread widely within the body.
Immunotherapy
A treatment that helps your immune system fight cancer.

MRI
An imaging test that uses magnets and radio waves to create pictures of the inside of your body.
OS
Overall survival, the length of time from diagnosis or starting a treatment until death from any cause.
PFS
Progression-free survival, the length of time during and after treatment that a patient lives without the cancer getting worse.
QALYs
Quality-adjusted life years, a measure that takes into account both the quantity and quality of life gained from healthcare interventions.
WHO performance status
A scale developed by the World Health Organisation to measure a patient's ability to perform daily activities.
X-ray
A quick imaging test that uses radiation to create pictures of the inside of your body, often used to see bones.

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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21. Zhang C, Xu C, Gao X, Yao Q. Platinum-based drugs for cancer therapy and anti-tumor strategies. Theranostics. 2022;12(5):2115-32.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

Clarification questions

February 2025

File name	Version	Contains confidential information	Date
ID6346 serplulimab clarification questions – company response [CON]	June update 2025	Yes	27th June 2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on decision problem

A1. Priority question: Durvalumab as a newly approved comparator for serplulimab

The EAG note that durvalumab with etoposide and either carboplatin or cisplatin was recommended as of 19 February 2025 as an option for untreated extensive-stage small cell lung cancer (ES-SCLC), only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and the Company provides durvalumab according to the commercial agreement.(1) Durvalumab was in the final scope issued by NICE for this appraisal,(2) however the Company did not include it in their appraisal as it was not recommended at the time of submission.(3)

a) **Therefore, the EAG request that the Company conduct further analyses including durvalumab as a comparator in both their clinical effectiveness and cost effectiveness analyses. Instead of conducting another matching-adjusted indirect comparison (MAIC) using the ASTRUM-005 and CASPIAN trials, the EAG preferred approach would be for the Company to conduct a multilevel network meta regression (ML-NMR), which allows flexibility to generate population-adjusted indirect treatment comparison (ITC) estimates from any number of treatments and studies and enables a full incremental cost-effectiveness**

analyses.(4) This would comprise using individual patient level data from ASTRUM-005 with aggregate data from IMpower133 and CASPIAN (using subgroup data from the durvalumab with carboplatin arm listed in Goldman et al. 2021)(5) to determine the relative efficacy of serplulimab in comparison to durvalumab and atezolizumab (and chemotherapy). This would also allow the Company to conduct a full incremental cost health model across all relevant comparators.

b) **If the Company choose to conduct ML-NMR analyses, please could they report results for the target population most relevant to the NHS with an accompanying rationale for the choice of this target population.**

c) **If the Company does not consider this to be feasible, please state why; could a MAIC or network meta-analysis be undertaken with the two other comparators? Could the Company please provide a clear rationale as to which approach they decide to implement?**

Durvalumab has been included in the economic model using aggregate data from CASPIAN, as requested by the EAG. Indirect estimates of comparative efficacy have been derived from a MAIC, with the methodology aligned to the approach used for the comparison with atezolizumab and reported in the company submission. A comparison of included clinical trial data, alongside detailed results from the MAIC versus durvalumab, is provided in the answer to question B8.

As was the case for atezolizumab, the MAIC for durvalumab offers a robust methodology by addressing between-trial differences in baseline characteristics through matching and reweighting of the ASTRUM-005 IPD to match the baseline characteristics of the aggregate CASPIAN data. This reduces bias in indirect treatment comparisons and improves the validity of comparative efficacy estimates.

Although a ML-NMR allows estimation of comparative treatment effects within a single statistical model, and consequently a singular target patient population, a MAIC remains a suitable and recognised method for adjusting for baseline differences, especially when the number of studies or the data structure does not lend itself to a full ML-NMR approach. Furthermore, the use of a MAIC in the current context was deemed appropriate due to the similarity between unadjusted and adjusted efficacy estimates in comparison with both atezolizumab and durvalumab. Consequently, the

effect of utilising two MAICs with respect to the target patient population (i.e., the MAICs effectively provide estimates of efficacy in the IMpower133 and CASPIAN study populations) is not anticipated to meaningfully impact either the point estimates for the comparison, or their interpretability within the context of this submission.

Full base-case results for serplulimab at list price and PAS price compared with carboplatin-etoposide, atezolizumab, and durvalumab are provided below. Durvalumab is dominated by serplulimab at list price and PAS price.

Table 1: Base-case results, pairwise (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	£79,427	2.47	2.10				
Durvalumab	£87,577	1.87	1.64	-£8,150	0.60	0.46	Dominant
Atezolizumab	£54,671	1.74	1.50	£24,756	0.74	0.60	£41,447
Carboplatin-etoposide	£21,561	1.38	1.21	£57,866	1.09	0.89	£64,799

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

Table 2: Base-case results, pairwise (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	[redacted]	2.47	2.10				
Durvalumab	£87,577	1.87	1.64	[redacted]	0.60	0.46	[redacted]
Atezolizumab	£54,671	1.74	1.50	[redacted]	0.74	0.60	[redacted]
Carboplatin-etoposide	£21,561	1.38	1.21	[redacted]	1.09	0.89	[redacted]

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

Table 3: Base-case results, full incremental analysis (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Durvalumab	£87,577	1.64			
Serplulimab	£79,427	2.10	£8,150	-0.64	-£17,544
Atezolizumab	£54,671	1.50	£24,756	0.60	£41,447
Carboplatin-etoposide	£21,561	1.21	£33,110	0.30	£111,968

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

Table 4: Base-case results, full incremental analysis (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Durvalumab	£87,577	1.64			
Atezolizumab	£54,671	1.50	£32,907	0.13	£247,911
Serplulimab	[redacted]	2.10	[redacted]	-0.60	[redacted]

Carboplatin-etoposide	£21,561	1.21	[redacted]	0.89	[redacted]

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.*

Section B: Clarification on effectiveness data

Systematic Literature Review

B1. Systematic exclusion of Non-Small Cell Lung Cancer (NSCLC) from the clinical and economic/quality of life systematic reviews

The EAG note that on the reported searches for the Population concept on both the Clinical Systematic Literature Review (SLR) and the Economic/Quality of life SLR the NSCLC population has been systematically excluded from the search by using the 'NOT' operator.(6, 7) This approach is not best practice in systematic literature reviews and is not recommended as it effectively excludes any record in which the NSCLC terms would be present including those records where both populations (SCLC and NSCLC) are present. This approach automatically reduces the sensitivity of the searches to retrieve all possible evidence.(8) Given this issue, can the Company confirm whether they remain confident in the ability of these searches to retrieve all relevant literature on SCLC? And if so, can the Company provide a rationale for the systematic exclusion of NSCLC population from the literature searches?

Creating search strategies require finding a balance between sensitivity and specificity, and inclusivity and precision. To ascertain this balance, firstly, we determined the focused research question, next, we made attempts to describe the articles that could give response to it, and finally, we determined the key concepts that would address the different elements of the question. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are two different clinical entities that differ in their biology, behaviour, treatment strategies, and prognosis. Consequently, there are also differences in terms of the humanistic and economic impact between them. Both diagnostic and treatment follow different patterns, which are linked to cellular and molecular differences, growth and spread (i.e., SCLC is extremely aggressive, being metastasis common), genetic and molecular features (e.g., different mutations, which in case of SCLC are harder to target than Epidermal Growth Factor Receptor (EGFR), Kirsten Rat Sarcoma (KRAS), Anaplastic Lymphoma Kinase (ALK) and C-Ros Oncogene 1 (ROS 1) in NSCLC), for instance. Overall, SCLC is much more aggressive

and harder to treat, whereas NSCLC offers more opportunities for targeted and long-term treatment strategies.

Even guidelines are differentiated, due to the different clinical management and nature of the diseases. For SCLC, please refer to the ESMO guidelines (9).

Hence, we acknowledge that there are publications that bundle information from both NSCLC and SCLC but expecting to describe mostly the general information on burden of disease, review on the current status of both conditions, and the description on the above-mentioned differences. Therefore, the trade-off between introducing noise in the search strategy and maintaining the accuracy (or best practice on SLR) was considered significant enough that we opted to exclude NSCLC from the search strings when determining the appropriate route to optimising the search strategy. In addition, we conducted preliminary searches to understand the impact of our choice of index terms, synonyms, variations in search terms and choice of syntax, Boolean operators and field codes.

To support our rationale, we have conducted a post-review checking exercise by re-running the biomedical database search without excluding NSCLC from search strings (e.g., deletion of rows 4 and 5 in EMBASE and PubMed; deletion of rows 6-9 in Cochrane) from all search strategies. The number of hits considering the complete search as of March 11th 2025, is n=23,186:

- Cochrane Clinical: 8,872
- Cochrane Ec&Hum: 3,593
- Embase Clinical: 8,953
- Embase Ec&Hum: 3,808
- Pubmed Clinical: 5,676
- Pubmed Ec&Hum: 2,659
- **Total:** 33,540 (including duplicates); **23,186 after duplicates removal**

In case of only considering new hits from 2024 to March 11th, 2025, the results are n=241:

- Cochrane Clinical: 112
- Cochrane Ec&Hum: 33
- Embase Clinical: 62
- Embase Ec&Hum: 42
- Pubmed Clinical: 60
- Pubmed Ec&Hum: 35

- **Total:** 344 (including duplicates); **241 after duplicates removal**

Given our preliminary strategy towards optimising the database searches and following this checking exercise to test and reiterate the balance we tried to achieve, we remain confident that our comprehensive literature search was a successful balance between inclusivity and precision, minimising irrelevant results while preserving comprehensiveness to retrieve articles for SCLC.

B2. Date of last search is more than nine months old

The EAG note that in the reported searches on both the Clinical SLR and the Economic/Quality of life SLR the date for clinical effectiveness searches (April 2024) and economic/quality of life studies (May 2024) is over 9 months ago.(6, 7) Can the Company confirm if a more up-to-date search has been run since then and, if so, could the EAG have the details of the search strategies with updated results?

The latest NICE Methods Guide does not specify a particular timeframe for the validity of SLR results. In addition, research by Stokes et al. (2023) concluded that "not all SRs are equally at risk of being 'out of date' at 12 months." (10) As clinical research in SCLC is not regarded as a 'fast-moving area', we do not anticipate that our intervention review can be considered as being potentially out-of-date. Therefore, a more recent search is therefore not available for the Clinical and Economic/Quality of life SLRs.

B3. Grey literature searches are missing

The Company reports searching on grey literature sources for both the clinical SLR and the economic/quality of life SLR.(6, 7) These sources are valuable for avoiding the introduction of bias. For transparency in the identification and selection of grey literature records, it is considered good practice to report these searches in the same manner as the bibliographic database searches are reported. Could the Company supply details of the search strategies undertaken for each of the grey literature sources searched with results of retrieved records per source? The EAG would recommend providing the following information:

- Name of source searched;
- Date of search;
- Detailed search strategy (e.g. key words or terms used to interrogate those sources);

- Number of retrieved records overall.

According to the SLR protocol, in addition to the searches of electronic databases, hand searches were conducted to capture data from recent studies not yet published. Searches of conference proceedings were limited to the last three years as it was assumed that studies are usually published within two to three years (2021, 2022, 2023, 2024) following presentation to a conference. Hand searches were anticipated to include:

- Google Scholar
- American Society of Clinical Oncology (ASCO) Annual Meeting
- European Cancer Organization (ECCO) Congress
- European Society for Medical Oncology (ESMO) Congress
- European Lung Cancer Congress (ELCC)
- International Association for the Study of Lung Cancer World Conference (IASLC)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – International, European and Asia-Pacific annual congresses

Additionally, the following clinical trial repositories were scrutinized to identify additional potential trials and results of interest to this research:

- www.clinicaltrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP) (via cochranelibrary.com)
- EU Clinical Trials Register (via www.clinicaltrialsregister.eu/)

Established HTA agencies' websites were consulted, including but not limited to:

- UK: National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG)
- France: Haute Autorité de Santé (HAS)
- Germany: Gemeinsamer Bundesausschuss (GBA) and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesenis (IQWiG)
- Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)
- Australia: Pharmaceutical Benefits Advisory Committee (PBAC)
- US: Institute for Clinical and Economic Review (ICER)

Systematic literature reviews and indirect treatment comparisons were not included in the review process but were consulted for cross-referencing purposes, ensuring comprehensive coverage of the existing evidence base. Overview of hand searches: sources listed in Table 5 were searched against eligibility criteria for 2021, 2022, 2023 and 2024.

Table 5: Summary of hand searching

Conference proceedings	**Website**
American Society of Clinical Oncology (ASCO) Annual Meeting	www.asco.org/meetings
European Cancer Organisation (ECCO) Congress	www.europeancancer.org
European Society for Medical Oncology (ESMO) Congress	www.esmo.org/meetings/esmo-congresses
European Lung Cancer Congress (ELCC)	www.esmo.org/meetings
Health Technology Assessment International (HTAi)	https://htai.org/
Society for Medical Decision Medicine (SMDM)	https://smdm.org/
International Association for the Study of Lung Cancer (IASL)	https://www.iaslc.org/
HTA Body Websites	**Website**
NICE (UK) SMC (Scotland) CDA/AMC (Canada) IQWIG (Germany) HAS (France) AWTTC (Wales) SBU (Sweden) ICER (US) PBAC (Australia)	https://www.nice.org.uk/guidance https://scottishmedicines.org.uk/ https://www.cda-amc.ca/ https://www.iqwig.de/ https://www.has-sante.fr/ https://awttc.nhs.wales/ https://www.sbu.se/en/ https://icer.org/ https://pbac.pbs.gov.au/
ISPOR	**Website**
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	www.ispor.org
Additional resources (cost effectiveness)	**Website**
Cost-Effectiveness Analysis Registry (CEA)	https://cevr.tuftsmedicalcenter.org/databases/cea-registry
Research Papers in Economics (RePEc)	http://repec.org/
International HTA database (INAHTA)	https://database.inahta.org/
National Institute for Health and Care Research (NIHR)	https://www.nihr.ac.uk/
Additional resources (HRQoL)	**Website**
EuroQoL website	https://euroqol.org/
ScHARRHUD database	https://scharr-outcomes.sites.sheffield.ac.uk/resources

Cross-reference of studies	Website
SLRs and ITCs cross-reference	Does not apply
Grey literature (Google Scholar, other)	
Grey literature	Does not apply

For more details on the results retrieved from hand searches, please refer to the additional Excel file provided (ID6346_Hand searching grid).

B4. Clarification on the search fields used

The reported bibliographic database searches for the clinical and economic/quality of life SLRs do not specify in all instances the fields in which the terms have been searched. All three databases searched by the Company (Embase, PubMed and Cochrane Library) allow at least title and abstract searches as well as controlled vocabulary searches using MeSH (PubMed and Cochrane) or EMTREE (Embase.com). Could the Company confirm the fields in which the terms were searched for the reported searches in Embase.com, PubMed and Cochrane? For example, in the clinical SLR, Section 6, Table 13 (Embase.com searches), should the EAG assume that search strings #7 to #16 (for the intervention and comparators' searches) were searched as controlled vocabulary terms (i.e., EMTREE terms)? Or have they been searched in title, abstract (and keyword) fields instead (or both)? Could the Company also provide the search strategies where both methods (controlled vocabulary and text words (ti,ab, and keywords) were used?

The tables included in the appendix, which have the detail on the search strings, include this information for each of the strategies. For instance, in EMBASE, the "/exp" notation is used to indicate that a search term is being exploded to include all narrower (more specific) terms in the EMTREE thesaurus. The use of "/exp" is intentional when a broader search that includes all related subtopics is pursued, because results for that term and all its more specific (nested) terms in the hierarchy are retrieved.

In case of Pubmed, free terms (no MeSH) were used for search strategies.

In addition, those terms for title and abstract scrutiny appear under “ti; ab” or “ab, ti” notation.

B5. Clarification on comparator names

The EAG note that the range of alternative names for comparators reported in the clinical SLR is not consistent across databases. For example, whilst searching on Cochrane, 19 different terms were used to search for 'carboplatin', on Embase.com only 15 terms were used and on PubMed 16 terms. Could the Company provide a rationale for such discrepancies across databases for the comparators searches?

As stated earlier, we conducted preliminary searches while crafting the search strategy to ensure that each database search was well balanced and optimized to retrieve relevant literature. As part of this exercise, the names and synonyms of each comparator were tested in each database prior to launching the search strategies. Consequently, database search strategy may have different synonyms in the reported search strings due to this tailoring exercise (otherwise errors would have been retrieved).

B6. Data extraction spreadsheet

The EAG note that the 16 studies identified in the SLR have a completed risk of bias (in the 'Seplulimab in ES-SCLC Clinical SLR_RoB file'), however in the Data extraction spreadsheet ('Seplulimab in ES-SCLC Clinical SLR_Data Extraction') only the three articles related to the CASPIAN study are listed. Could the Company please clarify why all 16 studies are not included here, and if appropriate, populate this spreadsheet with all the relevant data?

The Cochrane risk-of-bias tool for randomised trials (RoB 2) was used on the Clinical SLR to assess the quality of clinical trials and 16 studies were identified.

Most studies reported adequate methodological characteristics for at least three domains, although the overall risk of bias was frequently rated as some concerns (9/16 studies). Three out of sixteen studies were deemed as high-quality across all domains. However, the randomization method (D1) generally raised some concerns in eight of the studies considered: treatment allocation blinding was unclear in 11 of the 16 studies, often due to an open-label design and limited information regarding the execution of the randomization process and leading to the resulted bias in this domain.

Figure 1: Quality Assessment - Risk of Bias Rob2 assessment of included studies (n=16 studies)

Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
Noda et al., 2002	Irinotecan + Cisplatin	Etoposide + Cisplatin	+	+	+	+	+	+
Quoix et al., 2005	Topotecan + Cisplatin	Etoposide + Cisplatin	!	+	+	+	+	!
Schmittel et al., 2006	Irinotecan + Carboplatin	Etoposide + Carboplatin	!	+	+	+	+	!
Eckardt et al., 2006	Topotecan + Cisplatin	Etoposide + Cisplatin	!	+	+	+	+	!
Hanna et al., 2006	Irinotecan + Cisplatin	Etoposide + Cisplatin	+	+	+	+	+	+
Okamoto et al., 2007	Etoposide + Carboplatin	Etoposide + Cisplatin	!	+	+	+	+	!
Hermes et al., 2008	Irinotecan + Carboplatin	Etoposide + Carboplatin	+	+	+	+	+	+
Lara et al., 2009	Irinotecan + Cisplatin	Etoposide + Cisplatin	+	+	+	+	+	+
Zatloukal et al., 2010	Irinotecan + Cisplatin	Etoposide + Cisplatin	!	+	+	+	+	!
Schmittel et al., 2011	Irinotecan + Carboplatin	Etoposide + Carboplatin	!	+	+	+	+	!
Fink et al., 2012	Topotecan + Cisplatin	Etoposide + Cisplatin	+	+	+	+	+	+
Kim et al., 2019	Irinotecan + Cisplatin	Etoposide + Cisplatin	!	+	+	+	+	!
Shimokawa et al., 2021, 2023	Irinotecan + Carboplatin	Etoposide + Carboplatin	!	+	+	+	+	!
ASTRUM-005	Serplulimab + Carboplatin + Etoposide	Carboplatin + Etoposide	+	+	+	+	+	+
IMpower133	Atezolizumab + Carboplatin + Etoposide	Carboplatin + Etoposide	+	+	+	+	+	+
CASPIAN	Durvalumab + Platinum- Etoposide	A: Platinum + Etoposide B: Durvalumab + Tremelimumab + PtE	+	+	+	+	+	+

***Abbreviations**: PtE: Platinum-etoposide.*
***Notes**: Cochrane RoB 2 Tool assessment domains (version 22 August 2019 (12)): randomisation process (D1), deviations from the intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4), and selection of the reported result (D5)*

For more details on the results retrieved from hand searches, please refer to the additional SLR report provided (ID6346_Serplulimab in ES-SCLC Clinical SLR).

Trial Evidence

B7. Generalisability of ASTRUM-005 in English clinical practice

Please could the Company clarify what approaches they used to ascertain whether the trial population in ASTRUM-005 is generalisable to the UK population? Was clinical input sought? If so, please provide further details.

As described in Appendix M of the Company evidence submission, a 2-round modified Delphi panel was conducted to gather expert clinical consensus on key areas of clinical uncertainty to support the upcoming UK and Irish HTA submissions in ES-SCLC. Please see Table 6 below for more details.

During the Round 1 survey, participants were asked about the generalisability of ASTRUM-005 in English clinical practice.

[redacted]

[redacted]

The clinicians agreed that although there are some differences in baseline characteristics between ASTRUM, IMpower133, and CASPIAN including a lower proportion of non-Asian participants, sub-group analyses show no differences in OS and PFS between Asians and non-Asians. Therefore, the clinicians believed that results from ASTRUM-005 were generalisable to clinical practice in the NHS.

Table 6: Modified Delphi panel (Appendix M), summary of methodology

Topics of focus	• The diagnosis and prevalence of ES-SCLC in the UK and Ireland • The treatment and management of ES-SCLC in the UK and Ireland • The applicability of ASTRUM-005 clinical trial data to the UK and Irish population • The anticipated uptake and resource utilisation of serplulimab for first-line ES-SCLC in UK and Irish clinical practice • The anticipated long-term treatment effect of PD-1/PD-L1 inhibitors for ES-SCLC
Recruitment criteria	• >5 years' experience in managing ES-SCLC patients • Lung cancer-relevant KOL status, i.e. publications, conference presentation, working group membership • Representation across the UK and Ireland
Round 1: online survey	• Throughout December 2024 and January 2025, a panel composed of 5 clinical experts was provided with a 1-hour virtual survey to complete. The online survey included a range of open-ended as well as closed qualitative and quantitative questions. For some questions, data summaries and references were provided. The results of the survey were analysed using thematic analysis and descriptive statistics where appropriate. • The topics in the Round 1 survey included the prevalence of ES-SCLC in the UK and Ireland, present management of ES-SCLC, the applicability of clinical trial data to the UK and Irish population, and the anticipated long-term treatment effect of PD-1/PD-L1 inhibitors for ES-SCLC.
Round 2: group consensus meeting	• Of the 5 clinicians who participated in the Round 1 online survey, 3 clinical experts took part in a group consensus meeting on 30th January 2025, to consider results from the individual interviews and seek further understanding. • The Round 2 meeting was conducted by three researchers and lasted approximately 2 hours. This was split into two parts: - Discussion of anonymised and consolidated findings from Round 1: discussion points in the first part of the Round 2 meeting included the diagnosis, prevalence, treatment, and management of ES-SCLC in the UK and Ireland, as well as the applicability of clinical trial data to the UK and Irish population, the anticipated uptake and resource utilisation of serplulimab for first-line ES-SCLC in UK and Irish clinical practice, and the anticipated long-term treatment effect of PD-1/PD-L1 inhibitors for ES-SCLC. - Consensus-building: where consensus was reached in Round 1, findings were presented to the panellists, with opportunity to comment on the consensus opinion. Where consensus was not

		reached in Round 1, findings were presented to the panellists, with the facilitator opening a discussion to understand the rationale. After discussions, panellists then submitted their level of agreement on a 5-point Likert scale and anonymised results of the vote were presented. Depending on whether consensus was reached or not, the facilitator would provide time for further discussion, presenting of rationale, and opportunity to vote once again before moving on to further topics. The threshold for consensus was set at 70% agreement across all participants (equivalent to N=3/3 participants), as per standard modified Delphi practice (13-15).

***Abbreviations**: ES-SCLC, extensive-stage small cell lung cancer; KOL, key opinion leader; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.*

B8. Transitivity of ASTRUM-005 with IMpower133 and CASPIAN

a) Table 23 in the Company submission (CS) details a rationale for variable selection for population adjustment across ASTRUM-005 and IMpower133.(3) Please can the Company provide further justification on how they derived their final list of adjusted variables? Did the Company receive clinical advice as to whether differences between the two trials were clinically meaningful? Was clinical advice used to identify/rank treatment-effect modifiers used in the ITC? If so, please provide details.

Adjustments were made for key prognostic variables based on their impact on OS and confounders identified through systematic literature review, with advice from clinical and statistical experts. The rationale for variable selection was as follows:

Age group considerations

1. Age is a critical prognostic factor in oncology, as elderly patients often exhibit greater comorbidities and reduced treatment tolerance, both of which compromise therapeutic efficacy. Aging also leads to immunosenescence, impairing immune function and altering the tumour microenvironment, potentially impacting the efficacy of immunotherapy. Age, along with ECOG performance status, may indirectly modify treatment outcomes through its impact on physical condition (16).
2. Age group is commonly used as a stratification factor and has been identified as a key covariate in many MAIC studies (17).
3. In the ASTRUM-005 and IMpower133 studies, patients aged ≥65 years represented [redacted] and 39.3%, and [redacted] and 47.5% of the experimental and control groups, respectively. Based on clinical advice and pre-specified selection criteria, the age group was selected as a key variable for adjustment in the comparison.

ECOG PS considerations

1. ECOG performance status (PS) is a widely recognized key prognostic factor for immunotherapy in ES-SCLC. Lower scores correlate with better treatment tolerance, enhanced immune function, and higher treatment completion rates, ultimately leading to improved survival outcomes.
2. The NCCN guidelines emphasize ECOG PS as a critical factor in treatment decisions and prognosis. Multivariable analysis by Veena PS et al. further confirmed that ECOG PS is an independent prognostic factor for OS and PFS in ES-SCLC (HR for OS: 1.41 [95% CI: 1.02-1.94, P=0.037], HR for PFS: 1.49 [95% CI: 1.09-2.04, P=0.012]) (18).
3. Given its prognostic significance and uneven distribution in the ASTRUM-005 and IMpower133 trials, ECOG PS was selected as a key variable for adjustment in ITCs.

Smoking status considerations

1. Several retrospective studies have identified smoking as an independent adverse prognostic factor for overall survival (OS) in ES-SCLC patients. Huang et al. found that a high smoking index (≥400 vs. <400) was associated with a 46% increased risk of death (HR=1.46, 95% CI: 1.07-2.00, *P*=0.036) (19).
2. Clinical trials, such as ASTRUM-005 and CASPIAN, have demonstrated a negative correlation between smoking and immunotherapy efficacy, potentially due to tumour microenvironment heterogeneity in smokers, which may also enhance immunotherapy sensitivity.
3. A MAIC analysis in the NICE TA789 submission also included smoking status as a matching variable, highlighting its prognostic impact on lung cancer outcomes.
4. Due to the complexity of smoking's effect on immunotherapy in ES-SCLC and the higher proportion of never-smokers in East Asian populations, smoking status was selected as a key adjustment variable to account for its impact across studies.

Brain metastasis considerations

1. Brain metastasis is an independent adverse prognostic factor in SCLC, significantly reducing overall survival, potentially due to the blood-brain barrier, the aggressive nature of brain metastases, and the immunosuppressive tumour microenvironment.

2. A study by Li et al., using Cox regression analysis, found that patients with brain metastasis had a significantly shorter median survival (6 months vs. 13 months), with factors like age, tumour size, and stage also influencing survival (20).
3. Furthermore, varying proportions of brain metastasis patients and different immunotherapies appear to impact survival outcomes. The HR for OS in brain metastasis patients was [redacted] in ASTRUM-005, and 1.07 (95% CI: 0.47-2.43) in IMpower133.
4. To account for the complex impact of brain metastasis proportions, it was included as a matching variable for indirect comparisons.

Liver metastases considerations

1. Liver metastasis may reduce immunotherapy response by modulating systemic immune status (e.g., T-cell tolerance and exhaustion) and act as an effect modifier.
2. Veena PS et al. demonstrated that liver metastasis is an independent adverse prognostic factor in ES-SCLC (HR=1.45, P=0.02) through multivariate analysis (18).
3. Liver metastases were also included as an adjustment variable in an MAIC study on NSCLC to control for heterogeneity in visceral metastatic burden (17).
4. Given its significance in lung cancer prognosis and the imbalance in liver metastasis proportions observed in ASTRUM-005 and IMpower133 (25.4% and 26.0% vs. 38.8% and 35.6%, respectively), liver metastasis was identified as a key variable in the ITC.

The considerations for the variables not included were as follows:

Gender considerations

1. Although some studies suggest that females may benefit more from immunotherapy, not all studies support gender as an independent treatment-effect modifier. This may be related to factors such as a higher proportion of non-smokers, earlier disease detection, and potential hormonal or immune differences in women, but the exact mechanisms require further investigation.
2. A sensitivity analysis was conducted to assess whether including gender in matching affects the conclusion. Detailed results can be found in Table 9.

Race considerations

1. If both race and other confounding factors were included in the matching, the ESS reduced to unworkable levels of approximately 30% of the original sample size (Table 7). This led to a weighting scheme that made the final comparison results unstable, unreliable, and difficult to interpret.
2. Additionally, population pharmacokinetics (pop-PK) and exposure-response (E-R) analyses indicated that including or excluding race as a covariate showed no effect, supporting the conclusion that race is not an effect modifier.
3. In addition, sensitivity analyses on race were also conducted, with detailed results provided in Table 9.

Table 7: Summary of effective sample size (ESS) after matching race

Treatment Group	IMpower133	ASTRUM-005 pre-matching	ASTRUM-005 post-matching
Both Race and other confounders were included			
Active	201	[redacted]	[redacted]
Control	202	[redacted]	[redacted]

Disease stage considerations

1. Not reported in IMpower133 study.
2. Disease stage was included as a matching variable in an exploratory sensitivity analysis. For the variables “Brain Metastasis” and “Liver Metastasis”, potentially correlated with disease stage, the following sensitivity analyses were conducted (assumed that the proportion of stage IV patients was to mimic the proportion seen in the CASPIAN study). Detailed results are provided in Table 8.

Tumour burden at baseline considerations

1. The IMpower133 study only reported the median and range of the sum of the longest diameter of target lesions at baseline, without providing the mean and standard deviation. Therefore, this did not meet the matching requirements of the MAIC method.
2. The sum of the longest diameter of target lesions at baseline was essentially comparable between the ASTRUM-005 and IMpower133 studies. Detailed comparison information can be found in Table 8.
3. To assess the potential impact of tumour burden on the MAIC results, we used the median of the sum of the maximum diameters of target lesions as a substitute for the mean and referenced the standard deviation of this variable from the

ASTRUM-005 study as a sensitivity analysis. Detailed results are provided in Table 9.

Table 8 Baseline tumour burden of the ASTRUM-005 and IMpower133 studies

	ASTRUM-005		IMpower133	
	serplulimab	**control**	**atezolizumab**	**control**
Sum of longest diameter of target lesions at baseline, mm				
Mean (SD)	120.8 (53.6)	123.2 (50.9)	—	—
Median (Range)	117.7 (13.8-323.7)	120.5 (14.5-269.6)	113.0 (12.0-325.0)	105.5 (15.0-353.0)

Note: The IMpower133 study only reported the median and range of the sum of the longest diameter of target lesions at baseline, didn't report mean and standard deviation (SD).

Tumour mutational burden (TMB) considerations

1. Not all individuals were tested in the ASTRUM-005 and IMpower133 studies, which may result in insufficient matching to calculate weights for each subject in ASTRUM-005 and potentially disrupt the original randomization.
2. Different panel: The FoundationOne (F1) CDx NGS assay was used in the IMpower133 study, while Med1CDxTM was used in the ASTRUM-005 study. These two panels differ in probe design and TMB algorithms.
3. Different samples: TMB was measured using blood samples in the IMpower133 study, while tumour tissue was used in the ASTRUM-005 study. Therefore, a direct comparison is not appropriate.

PD-L1

Not all individuals were tested in the ASTRUM-005 and IMpower133 studies, which may result in insufficient matching to calculate weights for each subject in ASTRUM-005 and potentially disrupt the original randomization.

Sensitivity analyses with various combinations of matching variables were also conducted. The results demonstrated high consistency and supported the same conclusion. The HRs for OS consistently ranged from [redacted], with the upper bounds of the 95% CIs approaching statistical significance, further reinforcing the robustness of the significant benefit that ES-SCLC patients can derive from serplulimab. Detailed MAIC results are provided in Table 9 and **Error! Reference s ource not found.**.

Table 9: Results of MAIC Analyses for OS in ASTRUM-005 vs. IMpower133

Type	Matching Baseline Characteristics Variables	HR (95% CI)

Primary analysis	Age Group; ECOG; Smoking Status; Brain Metastases; Liver Metastases	[redacted]
Sensitivity analysis 1	Based on the list of variables used in the primary analysis, excluding ECOG	[redacted]
Sensitivity analysis 2	Based on the list of variables used in the primary analysis, including Sex	[redacted]
Sensitivity analysis 3	Based on the list of variables used in the primary analysis, including Disease Stage [1]	[redacted]
Sensitivity analysis 4	Based on the list of variables used in the primary analysis, including Disease Stage [1], excluding Brain Metastasis and Liver Metastasis	[redacted]
Sensitivity analysis 5	Based on the list of variables used in the primary analysis, excluding all never-smokers from ASTRUM-005	[redacted]
Sensitivity analysis 6	Based on the list of variables used in the primary analysis, including Baseline Tumour Burden [2]	[redacted]
Sensitivity analysis 7	Based on the list of variables used in the primary analysis, including Race	[redacted]
Sensitivity analysis 8	Based on the list of variables used in the primary analysis, only including non-Asians from ASTRUM-005	[redacted]
Sensitivity analysis 9	Include all baseline characteristic variables, but only retain cases with available TMB values [3]	[redacted]

Abbreviations: *HR, Hazard Ratio; CI-Confidence Interval; NA, Not Available (unable to obtain a valid result).*
Note*: Since the 'Disease Stage' proportion was not reported in the IMpower133 study, it is assumed that the proportion of stage IV patients was to mimic the proportion seen in the CASPIAN study.*
The mean and standard deviation (SD) of the sum of the longest diameters of target lesions at baseline in the ASTRUM-005 study were calculated using actual values. In the IMpower133 study, the mean value was replaced with the median, and the SD referred to the ASTRUM-005 study. The baseline tumour burden was not reported in the CASPIAN study.

[redacted]

Abbreviations*: ESS, effective sample size: HR, hazard ratio; IPD, individual patient data; MAIC, matched adjusted indirect comparison; NA, not available; OS, overall survival.*

b) As detailed in question A1, the EAG note that durvalumab has now been given NICE approval (TA1041)(1). Could the Company please assess the transitivity between CASPIAN, ASTRUM-005 and IMpower133?

A comparative summary of the ASTRUM-005, IMpower133 and CASPIAN is presented in Table 10.

All three studies were Phase 3, randomised controlled trials. However, CASPIAN was an open-label study, whereas both ASTRUM-005 and IMpower133 were placebo-controlled trials. All trials assessed both OS and PFS and enrolled similar numbers of patients. All three studies evaluated the efficacy of an intervention used in addition to carboplatin + etoposide, in comparison with carboplatin + etoposide alone (with or without placebo).

Inclusion criteria were generally consistent between studies, enrolling patients with histologically or cytologically documented ES-SCLC, and with ECOG performance status of 0 or 1. All three studies required that patients has received no prior systemic

therapy for ES-SCLC, with ASTRUM-005 and IMpower133 only including patients who had received chemoradiotherapy for previous limited-stage SCLC if they had been treated with curative intent and were treatment-free for 6 months.

Outcomes in control arms of each study (carboplatin + etoposide +/- placebo) were generally comparable: the median OS in the control arm was 11.1, 10.3, and 10.5 months in ASTRUM-005, IMpower133, and CASPIAN, respectively. Similarly, median PFS was consistent between the control arms of each study: 4.3, 4.3, and 5.4 months in ASTRUM-005, IMpower133, and CASPIAN, respectively.

Table 10: Summary of ASTRUM-005, IMpower133, and CASPIAN

	ASTRUM-005 (HLX10-005-SCLC301)	IMpower133	CASPIAN
Intervention	Serplulimab + carboplatin + etoposide	Atezolizumab + carboplatin + etoposide	Durvalumab + carboplatin + etoposide
Comparator	Placebo + carboplatin + etoposide	Placebo + carboplatin + etoposide	Carboplatin + etoposide
Target	PD-1	PD-L1	PD-L1
Study design	Randomised, double-blind, multicentre, Phase 3 study	Randomised, Phase 1/3, multicentre, double-blinded, placebo-controlled study	Randomised, open-label, multicentre, Phase 3 trial
Key inclusion criteria	• Histologically or cytologically diagnosed with ES-SCLC • No prior systemic therapy for ES-SCLC • Patients who had received chemoradiotherapy for previous limited-stage SCLC had to have been treated with curative intent and be treatment-free for 6 months • At least one measurable lesion as assessed by the independent radiology review committee • An ECOG PS score of 0 or 1 • Normal major organ functions as defined by the following criteria (no blood transfusions, or treatment with albumin, recombinant human thrombopoietin, or colony-stimulating factor within 14 days prior to the first dose in this study)	• Histologically or cytologically confirmed ES-SCLC • No prior systemic treatment for ES-SCLC • ECOG performance status of 0 or 1 • Measurable disease, as defined by RECIST v1.1 • Adequate haematologic and end organ function • Treatment-free for at least 6 months since last chemo/radiotherapy, among those treated (with curative intent) with prior chemo/radiotherapy for limited-stage SCLC	• 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 a platinum-based chemotherapy regimen as 1st line treatment • Life expectancy ≥12 weeks at Day 1 • ECOG 0 or 1 at enrolment • No prior exposure to immune-mediated therapy excluding therapeutic anticancer vaccines
Primary endpoints	OS	OS, Investigator-assessed PFS	OS
Sample size	585 (Active arm: 389, Control arm: 196)	403 (Active arm: 201, Control arm: 202)	537 (Active arm: 268, Control arm: 269)
Primary outcomes	OS: 15.77 mon vs 11.10 mon HR=0.60 (95% CI: 0.49, 0.73; p<0.001) 2-year OS rate: 32.7% vs 16.4% median follow-up: 42.38 months (Cutoff date: 7th May 2024)	OS: 12.3 mon vs 10.3 mon HR=0.76 (95% CI: 0.60, 0.95; p=0.0154) 2-year OS rate: Both < 25% median follow-up: 22.9 mon (Cutoff date: 24th January 2019)	OS: 12.9 mon vs 10.5 mon HR (95% CI): 0.71 (0.60-0.86), p = 0.0003 2-year OS rate: 22.9% vs 13.9% median follow-up: 39.4 mon (Cutoff Date: 22 March 2021)

	ASTRUM-005 (HLX10-005-SCLC301)	IMpower133	CASPIAN
	PFS (assessed by Investigator): 5.49 mon vs 4.34 mon HR=0.57 (95% CI: 0.47, 0.69; p<0.001) Confirmed ORR (assessed by investigator): [redacted] Confirmed DOR (assessed by investigator): [redacted]Median follow-up: 42.38 months (Cutoff date: 7th May 2024)	PFS (assessed by Investigator): 5.2 mon vs 4.3 mon HR=0.77 (95% CI: 0.62,0.96; p=0.02) Confirmed ORR (assessed by investigator): 60.2% vs 64.4% Confirmed DOR (assessed by investigator): 4.2 mon vs 3.9 mon Median follow-up: 13.9 mon (Cutoff date: 24th April 2018)	PFS (assessed by Investigator): 5.1 mon vs 5.4 mon HR (95% CI): 0.78 (0.65-0.94) ORR (assessed by Investigator): 68% vs 58% DOR (assessed by Investigator): 5.1 mon vs 5.1 mon median follow-up: 14.2 mon (Cutoff Date: 11 March 2019)

***Abbreviations**: CI, confidence interval; DOR, duration of response; ECOG PS, European Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; HR, hazard ratio; mon, month; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.*
***Source**: (21, 22)*

A summary of patient characteristics for ASTRUM-005, IMpower133, and CASPIAN is presented in Table 11. There were notable imbalances in patient characteristics between the study populations of ASTRUM-005 and IMpower133: patients in ASTRUM-005 were typically younger, more likely to be male, more likely to be of Asian ethnicity, more likely to have ECOG performance status of 1 versus 0, less likely to be smokers, more likely to have existing brain metastases, less likely to have liver metastases, and less likely to have received previous anticancer treatments. Similarly, there were imbalances in characteristics between patients enrolled in ASTRUM-005 and CASPIAN. Patients enrolled in ASTRUM-005 were more frequently male, more likely to be of Asian ethnicity, more likely to have ECOG performance status of 1 versus 0, and more likely to have brain metastases, and less likely to have liver metastases. Data describing disease stage and PD-L1 status were not reported for either IMpower133 or CASPIAN, and consequently, the potential impact of imbalances in these factors is unknown.

Table 11: Summary of patient baseline characteristics in ASTRUM-005, IMpower133, and CASPIAN

	ASTRUM-005		IMpower133		CASPIAN	
	Serplulimab	Control	Atezolizumab	Control	Durvalumab	Control
Age group (≥65 yr), %	39.6	39.3	44.8	47.5	37.7	41.6
Sex (male), %	81.5	83.7	64.2	65.3	70.9	68.4
Race (Asian), %	67.4	70.9	16.4	17.8	13.4	15.6
Disease stage (IV), %	81.7	79.1	NR	NR	89.6	91.1
ECOG (PS 1), %	81.7	83.7	63.7	66.8	63.1	66.5
Smoking status (Current/former smoker), %	79.2	82.1	95.5	98.5	91.8	94.4
Brain metastases (Yes), %	12.9	14.3	8.5	8.9	10.4	10.0
Liver metastases (Yes), %	25.4	26.0	38.8	35.6	40.3	38.7
Blood-based tumour mutational burden ≥10 mutations/Mb, %	11.3 (195 pts)	3.6 (110 pts)	59.0 (173 pts)	61.8 (178 pts)	NR	NR
PD-L1 TPS >1%, %	16.4 (379 pts)	18.3 (186 pts)	NR	NR	NR	NR
Previous anticancer treatments, %	2.6	2.6	32.8	32.2	NR	NR

***Note**: In cases where data was not evaluable for some patients, the number of patients for which it was evaluable is indicated in brackets.*
***Abbreviations**: ECOG PS, European Cooperative Oncology Group; Mb, mutational burden; NR, not recorded; PD-L1, programmed death-ligand 1; PS, performance status; pts, patients; TPS, tumour proportion score.*
***Source**: (22, 23)*

As described in NICE TSD18, differences in patient characteristics between studies have the potential to bias indirect estimates of efficacy. As such, characteristics were assessed for population adjustment based on the following factors:

- Availability of data or aggregated results from the studies being compared

- Significant impact on the treatment effect
- Imbalance in distribution across studies
- The number of cases with a particular characteristic as at least 10% of the total cases, without leading to an excessively low ESS

Based on these principles, patient characteristics were selected for adjustment in a comparison versus CASPIAN based on the rationale presented in Table 12.

Table 12: Rationale for variable selection for population adjustment

Variable	Adjusted	Rationale
Age group (≥65 yr)	No	Patient age in ASTRUM-005 and CASPIAN were balanced.
Sex	No	Subgroup analysis in ASTRUM-005 and CASPIAN showed no impact of sex on treatment effect.
Race	No	Adjustment would lead to excessively low ESS resulting in unreliable outcomes, furthermore subgroup analysis in ASTRUM-005 showed no impact of race on treatment effect.
Disease stage	No	Cases of stage III or others accounted for about 10% or less of the total cases in CASPIAN and nearly balanced across studies.
ECOG	Yes	Imbalance in patient ECOG status between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Smoking status	Yes	Imbalance in patient smoking status between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Brain metastases	Yes	Imbalance in the presence of brain metastases between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Liver Metastases	Yes	Imbalance in the presence of liver metastases between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Blood-based tumour mutational burden	No	Not reported in CASPIAN.
PD-L1	No	Not reported in CASPIAN.
Previous anticancer treatments	No	Not reported in CASPIAN.

***Abbreviations**: ECOG, European Cooperative Oncology Group; PD-L1, programmed death-ligand 1*.

Outcomes considered in the ITC were OS and investigator-assessed PFS, representing primary and secondary endpoints of both ASTRUM-005 and CASPIAN. Analysis was based on the latest data cut from ASTRUM-005, with a median follow-up of 42.38 months, in comparison with a median follow-up of 39.4 months and 14.2 months in CASPIAN for OS and PFS analysis, respectively. HRs for OS and PFS for patients treated with durvalumab + carboplatin + etoposide in comparison with carboplatin + etoposide alone in CASPIAN are presented in Table 10.

An anchored comparison was performed using individual patient data from ASTRUM-005 and aggregate data from CASPIAN. This assumed that placebo + carboplatin + etoposide was equivalent to carboplatin + etoposide, an assumption that is supported by the similarity in absolute outcomes between the studies. Unadjusted HRs for

serplulimab in comparison with durvalumab were first estimated under the assumption that differences in patient characteristics between the trials would not impact the estimated treatment effect of serplulimab. This analysis was conducted utilising the Bucher method for indirect treatment comparisons on the log scale for HRs. However, the Bucher method may produce biased estimates of comparative efficacy where imbalances in treatment effect modifying factors existing between the two studies.

Consequently, population-adjusted methods were also conducted using the MAIC method described by Signorovitch et al., 2010 (24). Weights for each patient in the ASTRUM-005 study were calculated using the Newton-Raphson optimisation procedure. The weighted baseline characteristics for the patients were then verified to ensure that they matched those aggregate characteristics from CASPIAN and calculated ESS. MAIC analyses were then conducted to obtain the relative HRs and 95% CIs for OS and PFS. The analysis used a Cox proportional hazards model with weights to obtain the weighted hazard ratios (HRs) for the ASTRUM-005 study, then compared with the CASPIAN study to determine the relative HR and 95% CI.

Unadjusted analysis showed that treatment with serplulimab was anticipated to improve both OS and PFS in comparison with durvalumab, with estimated HRs of [redacted] and [redacted], respectively (.

Table 15). Estimated improvements in PFS were statistically significant.

In the matched analysis, patient characteristics for matching variables were well aligned between study populations (Table 13). The matching process retained approximately 67% of the ESS of ASTRUM-005, with a combined ESS of 390 patients across both study arms.

Table 13: Patient characteristics in matched analysis

Baseline variables	ASTRUM-005		ASTRUM-005: Adjusted		IMpower133	
	Serplulimab (n=389)	Placebo (n=196)	Serplulimab (ESS=256)	Placebo (ESS=134)	Control (n=269)	Durvalumab (n=268)
Age group, n (%)						
≥ 65 years	154 (39.6)	77 (39.3)	93 (36.5)	52 (38.5)	112(41.6)	101 (37.7)
< 65 years	235 (60.4)	119 (60.7)	163 (63.5)	82 (61.5)	157 (58.4)	167 (62.3)
Sex, n (%)						
Male	317 (81.5)	164 (83.7)	228 (89.1)	122 (91.0)	184 (68.4)	190 (70.9)
Female	72 (18.5)	32 (16.3)	28 (10.9)	12 (9.0)	85 (31.6)	78 (29.1)
Race, n (%)						
Asian	262 (67.4)	139 (70.9)	159 (62.1)	88 (65.9)	42 (15.6)	36 (13.4)
Non-Asian	127 (32.6)	57 (29.1)	97 (37.9)	46 (34.1)	227 (84.4)	232 (86.6)
Disease stage, n (%)						

Baseline variables	ASTRUM-005		ASTRUM-005: Adjusted		IMpower133	
	Serplulimab (n=389)	Placebo (n=196)	Serplulimab (ESS=256)	Placebo (ESS=134)	Control (n=269)	Durvalumab (n=268)
IV	318 (81.7)	155 (79.1)	217 (84.9)	106 (79.4)	245 (91.1)	240 (89.6)
III or other	71 (18.3)	41 (20.9)	39 (15.1)	28 (20.6)	24 (8.9)	28 (10.4)
ECOG, n (%)						
PS 1	318 (81.7)	164 (83.7)	**162 (63.1)**	**89 (66.5)**	**179 (66.5)**	**169 (63.1)**
PS 0	71 (18.3)	32 (16.3)	**94 (36.9)**	**45 (33.5)**	**90 (33.5)**	**99 (36.9)**
Smoking status, n (%)						
Current/former smoker	308 (79.2)	161 (82.1)	**235 (91.8)**	**126 (94.4)**	**254 (94.4)**	**246 (91.8)**
Never	81 (20.8)	35 (17.9)	**21 (8.2)**	**8 (5.6)**	**15 (5.6)**	**22 (8.2)**
Brain metastasis, n (%)						
Yes	50 (12.9)	28 (14.3)	**27 (10.4)**	**13 (10.0)**	**27 (10.0)**	**28 (10.4)**
No	339 (87.1)	168 (85.7)	**229 (89.6)**	**121 (90.0)**	**242 (90.0)**	**240 (89.6)**
Liver metastasis, n (%)						
Yes	99 (25.4)	51 (26.0)	**103 (40.3)**	**52 (38.7)**	**104 (38.7)**	**108 (40.3)**
No	290 (74.6)	145 (74.0)	**153 (59.7)**	**82 (61.3)**	**165 (61.3)**	**160 (59.7)**
Tumour mutational burden, n (%)						
≥10 mutations/Mb	22/195 (11.3)	4/110 (3.6)	14/128 (10.8)	2/75 (3.0)	NR	NR
<10 mutations/Mb	173/195 (88.7)	106/110 (96.4)	114/128 (89.2)	73/75 (97.0)	NR	NR
Previous anticancer treatments, n (%)						
Yes	10 (2.6)	5 (2.6)	6 (2.5)	4 (2.8)	NR	NR
No	379 (97.4)	191 (97.4)	250 (97.5)	130 (97.2)	NR	NR

Bold *data indicate matching variables.*
Abbreviations*: ECOG, European Cooperative Oncology Group; ESS, effective sample size; Mb, mutational burden; NR, not recorded; PS, performance status.*
Source*: (22, 23)*

[redacted] Histograms of estimated weights and rescaled weights for both study arms, and summary statistics of the weights are presented in Figure 2 and Table 14, respectively.

Table 14: Distribution of patient weights

	ASTRUM-005 vs CASPIAN	
	Active arm (n=389)	Control arm (n=196)
Weights		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
= 0, n(%)	[redacted]	[redacted]
>0 and <=0.1, n(%)	[redacted]	[redacted]
>0.1 and <=0.5, n(%)	[redacted]	[redacted]
>0.5 and <=1, n(%)	[redacted]	[redacted]
>1, n(%)	[redacted]	[redacted]

Abbreviations*: SD, standard deviation.*

Figure 2: Distribution of patient weights

In matched analysis, treatment with serplulimab was estimated to result in improved OS and PFS in comparison with durvalumab, [redacted]

[redacted]

Improvements in PFS were statistically significant (.

Table 15).

Table 15: Results of indirect treatment comparison based on ASTRUM-005 and CASPIAN

	Bucher	Matched
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

***Abbreviations**: PFS, progression-free survival; OS, overall survival.*

Overall, the results of the MAIC demonstrate improvements in both PFS and OS with serplulimab + carboplatin-etoposide (ASTRUM-005) compared with durvalumab + carboplatin-etoposide (CASPIAN), regardless of the adjustments for baseline characteristics. In general, greater improvements were observed after adjustments, especially for OS. This may be attributed to the higher percentage of patients with ECOG PS 1 and brain metastasis enrolled in ASTRUM-005, both of which are associated with poor prognosis. Improvements in PFS were statistically significant, supporting the findings of improvements in OS, given that PFS is predictive of OS in SCLC. This was despite ASTRUM-005 being powered to detect differences in treatment effect in comparison with placebo, rather than an active comparator, and loss of sample size in the matching process.

B9. Subsequent treatments

For the EAG to assess the generalisability of the ASTRUM-005 findings to a UK population, it is helpful to receive further information about subsequent treatment options and provision received by patients.

a) Could the Company please detail any differences in subsequent treatments for those patients recruited from Asia versus elsewhere in ASTRUM-005?

[redacted]

[redacted],(3) the EAG want to understand any potential confounding factors that may impact the generalisability of the trial population to that seen in UK clinical practice. The EAG note a similar table is available in Supplement 2 (eTable 2) of the main trial paper,(12) however this does not use the most recent data cutoff and is not disaggregated by population subgroups (Asian versus non-Asian).

Could the following table (or similar) please be populated?

The subsequent anticancer treatment after first disease progression (PD) (data cutoff: 7th May 2024) is summarized in Table 16. Similar to Supplement 2 (eTable 2), the proportion of subsequent treatments is comparable between the serplulimab group and the placebo group. 53.0% and 48.0% patients in the serplulimab group and placebo group received ≥1 treatment after first disease progression, with a similar proportion of Asian and non-Asian subjects. [redacted]

Regarding the therapy type, the percentages of subjects with chemotherapy were about [redacted] across treatment arms in Asian and non-Asian subjects. In the serplulimab group, the proportion of immunotherapy was [redacted] in non-Asian ([redacted] than in Asian subjects ([redacted] while in the placebo group, more subjects received immunotherapy in Asian ([redacted] than in non-Asian subjects ([redacted] [redacted] in the serplulimab group, [redacted] in the placebo group) received targeted therapy, [redacted] in the serplulimab group, [redacted] in the placebo group) received 'other' therapy. All of them were Asian. Other therapy included traditional Chinese medicine, immunomodulator, antineoplastic agent (unknown) and other clinical trial therapy.

Table 16: Summary of subsequent anticancer treatment after first disease progression (cutoff date: 7th May 2024)

	Serplulimab group			Placebo group		
	All serplulimab arm	**Asian**	**Non-Asian**	**All placebo arm**	**Asian**	**Non-Asian**
	N=389	N=262	N=127	N=196	N=139	N=57
Number of patients with ≥1 treatment after	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

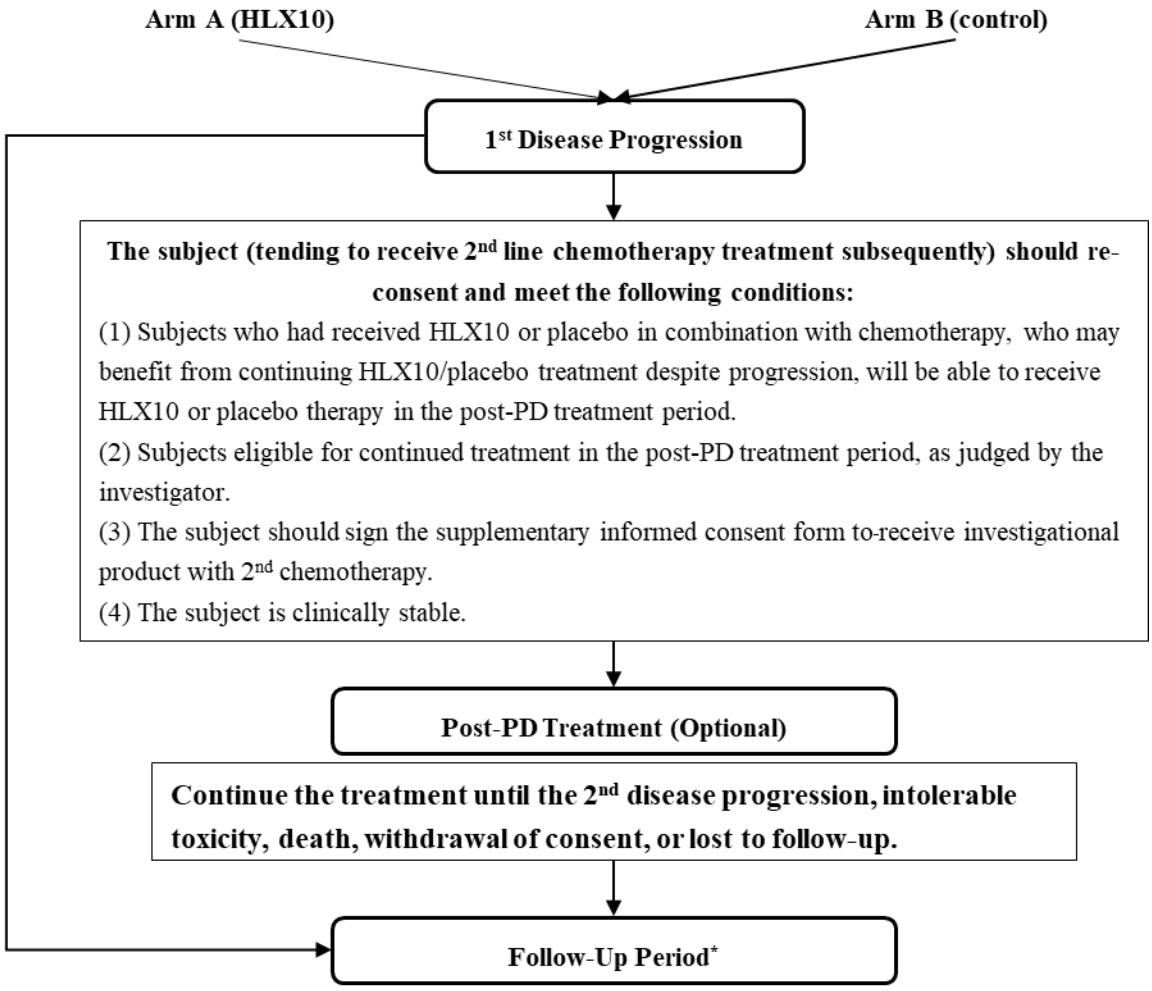
first disease progression						
Line of therapy						
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 and other[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Therapy type						
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Target Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] *Other lines of therapy included herbal or Traditional Chinese Medicine, thermo-chemotherapy perfusion, and non-systemic treatment, among others.*
[b] *Other therapies include herbal or Traditional Chinese Medicine, immunomodulator (lentinan, thalidomide, spleen amino peptide oral lyophilized powder, thymopolypeptides for injection, etc), antineoplastic agent (unknown) and other clinical trial.*

b) The CS notes the recommended dose of serplulimab should continue until disease progression or unacceptable toxicity, and it was at the discretion of the investigator to continue treating the subject with blinded serplulimab or placebo assignment per protocol in addition to the second-line chemotherapy.(3) The EAG note that 44.2% and 43.4% of participants in the serplulimab and placebo arms, respectively, had subsequent treatment after first disease progression.(25) Could the Company please outline what methods were used to determine whether patients should continue with serplulimab or use other therapies? Could the Company also clarify whether there were any differences in subsequent treatments/lines of treatment across trial sites?

It was at the discretion of the investigator to continue the study treatment or start other anticancer therapies after the first disease progression (PD). The willingness of subjects was also taken into consideration. A subject could be treated with original study treatment within the protocol scope or end the study treatment and seek for other therapies. A supplementary informed consent form for post-PD treatment had to be signed before continuing serplulimab/placebo treatment after first PD. The schematic of study treatment was outlined in the protocol and is reproduced here with an arrow added in Figure 3. If subjects in the placebo group continued the original treatment after first PD (i.e. placebo), it was not accounted for in Table 16. Serplulimab was treated as immunotherapy in Table 16.

Figure 3: Schematic of study treatment



***Abbreviations**: HLX10, serplulimab; PD, progressed disease.*

In the ASTRUM-005 study, subjects were enrolled in 103 trial sites. As only very few patients were enrolled in several sites, comparing subsequent treatment by site was not feasible. Instead, a summary of subsequent anticancer treatments by country is presented in

Table 17. Almost all Asian subjects were Chinese (400 out of 401). As a result, the Chinese population is representative of the prespecified Asian subgroup in ASTRUM-005. In China, [redacted] subjects in the serplulimab group and placebo group were treated with subsequent anticancer treatment after first PD, including 2nd-line, 3rd-line, 4th-line, 5th-line and beyond. Most subjects received chemotherapy and immunotherapy.

[redacted]

In conclusion, most of the subsequent anticancer therapy received in ASTRUM-005 was 2nd-line. Chemotherapy and immunotherapy were the most common therapy type used in all countries.

[redacted]

Table 17: Summary of subsequent anticancer treatment after first disease progression by country (cutoff date: 7 May 2024)

	China		Georgia		Poland		Russia		Turkey		Ukraine	
	HLX10 (N=261)	Placebo (N=139)	HLX10 (N=37)	Placebo (N=13)	HLX10 (N=4)	Placebo (N=3)	HLX10 (N=30)	Placebo (N=12)	HLX10 (N=26)	Placebo (N=19)	HLX10 (N=31)	Placebo (N=10)
Total number of patients with at least one treatment (n, %)	[redacted]											
Line of therapy												
2nd-line (n, %)	[redacted]											
3rd-line (n, %)	[redacted]											
4th-line (n, %)	[redacted]											
Other[a] (n, %)	[redacted]											
Therapy type												
Chemotherapy (n, %)	[redacted]											
Immunotherapy (n, %)	[redacted]											
Target Therapy (n, %)	[redacted]											
Other[b] (n, %)	[redacted]											

[a] *Other lines of therapy included herbal or Traditional Chinese Medicine, thermo-chemotherapy perfusion, and non-systemic treatment, among others.*

[b] *Other therapies include herbal or Traditional Chinese Medicine, immunomodulator (lentinan, thalidomide, spleen aminopeptide oral lyophilized powder, thymopolypeptides for injection, etc), antineoplastic agent (unknown) and other clinical trial.*

B10. ASTRUM-005 CSR

The EAG note that the ASTRUM-005 CSR in the reference pack is version 2.0, dated 30 January 2023 using a data cutoff of 13 June 2022. In the Company reference pack, this document is dated 2024 yet the version date of the report is January 2023.

a) Could the Company confirm whether the results reported in the CS refer to this version using a June 2022 data cutoff (or a more recent data cutoff)?

The Company have provided the latest CSR as part of the responses to clarification questions (final data cutoff: 7th May 2024) (26). Only the interim CSR was included in the reference pack, which was an unintended error. The results reported in the CS refer to the latest data cut (7th May 2024), aside from the quality of life data presented in Section 2.6.3, which was taken from a poster publication (11) and uses data from an interim data cut (June 2022). No aggregate quality of life data was presented in the final CSR.

The data used in the economic model are also informed by the latest data cut (May 2024), aside from patient EQ-5D, which was informed by an interim data cut (June 2022). The model version provided as part of the responses to clarification questions has been updated with the latest EQ-5D data from the final CSR (May 2024).

The Company would also like to take the opportunity to correct an inconsistency in the trial results that was included in the CS. The highlighted confidence interval should read (-5.11, 6.03), and not (-5.11, -6.03) as provided in the original submission document.

Table 19: Change from baseline to Week 18 in 'pain in other parts' domain of EORTC QLQ-LC13

"Pain in other parts" in EORTC QLQ-LC13	Serplulimab (n=389)	Placebo (n=196)
Change from baseline to Week 18 LSM (95% CI)	-5.91 (-10.36, 1.46)	0.46 (-5.11, 6.03)
Difference in LSM (95% CI)	-6.37 (-11.59, -1.15)	
Nominal p-value	0.0170	

***Abbreviations**: CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, European Quality of Life-5 Dimension-5 Level; LSM, least square mean; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13.*
***Source**: Cheng et al., 2024 (27)*

b) Is there another more up-to-date CSR using the May 2024 data cutoff which the Company could share? Could any additional tables, figures, and listings (TFLs) also be shared?

The Company have provided the latest CSR as part of the responses to clarification questions (final data cutoff: 7th May 2024). The final CSR was unintentionally omitted in the reference pack. A .zip file containing all supplementary appendices is also provided (26).

c) Are further data cutoffs planned?

No further data cuts are planned for ASTRUM-005.

B11. Trial follow-up

In the CS, an overall survival (OS) and progression-free survival (PFS) ITC was carried out using a 3.5-year follow-up for ASTRUM-005 (median follow-up 42.38 months) and a 2-year follow-up for IMpower133 (median follow-up was 22.9 months).(3) Could the Company please provide a rationale for conducting an ITC using data from trials with differing follow-up periods? Could the analysis be repeated using approximately 2-year follow-up date from both trials for OS and PFS?

We have used the longest available follow-up periods from each trial (3.5 years and 2 years, respectively) to utilise all the available data characterising the relative treatment effect of both treatments. This approach minimises uncertainty by incorporating the most mature data on OS and PFS, providing the most robust point estimates of treatment efficacy. While the follow-up durations differ, using the longest available period from each trial aligns with best practices for ITCs, as it maximises data reliability and validity. As is stipulated in TSD18, it is best practice to incorporate the most comprehensive and reliable data available for robust outputs of an ITC. However, the requested analysis has been conducted with results summarised in Table 18. Results from the requested analysis are consistent with more certain estimates based on the full trial follow-up from ASTRUM-005.

Table 18: Results of indirect treatment comparison based on ASTRUM-005 and IMpower133, with ASTRUM-005 data censored at 24 months.

	Bucher	Matched
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

***Abbreviations**: PFS, progression-free survival; OS, overall survival.*

Section C: Clarification on cost-effectiveness data

C1. Priority question: Discrepancies in Results

In the CS document,(3) the results of cost-effectiveness analysis (section 3.8), sensitivity and scenario analyses (section 3.9), and subgroup analysis (section 3.10) do not match the corresponding results in the CS economic model.(28) Could the Company please produce a complete set of results tables for sections 3.8, 3.9 and 3.10 in the CS document based on analyses using the PAS price of serplulimab, and make necessary changes in the written text in relevant sections of the CS document?(3)

The Company has checked the CS and CS model and confirmed that the results are consistent between the two documents. The complete set of results tables at PAS price were included in Appendix N in the CS. These are reproduced below.

Table 19: Base-case results, pairwise (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	[redacted]	2.47	2.10				
Atezolizumab	£54,671	1.74	1.50	[redacted]	0.74	0.60	[redacted]
Carboplatin-etoposide	£21,561	1.38	1.21	[redacted]	1.09	0.89	[redacted]

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; PAS, patient access scheme.*

Table 20: Base-case results, full incremental analysis (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab	£54,671	1.50			
Serplulimab	[redacted]	*2.10*	[redacted]	*-0.60*	[redacted]
Carboplatin-etoposide	£21,561	1.21	[redacted]	0.89	[redacted]

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; PAS, patient access scheme.*

Table 21: Net health benefit (PAS price)

Technologies	NHB at £20,000	NHB at £30,000
Serplulimab vs atezolizumab	[redacted]	[redacted]
Serplulimab vs carboplatin-etoposide	[redacted]	[redacted]

***Abbreviations**: NHB, net health benefit; PAS, patient access scheme.*

Table 22: Probabilistic results vs atezolizumab (PAS price)

	Serplulimab	Atezolizumab	Incremental	ICER
Total costs (£)	[redacted]	£58,299	[redacted]	[redacted]
Total QALYs	2.10	1.55	0.55	

Abbreviations: *ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.*

Table 23: Probabilistic results vs carboplatin-etoposide (PAS price)

	Serplulimab	Carboplatin-etoposide	Incremental	ICER
Total costs (£)	[redacted]	£22,583	[redacted]	[redacted]
Total QALYs	2.10	1.21	0.89	

Abbreviations: *ICER, incremental cost effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.*

[redacted]

Abbreviations*: PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.*

[redacted]

Abbreviations*: PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.*

[redacted]

Abbreviations: *HR, hazard ratio; MAIC, matching adjusted indirect comparison; PAS, patient access scheme.*

[redacted]

Abbreviations: *PAS, patient access scheme.*

Table 24: Summary of scenario analysis – comparator atezolizumab (PAS price)

Scenario	Description	Value	Incremental QALYs	Incremental costs	ICER (£/QALY gained)
Base-case			0.60	[redacted]	[redacted]
OS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.49	[redacted]	[redacted]
		Weibull	0.43	[redacted]	[redacted]
		Gamma	0.42	[redacted]	[redacted]
		Log-normal	0.60	[redacted]	[redacted]
		Gompertz	0.66	[redacted]	[redacted]
		Gen. Gamma	0.59	[redacted]	[redacted]
PFS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.60	[redacted]	[redacted]
		Weibull	0.60	[redacted]	[redacted]
		Gamma	0.59	[redacted]	[redacted]
		Log-normal	0.60	[redacted]	[redacted]
		Gompertz	0.61	[redacted]	[redacted]
		Gen. Gamma	0.60	[redacted]	[redacted]
TTOT parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.60	[redacted]	[redacted]
		Weibull	0.60	[redacted]	[redacted]
		Gamma	0.60	[redacted]	[redacted]
		Log-normal	0.60	[redacted]	[redacted]
		Gompertz	0.59	[redacted]	[redacted]
		Gen. Gamma	0.60	[redacted]	[redacted]
Data source for atezolizumab extrapolation	HR from the MAIC (after matching) applied to the selected serplulimab extrapolation in the base-case. Scenarios using the before matching HR (more conservative) and using an independent model fitted to pseudo-IPD from IMpower133 (i.e., not HR-based) are presented.	HR from MAIC (before matching)	0.51	[redacted]	[redacted]
		Independent model fitted to pseudo-IPD from IMpower133	0.67	[redacted]	[redacted]
Time horizon (years)	A 20-year time horizon was selected in the base-case to reflect all important differences in costs and outcomes. Scenarios with shorter time	5	0.36	[redacted]	[redacted]
		10	0.50	[redacted]	[redacted]
		15	0.57	[redacted]	[redacted]

	horizons are presented.				
Utility derivation method	Utilities based on progression status were applied in the base-case, aligned with the Committee's stated preferences in TA638. Scenarios using the time-to-death approach and progression status by treatment status are presented.	Time-to-death	0.44	[redacted]	[redacted]
		Progression status by on/off treatment	0.58	[redacted]	[redacted]
Adverse events	AE rates from the ITT population were modelled in the base-case, with additional disutilities applied for AEs. Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities in case of double-counting are presented.	Exclude AE disutilities	0.60	[redacted]	[redacted]
		Non-Asian AEs	0.56	[redacted]	[redacted]
Treatment waning	No treatment waning is applied in the base-case, as there was no evidence for loss of treatment effect in the ASTRUM-005 trial. Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented. When treatment waning is	Immediate loss of treatment effect at 5 years	0.51	[redacted]	[redacted]
		Gradual loss of treatment effect from 5-10 years	0.55	[redacted]	[redacted]

	applied, the cycle probabilities in the serplulimab arm wane to the atezolizumab arm.				
Vial sharing assumed for serplulimab	No vial sharing is assumed in the base-case. A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	0.60	[redacted]	[redacted]

Abbreviations: *AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; MAIC, matched-adjusted indirect comparison; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTOT, time to off treatment.*

Table 25: Summary of scenario analysis – comparator carboplatin-etoposide (PAS price)

Scenario	Description	Value	Incremental QALYs	Incremental costs	ICER (£/QALY gained)
Base-case			0.89	[redacted]	[redacted]
OS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.79	[redacted]	[redacted]
		Weibull	0.75	[redacted]	[redacted]
		Gamma	0.75	[redacted]	[redacted]
		Log-normal	0.95	[redacted]	[redacted]
		Gompertz	1.10	[redacted]	[redacted]
		Gen. Gamma	0.98	[redacted]	[redacted]
PFS parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.89	[redacted]	[redacted]
		Weibull	0.89	[redacted]	[redacted]
		Gamma	0.89	[redacted]	[redacted]
		Log-normal	0.90	[redacted]	[redacted]
		Gompertz	0.91	[redacted]	[redacted]
		Gen. Gamma	0.90	[redacted]	[redacted]
TTOT parametric model	Log-logistic used in base-case. Scenarios using alternative parametric models are presented.	Exponential	0.88	[redacted]	[redacted]
		Weibull	0.89	[redacted]	[redacted]
		Gamma	0.88	[redacted]	[redacted]
		Log-normal	0.89	[redacted]	[redacted]
		Gompertz	0.88	[redacted]	[redacted]
		Gen. Gamma	0.89	[redacted]	[redacted]
Time horizon (years)	A 20-year time horizon was selected in the base-case to reflect all important differences in costs and outcomes. Scenarios with shorter time horizons are presented.	5	0.59	[redacted]	[redacted]
		10	0.78	[redacted]	[redacted]
		15	0.86	[redacted]	[redacted]

Utility derivation method	Utilities based on progression status were applied in the base-case, aligned with the Committee's stated preferences in TA638. Scenarios using the time-to-death approach and progression status by treatment status are presented.	Time-to-death	0.66	[redacted]	[redacted]
		Progression status by on/off treatment	0.85	[redacted]	[redacted]
Adverse events	AE rates from the ITT population were modelled in the base-case, with additional disutilities applied for AEs. Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities in case of double-counting are presented.	Exclude AE disutilities	0.91	[redacted]	[redacted]
		Non-Asian AEs	0.84	[redacted]	[redacted]
Treatment waning	No treatment waning is applied in the base-case, as there was no evidence for loss of treatment effect in the ASTRUM-005 trial. Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented. When treatment waning is applied, the cycle	Immediate loss of treatment effect at 5 years	0.81	[redacted]	[redacted]
		Gradual loss of treatment effect from 5-10 years	0.85	[redacted]	[redacted]

	probabilities in the serplulimab arm wane to the carboplatin-etoposide arm.				
Vial sharing assumed for serplulimab	No vial sharing is assumed in the base-case. A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	0.89	[redacted]	[redacted]

Abbreviations: *AE, adverse event; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTOT, time to off treatment*

C2. Selection of independent or joint parametric models

The Company stated in Sections 3.3.3 to 3.3.5 of the CS(3) that the fact that the proportional hazard assumption cannot be rejected by visual inspection of the log-cumulative hazard plots led to the conclusion that independent curves should be fitted. TSD14(29) recommends that if the lines are parallel in the log-cumulative hazard plots then proportional hazards and accelerated failure time models should be tested; it does not recommend that independent curves should be fitted. See Figure 3, TSD14.(29)

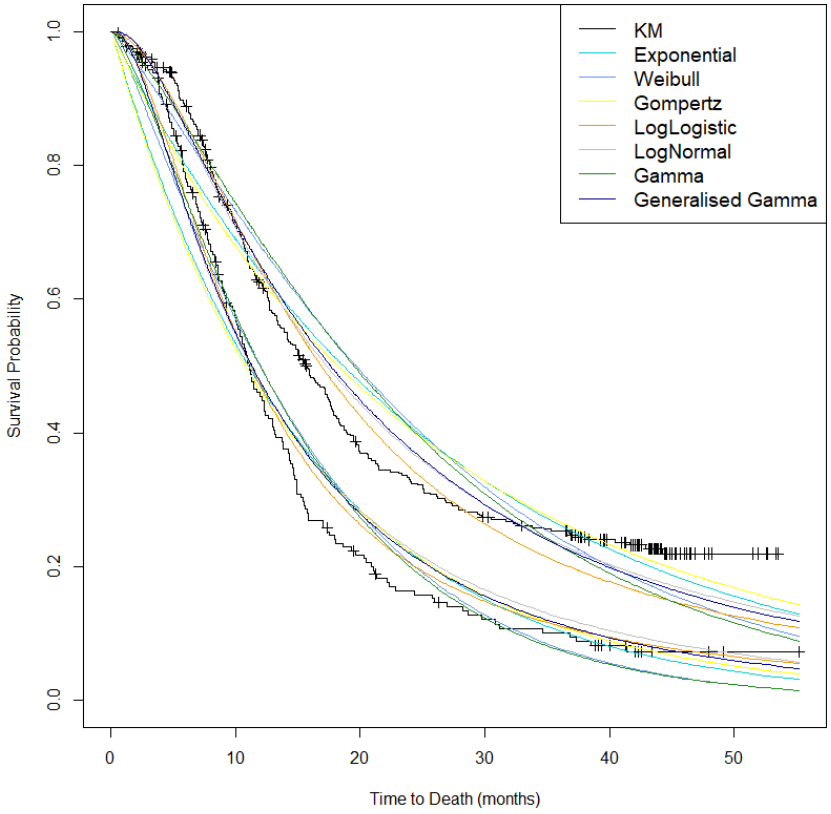
The EAG notes that the same parametric model has been selected for serplulimab and carboplatin plus etoposide. Could the Company clarify its rationale for preferring the selection of independently fitted parametric models instead of jointly fitted parametric models for serplulimab and carboplatin plus etoposide in the ASTRUM-005 trial(30) for PFS and OS?

The Company would like to clarify that the conclusion that independent models should be fitted was not based on the non-violation of the proportional hazards assumption. Rather, jointly fitted models were explored (and included in the CS model), consistent with the recommendations in TSD14; however, upon visual inspection of the fitted joint models, it was deemed most appropriate to fit independent models for each treatment arm in the base-case. The joint models fitted to the ASTRUM-005 data overlaid on the KM curves are presented in Figure 4 and **Error! Reference source not found.**.

TSD14 outlines that: *"Generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a*

proportional hazards modelling approach – the assumption should be tested which will indicate whether it may be preferable to separately fit parametric models to each treatment arm, or to allow for time-varying hazard ratios. Fitting separate parametric models to each treatment arm involves fewer assumptions, although it does also require the estimation of more parameters." Therefore, because patient-level data was available from the ASTRUM-005 trial and independent models fitted the trial data better compared to joint models, independent models were selected in the base-case. In line with recommendations in TSD14, independent models of the same type were fitted to both treatment arms.

Figure 4: OS joint models



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

[redacted]

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

C3. Priority questions: Choice of (semi-) parametric model fitted to the KM curves

The Company produced log-cumulative hazard plots to test whether the proportional hazards assumption could be rejected. In addition to informing the validity of the proportional hazard assumption, the log-cumulative hazard

plots can be used to inform whether models more flexible than the 6 common parametric models could be fitted. This is recommended if the log-cumulative hazard plots are not straight. TSD14 also recommends testing the fit of models more flexible than the 6 common parametric models if the lines in the log-cumulative hazard plots are not straight.(29) It is not clear whether a more flexible model would be a better fit. On the one hand, there is a visual suggestion that the log-cumulative hazard plots are not straight, and it looks as though the fitted curves may slightly underestimate outcomes early in the curves and overestimate outcomes later in the curves. On the other hand, the significant censoring, particularly in the control arm after 18 months for PFS and after 42 months for OS, may mean that a more flexible model is not a better fit.

Could the Company please:

a) **Comment on whether or not the log-cumulative hazard plots suggest that more flexible models should be tested?**

The Company agrees with the EAG that, as the log-cumulative hazard plots are not linear, more flexible models can be considered. However, the Company are aware of the risk of overfitting, especially at later timepoints, whereby more flexible models such as piecewise models or spline-based models fit the trial data well but provide an implausible long-term extrapolation of time-to-event outcomes. This is especially relevant given the relatively long tails in the KM curves from ASTRUM-005 and significant censoring at later timepoints.

b) **If the Company cannot fit appropriately flexible models among the selection of parametric models used in the multi-level network meta-regression analyses, could the Company please test the fit of more flexible joint models to the ASTRUM-005 trial data for OS, PFS and TTOT; provide the comparative fit statistics for the flexible models vs the standard models; and incorporate the flexible joint models into the CS Excel model?**

The log-cumulative hazard plots show a reasonably smooth, continuous change in the hazard function. Therefore, more flexible natural cubic spline models (Royston and

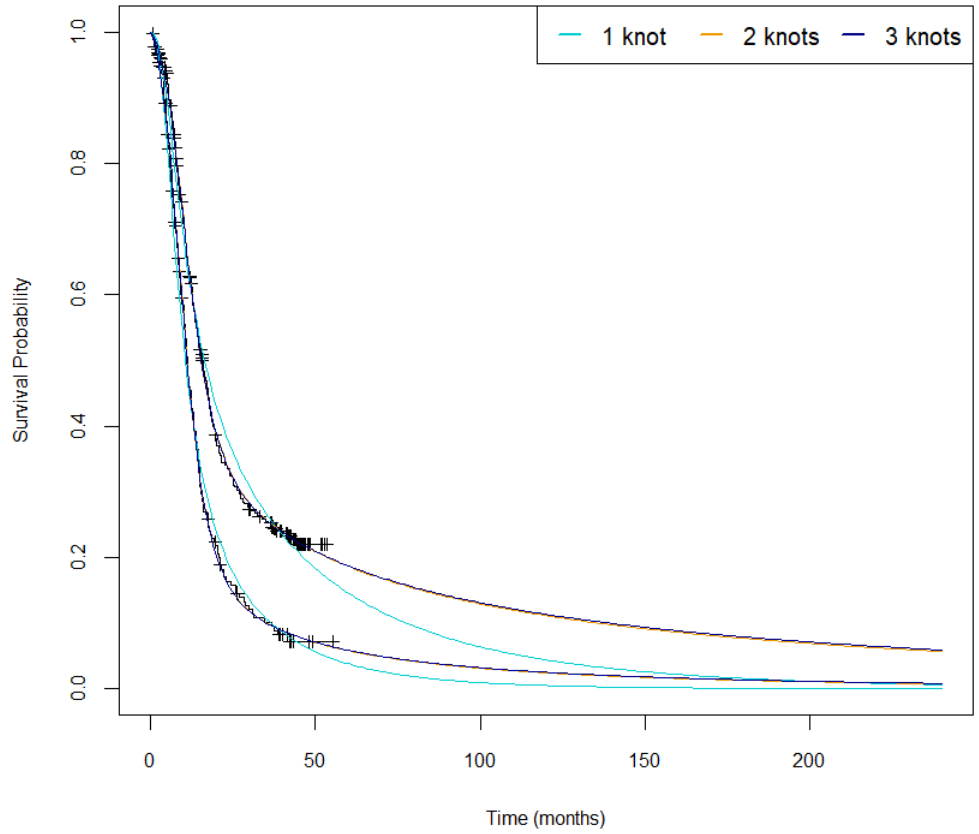
Parmar, 2002) which can capture such changes in the hazard function were explored. In line with guidance from Royston and Parmar, 2002, joint spline models (proportional hazards models) were fitted with one, two, and three knots for OS, PFS, and TTOT and the AICs were compared (Table 30). The fitted models for OS, PFS, and TTOT are presented in Figure 5, **Error! Reference source not found.** and **Error! Reference source not found.**, respectively. These models have been incorporated into the CS model and can be selected using the dropdowns in the model sheet "Scenario setting" (joint spline models are selected using the "OS/PFS – Serpulimab/Comparator 1/Comparator 2" dropdowns; the number of knots is selected using the "Parametric fit – OS/PFS" dropdowns).

Table 26: Comparative fit statistics for joint spline models with different degrees of freedom

Number of knots	AIC		
	OS	PFS	TTOT
1	4,880.6	3,858.6	4,582.4
2	4,838.3	3,843.8	4,366.9
3	4,839.2	3,783.9	4,371.5

***Abbreviations**: AIC, Akaike information criterion; OS, overall survival; PFS, progression-free survival; TTOT, time to off treatment.*

Figure 5: Joint spline models for OS



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

[redacted]

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

[redacted]

Abbreviations: *KM, Kaplan-Meier; TTOT, time to off treatment.*

c) Could the Company please comment on whether the Company thinks the fitted models for serplulimab are conservative or favourable for serplulimab?

For OS, the joint spline models with 2/3 knots have the best statistical fit and fit closely to the KM curves. However, these models appear to provide implausible overestimates of long-term OS, particularly in the serplulimab arm in which over 5% of patients are predicted to survive to year 20, which has the potential to overestimate benefits for patients treated with serplulimab. This is likely due to overfitting at the tail end of the KM as it begins to flatten where there is heavy censoring. Despite having a poorer overall statistical fit, the spline model with 1 knot provides a more plausible long-term extrapolation based on visual inspection (<1% survive to year 20). There appears to be a slight overestimation of survival within the trial period before the KM begins to flatten; however, this is observed in both arms and is therefore unlikely to bias results in favour of serplulimab.

For PFS, the joint spline model with 3 knots has the best statistical fit and fits closely to the KM curves. However, all 3 models provide implausible estimates of long-term PFS in the serplulimab arm. Notably, the curves all intersect with and cross over the most appropriate curve for OS (1 knot); therefore, at later timepoints these models predict PFS to be higher than OS, which is not possible. Whilst the CS model accounts for this impossibility by capping the PFS curve based on OS, this observation suggests that the flexible spline models are inappropriate for modelling PFS.

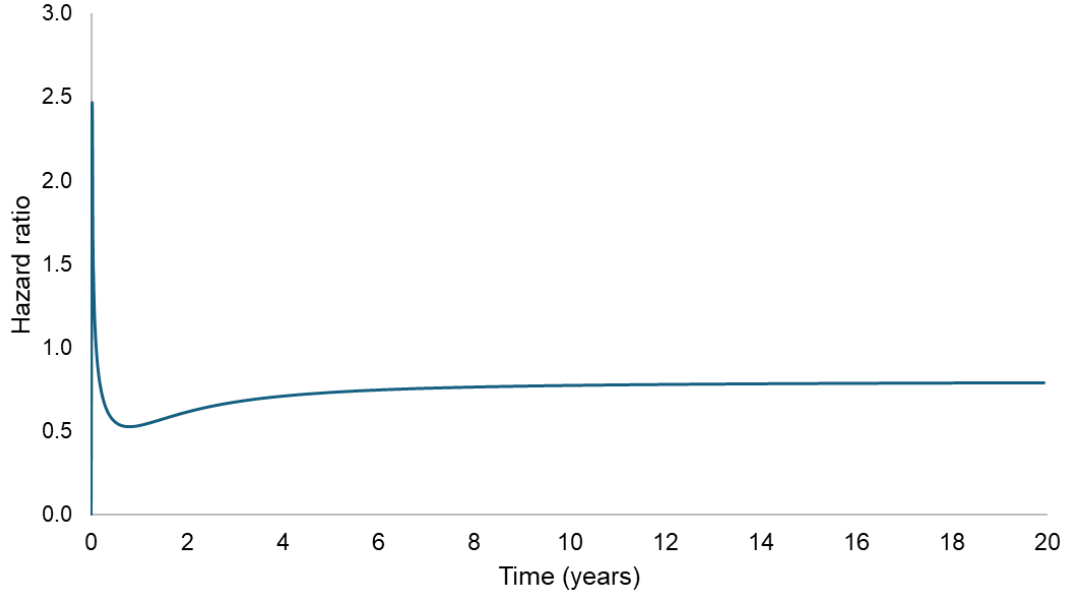
For TTOT, the joint spline models with 2/3 knots have the best statistical fit and fit closely to the KM curves. However, these models also appear to provide implausible overestimates of time on treatment in the long-term. Similar to OS, the model with 1 knot provides a more plausible long-term extrapolation based on visual inspection with a slight overestimation of time on treatment within the trial period before the KM flattens. Again, this potential overestimation is observed in both arms.

C4. Hazard ratio plots

Could the Company please produce OS and PFS hazard ratio plots for serplulimab vs each comparator for every comparator for which the hazard ratios are not constant?

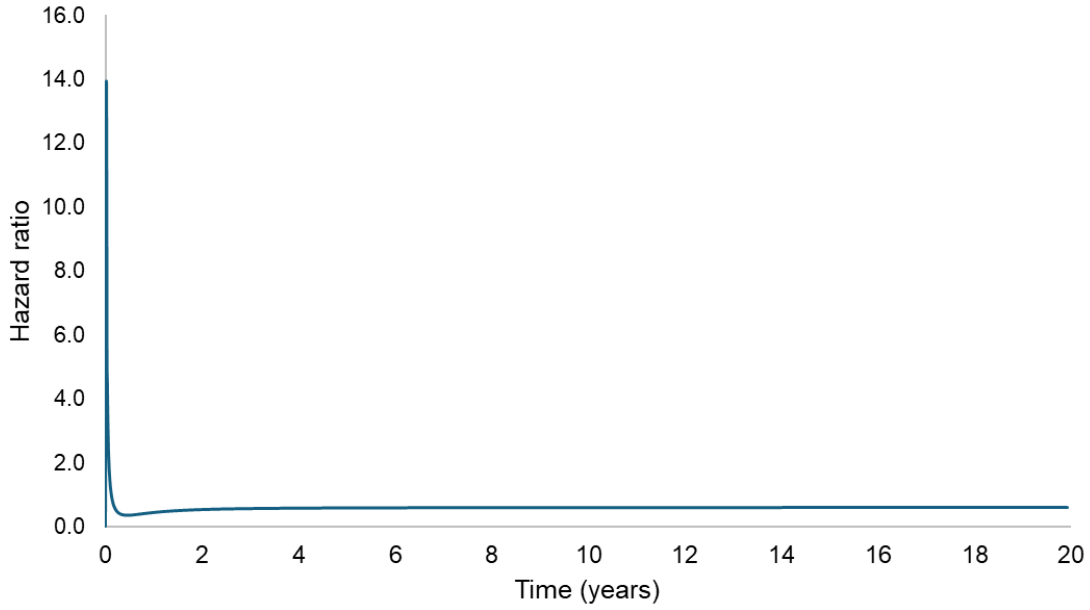
OS and PFS hazard ratio plots have been added into the model sheets “OS – In model” and “PFS – In model”. OS and PFS hazard ratio plots for serplulimab vs carboplatin-etoposide (independent models) are presented in Figure 6 and Figure 7, respectively.

Figure 6: OS hazard ratio plot vs carboplatin-etoposide



Abbreviations: *OS, overall survival.*

Figure 7: PFS hazard ratio plot vs carboplatin-etoposide



Abbreviations: *PFS, progression-free survival.*

C5. Adverse events

Table 35, page 108 CS. Could the Company please explain why serplulimab was associated with fractionally lower serious adverse events (SAEs) than the control for most of the SAEs?

Based on the aggregate data presented in the CSR (see Appendix G), the proportion of AEs are well distributed across arms. The lower overall count and number of events in the carboplatin-etoposide arm compared with the serplulimab arm is a result of lower patient numbers in the placebo arm of ASTRUM-005 (196 vs 386), as well as increased survival and time on treatment in the serplulimab arm, leading to an increased total duration over which patients were able to experience AEs. Therefore, as the weekly AE probabilities used in in the model were calculated by determining the ratio of the number of AE occurrences to the number of patient weeks at risk, with a much greater number of patient weeks at risk in the serplulimab arm compared to placebo, the AE probabilities in the serplulimab arm are lower.

C6. Price Year

Table 49, page 132 CS. The unit costs for resources are sourced with the price year 2022/23. The drug acquisition costs for atezolizumab were BNF January 2024 and apart from serplulimab the other drug acquisition costs are sourced from eMIT 2024. The CS reports that the mean cost of palliative care was inflated to 2024. There is a

discrepancy in the price years. Could the Company please confirm the price year and explain how prices were adjusted to the price year?

Unit costs for healthcare resource use were sourced from the latest NHS reference costs at the time of submission, dated 2022/23. At the time of submission, no later reference costs were available for 2024. However, the use of older NHS reference costs is not expected to significantly impact results, as resource use frequencies are similar across arms. Costs reported prior to 2024 that were not directly sourced from the NHS reference costs, for example the mean cost of palliative care, were inflated to 2024 prices using PSSRU HCHS and NHS cost inflation index values (NHSCII pay and prices) and included in the model sheet "General inputs". Because 2023/24 inflation indices were not yet available at the time of submission, the average rate of inflation over the previous three years was assumed.

C7. Systematic Review of Cost Effectiveness

The EAG noticed in Table 1 of Appendix H the Company states that Randomised Control Trials (RCTs) were excluded; however, some of the included studies are RCTs. Can the Company please confirm whether RCTs were included or excluded in the inclusion / exclusion criteria?

The Company confirms that RCTs were included.

C8. Resource Use

The Company state that the resource use for serplulimab was assumed to be equivalent to atezolizumab for the progression-free and post-progression states. Could the Company please provide a description of how these cost estimates were derived and validated by clinical experts in TA638?

No relevant published studies had been identified in TA638 to inform the resource use in ES-SCLC. As a result, the Company surveyed nine UK clinicians to inform resource use frequencies in their economic model (see p90/91 of TA638 CS) (31). Resource use for different treatment options and disease stages were surveyed from clinicians as the expected average resource use of a patient in each stage of treatment and disease. The Committee and EAG for TA638 found no limitations in the approach taken by the Company.

C9. Utility values and survival assumptions

Could the Company please provide summaries of the questions and responses from the clinical engagement on validating the utility values used, and survival assumptions beyond the duration of ASTRUM-005 trial (and consequently the long-term extrapolation for time-to-event curves) in the CS model?

As described in Appendix M of the Company evidence submission, a 2-round modified Delphi panel was conducted to gather expert clinical consensus on key areas of clinical uncertainty in order to support the upcoming UK and Irish HTA submissions in ES-SCLC. Please see Table 6 above for more details.

During the Round 1 survey, the participants were asked provide estimates of the long-term survival of ES-SCLC patients based on data presented for platinum-based chemotherapy treatment from the Flatiron Health Database for ES-SCLC (as included in the 2020 NICE appraisal for atezolizumab), and for serplulimab (with platinum-based chemotherapy) from ASTRUM-005 (23, 27, 31, 32). These are presented in Table 27 below.

Table 27 :Modified Delphi panel (Appendix M), Round 1 survey long-term survival estimates

Question		**Answer** *Mean response, N=5 participants*
For first-line ES-SCLC patients treated with platinum-based chemotherapy	What proportion of patients would you estimate to be alive 1-year after initiation of treatment?	[redacted]
	Of those patients alive after 1 year, what proportion would you estimate to still be alive 2 years after initiation of treatment?	[redacted]
	Of those patients alive after 2 years, what proportion would you estimate to still be alive 3 years after initiation of treatment?	[redacted]
	What proportion of patients would you estimate to be progression-free 6 months after initiation of treatment?	[redacted]
	Of those patients who are progression-free after 6 months, what proportion would you estimate to still be progression-free 1 year after initiation of treatment?	[redacted]
	Of those patients who are progression-free after 1 year, what proportion would you estimate to still be progression-free 2 years after initiation of treatment?	[redacted]
For first-line ES-SCLC patients treated with serplulimab (with platinum-based chemotherapy)	What proportion of patients would you estimate to be alive 1 year after initiation of treatment?	[redacted]
	Of those patients alive after 1 year, what proportion would you estimate to still be alive 3 years after initiation of treatment?	[redacted]
	Of those patients alive after 3 years, what proportion would you estimate to still be alive 5 years after initiation of treatment?	[redacted]
	What proportion of patients would you estimate to be progression-free 1 year after initiation of treatment?	[redacted]

	Of those patients who are progression-free after 1 year, what proportion would you estimate to still be progression-free 2 years after initiation of treatment?	[redacted]
	Of those patients who are progression-free after 2 years, what proportion would you estimate to still be progression-free 3 years after initiation of treatment?	[redacted]

Abbreviations: *ES-SCLC, extensive-stage small cell lung cancer; SD, standard deviation.*

These data were then used to calculate the percentage of patients who would be alive or progression-free at each key timepoint, as presented in Table 28 below.

Table 28: Modified Delphi panel (Appendix M), Round 1 key timepoint percentage survival calculations

Outcome	Treatment	Time since treatment initiation *(years)*			
		1	2	3	5
Percentage of ES-SCLC patients who are alive	Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
	Serplulimab (with platinum-based chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of ES-SCLC patients who are progression-free	Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
	Serplulimab (with platinum-based chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *ES-SCLC, extensive-stage small cell lung cancer; NA, not applicable.*

During Round 2, a series of curve fits for the long-term survival of ES-SCLC patients treated with platinum-based chemotherapy or serplulimab (with platinum-based chemotherapy) were presented to the participants. Values were extracted from these curve fits at several key timepoints and were presented to the participants in a table alongside the results of the Round 1 survey (i.e. those presented in Table 28).

The participants were then asked to select which curve fit(s) best matched the long-term survival that they would expect for ES-SCLC patients treated with platinum-based chemotherapy or serplulimab (with platinum-based chemotherapy), the results of which are shown in Table 29 below.

Table 29: Modified Delphi panel (Appendix M), Round 2 long-term extrapolation curve fit selection

Question	Curve fit selected (N=3)			Rationale
	[redacted]	[redacted]	[redacted]	
Which curve fit best matches the long-term overall survival that you would expect for	[redacted]	[redacted]	[redacted]	[redacted]

ES-SCLC patients after initiation of treatment with platinum-based chemotherapy?				
Which curve fit best matches the long-term overall survival that you would expect for ES-SCLC patients after initiation of treatment with serplulimab (with platinum-based chemotherapy)?	[redacted]	[redacted]	[redacted]	[redacted]
Which curve fit best matches the long-term progression-free survival that you would expect for ES-SCLC patients after initiation of treatment with platinum-based chemotherapy?	[redacted]	[redacted]	[redacted]	[redacted]
Which curve fit best matches the long-term progression-free survival that you would expect for ES-SCLC patients after initiation of treatment with serplulimab (with platinum-based chemotherapy)?	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *ES-SCLC, extensive-stage small cell lung cancer.*

Utilities were not directly validated with clinicians during the Delphi panel. However, the model includes a range of scenarios to explore the uncertainty associated with utility values, including values from TA638. A direct comparison between the base-case approach (progression-based utilities) and the utilities from IMpower133 was not feasible, as TA638 used time-to-death utilities in their base-case, which are not directly comparable.

C10. Subsequent treatment

In the CS model, 15% of the patients received subsequent therapies, in which 5% patients received a re-challenge with the first line and the rest was split equally among the two second-line therapies – topotecan and CAV (with cyclophosphamide, doxorubicin, and vincristine). In the CS document, it was mentioned that this was informed by the clinical experts' advice elicited to support the atezolizumab appraisal (TA638) to represent UK clinical practice. Could the Company please share the clinical expert's engagement details on the subsequent therapy distribution in ES-SCLC patients? Could the Company please also explain the difference in subsequent therapy distributions between the trials included in this evidence submission for serplulimab and its comparators, and which is most relevant to clinical practice in England?

The distribution of patients receiving different subsequent therapies in the CS model was informed by TA638 and more specifically, the company's response to the ERG's clarification question B10.a. in TA638. In TA638, the company, referencing an advisory board held in March 2019, stated that: *"Advice from UK practising oncologists is that after completion of first-line treatment, approximately 10-20% patients move to second-line treatment once their disease has relapsed. The pathway for treatment at second line is not standardised, however, in general in UK clinical practice patients are treated by either a re-challenge with their first-line chemotherapy, treated with topotecan, or treated with cyclophosphamide, doxorubicin, and vincristine (CAV). There is variation between treatment centres in terms of the proportion of patients receiving each of these treatments. The consensus from the advisory board meeting in March 2019 was that a third of patients would be attributed to each of the three predominant second-line therapies: re-challenge, topotecan and CAV. It is important*

to note that although topotecan is recommended by NICE for relapsed ES-SCLC, few patients receive topotecan as it is not regarded as an efficacious treatment in this setting by this group of advisors." This was deemed the most relevant representation of the second-line therapies that patients would receive in clinical practice in England and therefore included in the CS model.

C.11 Vial sharing

The EAG were unable to identify the details of the clinical opinion used to validate the assumption of no vial sharing for serplulimab used within the Company base case in Appendix M. Could the Company please provide a summary of the clinical opinion on vial sharing for serplulimab?

The Company did not elicit any clinical opinion on vial sharing and wish to correct their submission by removing this statement.

C.12 TTD model

Priority question: Cell Serplulimab!W75 suggests 7.9% of the cohort dies in the next 5 weeks while on treatment. Cell Serplulimab!V75 suggests 1.4% of the cohort dies in the 5 to 15 weeks while on treatment. On the face of it, that does not seem to make sense. In addition, the sum of those who die in the subsequent 5 weeks does not seem to sum to 7.9% or get close to it. Assuming it is correct, could the Company please explain this? If the formulae are in fact incorrect, could the Company please ensure the formulae across all of the TTD model states are correct?

The TTD formulae have been updated. The new formulae were validated by manually checking that the proportions in each TTD state in each cycle were equivalent to the sum of those dying in subsequent cycles according to the TTD state e.g., SUM(Serplulimab!O75:O80) = SUM(Serplulimab!W75+ Serplulimab!AA75) (= 4.4%).

C.13 Severity modifier

In Section 3.6 of Document B it states that serplulimab qualifies for a QALY severity weighting of 1.2. Please can you update this section to include the relevant details outlined in the severity section of the submission template, i.e. calculations and tables (for more information on severity see NICE's health technology evaluations

manual section 6.2.12 to 6.2.22 and TSD 23: A guide to calculating severity shortfall for NICE evaluations). In addition, please clarify how the severity weighting has been incorporated into the cost-effectiveness results. QALY weights should be applied to the incremental QALY gains, and ICERs should be presented with and without the severity modifier applied.

The Company used the R shiny tool to compute the number of remaining QALYs and the proportional and absolute shortfall applicable to the submission (QALY Shortfall Calculator). These are reproduced below. QALYs accumulated in the atezolizumab arm are 1.25 (discounted at 3.5% across a lifetime horizon). The mean age used in the model is 62, and 17.8% of patients are female (based on ASTRUM-005). Discounted QALYs in the general population are calculated using 2017-2019 life tables and EQ-5D tariffs (33-35). Table 30 provides additional information into the calculation of the severity modifier. Based on Table 31, serplulimab is eligible for a multiplier of 1.2. The multiplier is applied to the incremental discounted QALYs in the model. Full results of the pairwise analysis are presented in the tables below, with and without the severity modifier.

Table 30: Parameters used in the calculation of the severity modifier

Parameter			Value
Patient age			62
% female			17.8
QALYs with disease			1.25
	Male	**Female**	**Overall**
Life expectancy	21.3	23.8	21.75
QALYs	17.07	17.91	17.22
Discounted QALYs	11.86	12.16	11.91
Absolute shortfall	-		11.91 – 1.25 = 10.66
Proportional shortfall	-		10.66/11.91 = 0.89

Abbreviations: *QALY, quality-adjusted life year.*

Table 31: Absolute and proportional shortfall criteria for severity modifier

Multiplier	Proportional shortfall	Absolute shortfall
x1	<0.85	<12
x1.2	0.85–0.95	12–18
x1.7	≥0.95	≥18

Table 32: Base-case results, pairwise (list price) – with severity modifier of 1.2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	£79,427	2.47	2.10				
Atezolizumab	£54,671	1.74	1.50	£24,756	0.74	0.60	£41,447
Carboplatin-etoposide	£21,561	1.38	1.21	£57,866	1.09	0.89	£64,799

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

Table 33: Base-case results, pairwise (list price) – without severity modifier of 1.2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	£79,427	2.47	1.75				
Atezolizumab	£54,671	1.74	1.25	£24,756	0.74	0.50	£49,512
Carboplatin-etoposide	£21,561	1.38	1.01	£57,866	1.09	0.74	£78,197

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

Table 34: Base-case results, pairwise (PAS price) – with severity modifier of 1.2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	[redacted]	2.47	2.10				
Atezolizumab	£54,671	1.74	1.50	[redacted]	0.73	0.60	[redacted]
Carboplatin-etoposide	£21,561	1.38	1.21	[redacted]	1.09	0.89	[redacted]

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.*

Table 35: Base-case results, pairwise (PAS price) – without severity modifier of 1.2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	[redacted]	2.47	1.75				
Atezolizumab	£54,671	1.74	1.25	[redacted]	0.74	0.50	[redacted]
Carboplatin-etoposide	£21,561	1.38	1.01	[redacted]	1.09	0.74	[redacted]

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.*

Section D: Textual clarification and additional points

D1. Table 11, CS – potential textual errors

In Table 11 of Document B (p. 47),(3) under ‘Treatment discontinued’, there are two ‘progressive disease’ rows. Also, data in the text are for adverse events (AEs) whereas these data in the Table are written for ‘Poor compliance of study drug administration’. Could the Company please detail any errors in this table?

Please see a corrected version of the table below.

	Serplulimab group	Placebo group	Total
Screened, n	-	-	894
Screen fail	-	-	309
Randomised, n	389	196	585

	Serplulimab group	Placebo group	Total
Did not receive any study treatment, n (%)	[redacted]	[redacted]	[redacted]
Treatment ongoing, n (%)	[redacted]	[redacted]	[redacted]
Treatment discontinued, n (%)	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Poor compliance of study drug administration	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Study terminated by sponsor	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Signed inform consent for post-PD treatment, n (%)	[redacted]	[redacted]	[redacted]
Ever received treatment (serplulimab/placebo) after progressive disease, n (%)	[redacted]	[redacted]	[redacted]
Discontinued the study, n (%)	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]
Study terminated by sponsor	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Completed study	[redacted]	[redacted]	[redacted]

D2. Accessibility of submitted documents

In the submitted file location: Appendix D > Clinical SLR references >ASTRUM-005, the EAG note that the following three documents cannot be opened. Could the Company please resend these:

- Henlius ASTRUM-005 updated ms_first draft_v2.0_17Apr2024_clean_STC_MPI_comments removed (1).pdf
- UPDATED analysis_ASTRUM-005 ESMO Asia.pdf
- POSTER _ASTRUM-005_2024 ASCO poster_MPI_May 17 2024.pdf

These references have been resent (11, 36, 37). In addition to the above, the Company have also provided the EMA Assessment Report (38).

D3. Page 100, CS: text clarification

The Company states, “For PFS and OS, a diagnostic plot of the log-cumulative hazard for TTOT against log-time for the ASTRUM-005 arms was assessed to test the proportional hazards assumption, as presented in Figure 27.”

Should this read, “For TTOT, a diagnostic plot of the log-cumulative hazard for TTOT against log-time for the ASTRUM-005 arms was assessed to test the proportional hazards assumption, as presented in Figure 27”?

The reworded sentence is correct.

D4. Page 109, CS: text clarification

“To account for the potential differences, AE probabilities in the atezolizumab arm in the model were calculated by applying the difference in probability of an AE in the atezolizumab arm vs. carboplatin-etoposide from IMpower133 to the AE probabilities in the carboplatin-etoposide arm from ASTRUM-005.”

Should this read, “To account for the potential differences, AE probabilities in the atezolizumab arm in the model were calculated by adding the difference in probability of an AE in the atezolizumab arm vs. carboplatin-etoposide from IMpower133 to the AE probabilities in the carboplatin-etoposide arm from ASTRUM-005.”

The reworded sentence is correct.

D5. Page 121, CS: text clarification

“Therefore, in the model base-case it is assumed that 85% of patients receive second-line therapy, with 5% receiving a re-challenge with their first-line chemotherapy (carboplatin-etoposide), 5% receiving oral topotecan, and 5% receiving CAV.” In the Excel model, it states that 85% of patients do not receive second-line therapy.

Should this read, “Therefore, in the model base-case it is assumed that 85% of patients do not receive second-line therapy, with 5% receiving a re-challenge with their first-line chemotherapy (carboplatin-etoposide), 5% receiving oral topotecan, and 5% receiving CAV.”

The reworded sentence is correct.

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Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346] – Addendum to clarification response

Durvalumab with etoposide + platinum-based chemotherapy has been fully incorporated as a comparator in the revised economic model. In line with clinical feedback for this assessment, platinum-based chemotherapy in all arms of the model, including the durvalumab with etoposide + platinum-based chemotherapy arm, is carboplatin and etoposide (carboplatin-etoposide). This addendum provides a description of the changes made to the economic model to incorporate this new comparator, the assumptions and methods, as well as a complete set of results.

Changes to the revised economic model

A summary of the changes made to the CS model in response to clarification to incorporate durvalumab with carboplatin-etoposide as a comparator is presented in Table 1. Following further review of the published final draft guidance for TA1041, the economic model has been updated to provide a more accurate reflection of the cost-effectiveness of serplulimab with carboplatin-etoposide vs. durvalumab with carboplatin-etoposide. A summary of the further updates made to the revised economic model is presented in Table 2. These model updates impact only the results of the comparison against durvalumab (i.e., they have no effect on the results of the comparisons against carboplatin-etoposide and atezolizumab with carboplatin-etoposide). The model contains executable deterministic and probabilistic sensitivity analyses against any of the selected comparators, and different scenarios can be investigated by changing the settings in the model sheet “Scenario setting”.

Table 1: Changes to the CS model in response to clarification

Model sheets	Change	Description
“Scenario Setting”, “Comparator arm 1”, “Comparator arm 2”	Addition of durvalumab as a comparator	• The model engines for the comparators (sheets “Atezolizumab” and “Carboplatin-etoposide”) have been renamed to “Comparator arm 1” and “Comparator arm 2” to reflect the increased flexibility in the revised model in selecting different comparators • The different comparators can be selected using the “OS/PFS Comparator 1” and “OS/PFS Comparator 2” dropdowns in the model sheet “Scenario setting”. Selecting the comparator in this way will automatically update the costs, efficacy, and safety inputs in each of

		the comparator engines based on the selected comparator. The formulae in the comparator engines (in columns AV:AZ, BB:BF, BI:BJ, BO, and cell AP16) have been updated to accommodate this increased flexibility
"OS inputs All patients", "OS inputs NonAsians", "OS inputs Conversion", "OS In model", "PFS inputs All patients", "PFS inputs NonAsians", "PFS inputs Conversion", "PFS In model", "TTOT inputs All patients", "TTOT inputs NonAsians", "TTOT inputs Conversion", "TTOT In model"	Added OS/PFS/TTOT extrapolations for durvalumab	• The OS, PFS, and TTOT extrapolations for durvalumab have been added in a consistent way to the other comparators • OS, PFS, and TTOT extrapolations for the durvalumab arm were generated by applying HRs derived from the MAIC to the serplulimab survival curves. OS/PFS can also be modelled using independent models fitted to pseudo-IPD derived from CASPIAN. These can be selected using the "OS/PFS Comparator 1" and "OS/PFS Comparator 2" dropdowns in the model sheet "Scenario setting" • Added parameter estimates for the independent parametric models for durvalumab OS/PFS • Added HRs from the MAIC for durvalumab
"Cost inputs All patients", "Cost inputs Conversion", "AE inputs All patients", "AE inputs Conversion"	Added cost inputs for durvalumab	• Added drug acquisition costs inputs for durvalumab • Administration costs and resource use are assumed to be the same as serplulimab and atezolizumab • The rate of AEs in the durvalumab arm is assumed to be the same as serplulimab
"Scenario Setting", "OS inputs All patients", "OS inputs NonAsians", "OS inputs Conversion", "OS In model", "PFS inputs All patients", "PFS inputs NonAsians", "PFS inputs Conversion", "PFS In model", "TTOT inputs All patients",	Added joint spline models	• Joint spline models for OS, PFS, and TTOT, based on ASTRUM-005, have been added into the model for the serplulimab and carboplatin-etoposide arms. These can be selected using the "OS/PFS Serplulimab", "OS/PFS Comparator 1" and "OS/PFS Comparator 2" dropdowns in the model sheet "Scenario setting". Proportional hazards models with 1, 2 and 3 knots have been added. The number of knots is selected using the "Parametric fit OS" and "Parametric fit PFS" dropdowns in the model sheet "Scenario setting". • Parameter estimates for the joint spline models have been added and the survival extrapolations fully incorporated in a consistent way to the existing models

"TTOT inputs NonAsians", "TTOT inputs Conversion", "TTOT In model"		
"Serplulimab", "Comparator arm 1", "Comparator arm 2"	Updated TTD formulae	• The formulae in columns T:AA in the model engines have been updated to correct the TTD model states
"OWSA"	Update and re-run OWSA	• Updated the OWSA to incorporate the new model inputs (durvalumab and spline models) • Re-run OWSA
"Probabilistic sensitivity"	Re-run PSA	• Re-run PSA
"KM plots"	Added KM plots from CASPIAN	• Addition of KM plots for durvalumab and carboplatin-etoposide based on digitised curves from CASPIAN.
"OS In model", "PFS In model"	Added hazard ratio plots	• Added hazard ratio plots for OS and PFS
"Controls"	Updated controls	• Updated the "Controls" sheet to reflect additional model inputs and the increased flexibility in selecting different comparators

***Abbreviations**: AE, adverse event; HR, hazard ratio; KM, Kaplan-Meier; Matching-adjusted indirect comparison; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; TTD, time to death; TTOT, time to off treatment; RDI, relative dose intensity.*

Table 2: Updates to the revised economic model

Model sheets	Change	Description
"Cost inputs All patients", "Cost inputs Conversion"	Updated durvalumab monotherapy to be administered once every 4 weeks.	• The cost engine in the "Cost inputs All patients" sheet has been updated to reflect the 4-weekly dosing frequency of durvalumab monotherapy. A new table has been added in Cost inputs All patients!AZ156:BB420. • The formulae in columns U and AN in the model sheet "Cost inputs Conversion" have also been updated.
"Cost inputs All patients"	Added RDI for durvalumab	• The RDI reported in TA1041 has been added to the table "relative dosing intensity" in the model sheet "Cost inputs All patients". The formulae in Cost inputs All patients!I35 and J35 have been updated.
"AE inputs Conversion"	Error correction	• Corrected errors in the formulae of AE inputs Conversion!I347:I367.

***Abbreviations**: AE, adverse event; RDI, relative dose intensity.*

Assumptions and methods

Time-to-event outcomes (OS/PFS/TTOT extrapolations) for durvalumab

In the base case, OS, PFS, and TTOT extrapolations for the durvalumab arm were generated by applying HRs derived from the MAIC to the serplulimab survival

curves. Full details of the MAIC are provided in the CS and in the Company's response to clarification question B.8.

OS and PFS for the durvalumab arm can also be modelled using independent parametric models fitted to pseudo-IPD derived from the CASPIAN trial. Kaplan-Meier curves from the CASPIAN trial were digitised for the durvalumab arm using the software DigitizeIt version 2.5 and pseudo-IPD was reconstructed using the IPDfromKM software from trialdesign.org. This software uses the Liu et al. methodology, which is based on the Guyot et al. algorithm (Guyot et al., 2012, Liu et al., 2021a). This algorithm assumes a constant rate of censoring over time when simulating IPD.

These alternative methods of modelling OS and PFS can be selected using the "OS/PFS Comparator 1" and "OS/PFS Comparator 2" dropdowns in the model sheet "Scenario setting".

Dosing and time on treatment for durvalumab

Durvalumab with carboplatin-etoposide is modelled in line with the dosing schedule of the CASPIAN trial as described in TA1041. Durvalumab is given at a fixed dose of 1,500mg on Day 1 of every 3-week cycle until loss of clinical benefit or unacceptable toxicity. Carboplatin and etoposide are administered using the same dose and frequency as the serplulimab arm (AUC 5mg/mL on Day 1 of each 3-week cycle for 4 cycles of carboplatin; 100mg/m² on Days 1, 2, and 3 of each 3-weekly cycle for 4 cycles of etoposide). In the same way as serplulimab and atezolizumab, patients could continue with durvalumab monotherapy post-progression. Therefore, time on treatment was modelled in the same way using time to off treatment (TTOT) curves, with HRs from the MAIC informing the TTOT curve for durvalumab. However, durvalumab monotherapy is administered every 4 weeks, as opposed to once every 3 weeks for serplulimab/atezolizumab monotherapy. Relative dose intensity (RDI) is applied to account for missed doses. For the durvalumab arm, the RDI (95.4%) was sourced from TA1041.

Adverse events for durvalumab

In the durvalumab arm, the weekly probabilities of AEs included in the model, and hence the associated disutility and costs, are assumed to be the same as the serplulimab arm.

Drug acquisition costs for durvalumab

The drug acquisition costs for durvalumab were sourced from the BNF (£2,466.00 per 500mg/10mL vial). Durvalumab is given at a fixed dose of 1,500mg. The drug cost per treatment cycle for the combination regimen was assumed to be equal to the sum of the individual drugs' costs included in the combination regimen, with RDI applied to the individual drugs. Therefore, the total cost per 3-weekly treatment cycle for the durvalumab with carboplatin plus etoposide regimen was £7,106.88 (durvalumab: £7,059.60; carboplatin: £29.57; etoposide: £17.71). The total cost per 4-weekly treatment cycle with durvalumab monotherapy was £7,059.60.

Additional costs for durvalumab – administration, resource use, and subsequent treatment

Unit costs associated with treatment administration and healthcare resource use were assumed to be the same as the serplulimab and atezolizumab arms. Furthermore, the proportion of patients receiving each subsequent therapy in the durvalumab arm was assumed to be equivalent to the other treatment arms in the model.

Results

Base case deterministic results

Base-case deterministic results for serplulimab with carboplatin-etoposide compared with durvalumab with carboplatin-etoposide at list price are reported in Table 3 and Table 5, and the results at PAS price are presented in Table 4 and Table 6. In the pairwise analysis, serplulimab dominates durvalumab at list price and PAS price, yielding a lower total cost and greater total QALYs.

Table 3: Base-case results, pairwise (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)

Serplulimab	£79,427	2.47	2.10				
Durvalumab	£80,009	1.87	1.64	-£582	0.60	0.46	Dominant
Atezolizumab	£54,671	1.74	1.50	£24,756	0.74	0.60	£41,447
Carboplatin-etoposide	£21,561	1.38	1.21	£57,866	1.09	0.89	£64,799

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

Table 4: Base-case results, pairwise (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Serplulimab	[redacted]	2.47	2.10				
Durvalumab	£80,009	1.87	1.64	[redacted]	0.60	0.46	[redacted]
Atezolizumab	£54,671	1.74	1.50	[redacted]	0.74	0.60	[redacted]
Carboplatin-etoposide	£21,561	1.38	1.21	[redacted]	1.09	0.89	[redacted]

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

Table 5: Base-case results, full incremental analysis (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Durvalumab	£80,009	1.64			
Serplulimab	£79,427	2.10	£582	-0.46	-£1,252
Atezolizumab	£54,671	1.50	£24,756	0.60	£41,447
Carboplatin-etoposide	£21,561	1.21	£33,110	0.30	£111,968

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

Table 6: Base-case results, full incremental analysis (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Durvalumab	£80,009	1.64			
Atezolizumab	£54,671	1.50	£25,338	0.13	£190,890
Serplulimab	[redacted]	2.10	[redacted]	-0.60	[redacted]
Carboplatin-etoposide	£21,561	1.21	[redacted]	0.89	[redacted]

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.*

Exploring uncertainty

Uncertainty was assessed by means of deterministic and probabilistic sensitivity analyses, as well as scenario analyses.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with key model inputs. PSA results for 1,000 iterations are presented in Table 7 and Table 8 at list and PAS price, respectively. The mean

incremental costs and QALYs of serplulimab compared with durvalumab were calculated to estimate the probabilistic ICER. At both list price and PAS price, the mean incremental costs and QALYs in the probabilistic analysis were comparable with the deterministic results, with a dominant probabilistic ICER at both list and PAS price.

Table 7: Probabilistic results vs. durvalumab (list price)

	Serplulimab	Durvalumab	Incremental	ICER
Total costs (£)	£80,948	£84,080	-£3,133	Dominant
Total QALYs	2.10	1.69	0.41	

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

Table 8: Probabilistic results vs durvalumab (PAS price)

	Serplulimab	Durvalumab	Incremental	ICER
Total costs (£)	[redacted]	£84,442	[redacted]	[redacted]
Total QALYs	2.10	1.68	0.42	

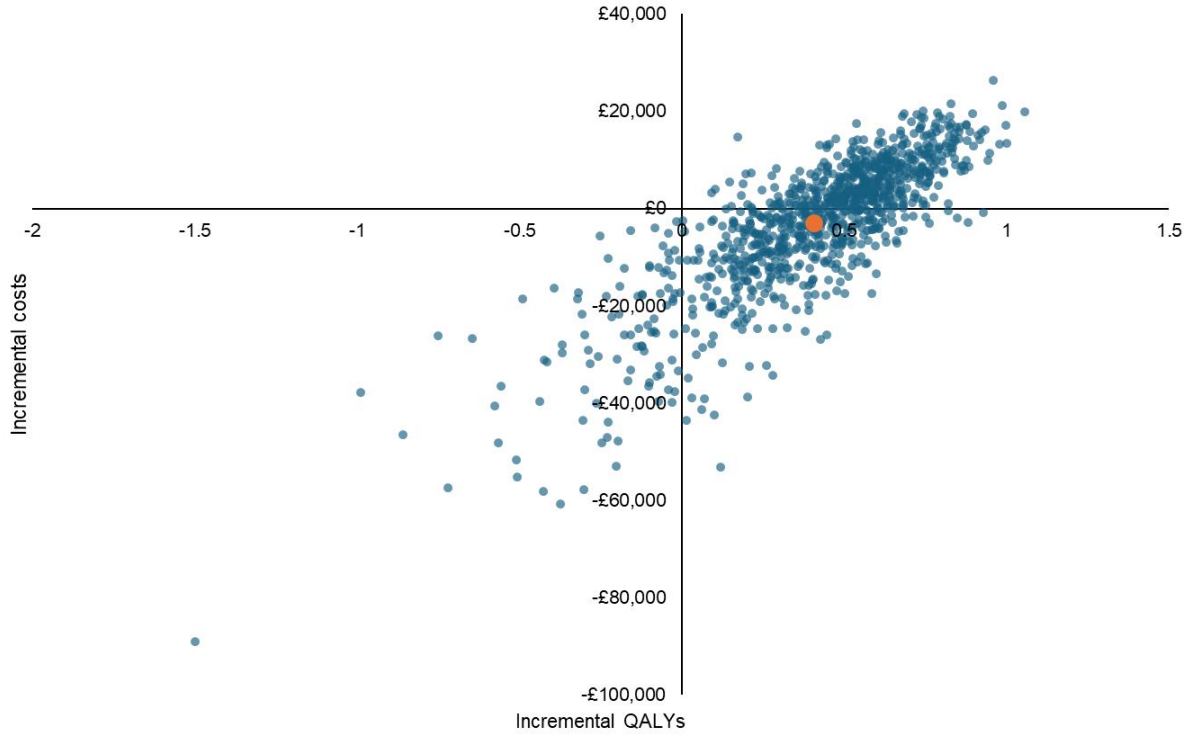
Abbreviations: *QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio;*

Table 9: Probability of cost-effectiveness vs durvalumab at different willingness to pay thresholds

WTP threshold (£/QALY)	Probability of cost-effectiveness (%)	
	List price	PAS price
30,000	98.9	[redacted]
50,000	99.0	[redacted]
100,000	97.3	[redacted]
150,000	95.5	[redacted]
200,000	94.5	[redacted]

Abbreviations: *PAS, patient access scheme; QALY: quality-adjusted life year; WTP, willingness-to-pay*

Figure 1: Cost-effectiveness plane from PSA (1,000 simulations) vs durvalumab (list price)

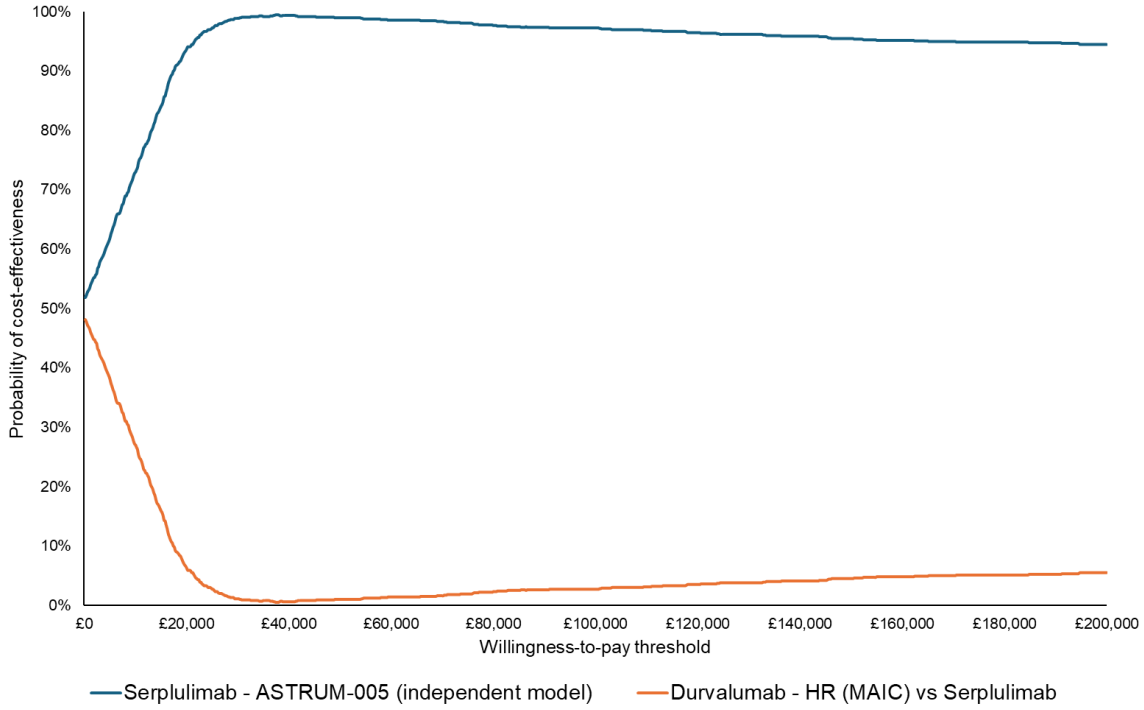


Abbreviations*: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.*

[redacted]

***Abbreviations**: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.*

Figure 2: Cost-effectiveness acceptability curve vs durvalumab (list price)



***Abbreviations**: HR, hazard ratio; MAIC, matched-adjusted indirect comparison*

[redacted]

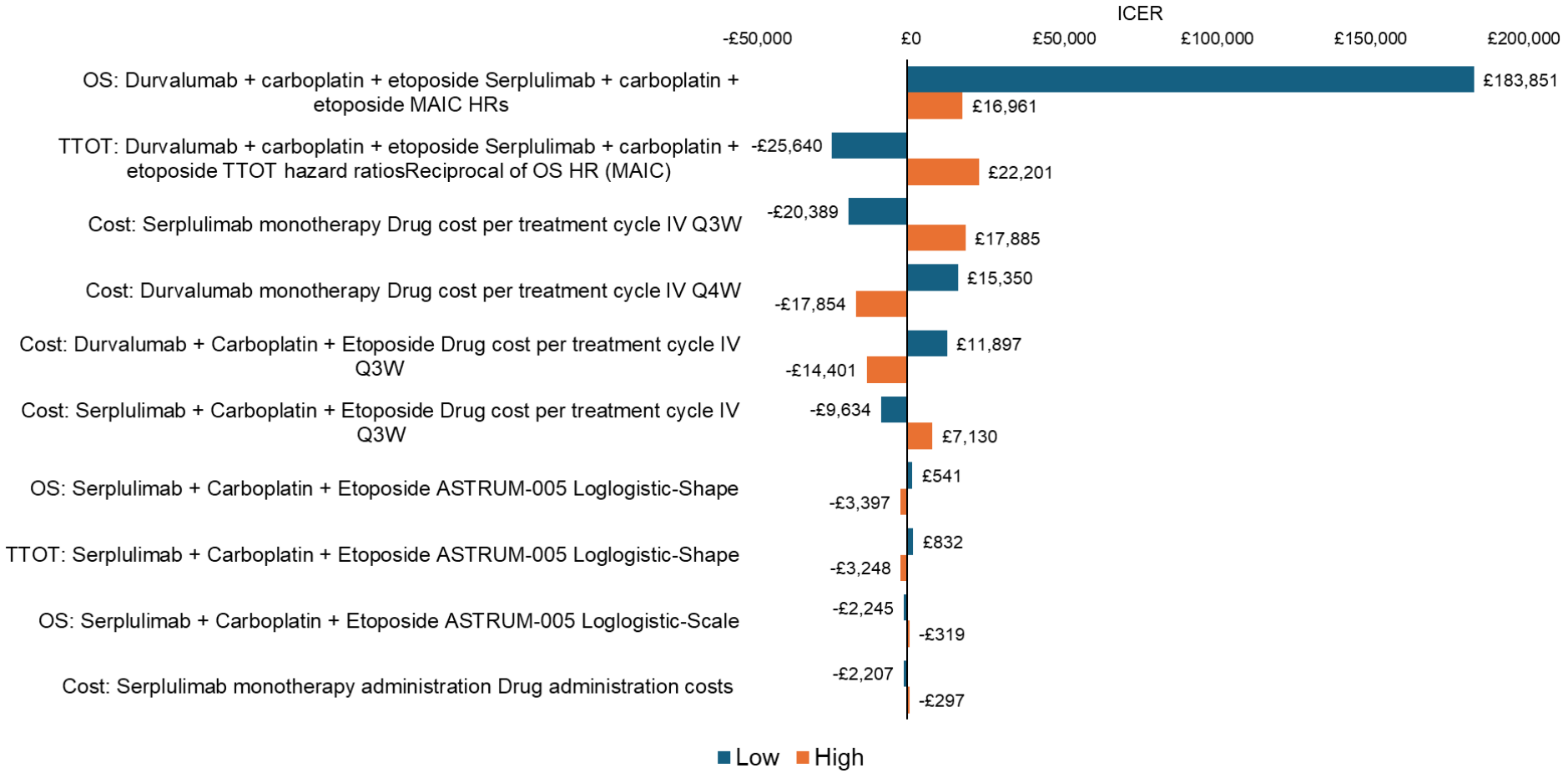
***Abbreviations**: HR, hazard ratio; MAIC, matched-adjusted indirect comparison*

Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were performed to explore the effect of uncertainty associated with varying individual model inputs. The inputs with the greatest impact on the ICER against durvalumab are presented in descending order as a tornado plot in Figure 3. The ICER was most sensitive to changes in the HR derived from the MAIC (durvalumab vs serplulimab, HR = [redacted] used to inform the OS extrapolation in the durvalumab arm, particularly when the HR was varied to the lower confidence interval value ([redacted]). Otherwise, the ICER was relatively insensitive to variations in the model

inputs with treatment costs and time on treatment parameters having the largest impact on the ICER.

Figure 3: Tornado plot of sensitive parameters in the DSA vs durvalumab (list price)



Abbreviations: *HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenous; MAIC, matched-adjusted indirect comparison; OS, overall survival; Q3W; every 3 weeks; TTOT, time to off treatment*

Scenario analysis

Different scenarios were performed on the base-case to assess the impact of key assumptions in the model on the results. The scenarios presented include different parametric models for OS, PFS, and TTOT extrapolation, alternative utility derivation methods, different sources for AEs, and scenarios around the long-term treatment effect of serplulimab. A description of the scenarios and the results (incremental QALYs, costs, and ICER) against durvalumab, at serplulimab list and PAS price, are presented in Table 10 and Table 11, respectively. Serplulimab is dominant compared to durvalumab in all modelled scenarios at PAS price, as well as the majority of scenarios at list price, with none of the ICERs exceeding £30k/QALY.

Table 10: Summary of scenario analysis vs durvalumab (list price)

Scenario	Description	Value	Incremental QALYs	Incremental costs	ICER (£/QALY gained)
Base-case			0.46	-£582	Dominant
OS parametric model	Scenarios using alternative parametric models are presented.	Exponential	0.37	-£436	Dominant
		Weibull	0.33	-£1,294	Dominant
		Gamma	0.32	-£1,626	Dominant
		Log-normal	0.47	-£365	Dominant
		Gompertz	0.52	£1,043	£2,016
		Gen. Gamma	0.46	-£437	Dominant
PFS parametric model	Scenarios using alternative parametric models are presented.	Exponential	0.46	-£573	Dominant
		Weibull	0.46	-£568	Dominant
		Gamma	0.46	-£586	Dominant
		Log-normal	0.46	-£605	Dominant
		Gompertz	0.48	-£561	Dominant
		Gen. Gamma	0.47	-£625	Dominant
TTOT parametric model	Scenarios using alternative parametric models are presented.	Exponential	0.47	-£3,253	Dominant
		Weibull	0.46	-£663	Dominant
		Gamma	0.47	-£1,425	Dominant
		Log-normal	0.46	£748	£1,619
		Gompertz	0.46	£3,462	£7,560
		Gen. Gamma	0.46	-£327	Dominant
Data source for durvalumab extrapolation	Scenarios with alternative approaches are presented.	HR from MAIC (before matching)	0.35	-£4,666	Dominant
		Independent model fitted to pseudo-IPD from CASPIAN	0.39	£183	£465
Time horizon (years)	Scenarios with shorter time horizons are presented.	5	0.26	-£2,453	Dominant
		10	0.38	-£1,185	Dominant
		15	0.44	-£755	Dominant
Utility derivation method	Scenarios using the time to death approach and progression status by treatment status are presented. Scenarios using the time to death approach and progression status by treatment status are presented.	Time to death	0.47	-£582	Dominant
		Progression status by on/off treatment	0.44	-£582	Dominant
Adverse events	Scenarios using AEs from the non-Asian	Exclude AE disutilities	0.48	-£582	Dominant

	population (more conservative) and excluding additional AE disutilities are presented.	Non-Asian AEs	0.47	-£642	Dominant
Treatment waning	Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented.	Immediate loss of treatment effect at 5 years	0.39	-£1,118	Dominant
		Gradual loss of treatment effect from 5-10 years	0.43	-£840	Dominant
Vial sharing assumed for serplulimab	A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	0.46	-£7,705	Dominant

Abbreviations: *AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; MAIC, matched-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTOT, time to off treatment*

Table 11: Summary of scenario analysis vs durvalumab (PAS price)

Scenario	Description	Value	Incremental QALYs	Incremental costs	ICER (£/QALY gained)
Base-case			0.46	[redacted]	Dominant
OS parametric model	Scenarios using alternative parametric models are presented.	Exponential	0.37	[redacted]	Dominant
		Weibull	0.33	[redacted]	Dominant
		Gamma	0.32	[redacted]	Dominant
		Log-normal	0.47	[redacted]	Dominant
		Gompertz	0.52	[redacted]	Dominant
		Gen. Gamma	0.46	[redacted]	Dominant
PFS parametric model	Scenarios using alternative parametric models are presented.	Exponential	0.46	[redacted]	Dominant
		Weibull	0.46	[redacted]	Dominant
		Gamma	0.46	[redacted]	Dominant
		Log-normal	0.46	[redacted]	Dominant
		Gompertz	0.48	[redacted]	Dominant
		Gen. Gamma	0.47	[redacted]	Dominant
TTOT parametric model	Scenarios using alternative parametric models are presented.	Exponential	0.47	[redacted]	Dominant
		Weibull	0.46	[redacted]	Dominant
		Gamma	0.47	[redacted]	Dominant
		Log-normal	0.46	[redacted]	Dominant
		Gompertz	0.46	[redacted]	Dominant
		Gen. Gamma	0.46	[redacted]	Dominant
Data source for durvalumab extrapolation	Scenarios with alternative approaches are presented.	HR from MAIC (before matching)	0.35	[redacted]	Dominant
		Independent model fitted to pseudo-IPD from CASPIAN	0.39	[redacted]	Dominant
Time horizon (years)	Scenarios with shorter time horizons are presented.	5	0.26	[redacted]	Dominant
		10	0.38	[redacted]	Dominant
		15	0.44	[redacted]	Dominant
Utility derivation method	Scenarios using the time to death approach and progression status by treatment status are presented. Scenarios using the time to death approach and progression status by treatment status are presented.	Time to death	0.47	[redacted]	Dominant
		Progression status by on/off treatment	0.44	[redacted]	Dominant
Adverse events	Scenarios using AEs from the non-Asian population (more conservative) and	Exclude AE disutilities	0.48	[redacted]	Dominant
		Non-Asian AEs	0.47	[redacted]	Dominant

	excluding additional AE disutilities are presented.				
Treatment waning	Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented.	Immediate loss of treatment effect at 5 years	0.39	[redacted]	Dominant
		Gradual loss of treatment effect from 5-10 years	0.43	[redacted]	Dominant
Vial sharing assumed for serplulimab	A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	0.46	[redacted]	Dominant

Abbreviations: *AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; MAIC, matched-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTOT, time to off treatment*

Overall assessment of uncertainty

Overall, the results of the PSA, DSA, and scenario analysis are relatively congruent in demonstrating that serplulimab with carboplatin-etoposide is cost-effective compared to durvalumab with carboplatin-etoposide at both list price and PAS price. In the PSA, the probabilistic ICER was dominant at both list and PAS price, with a probability of cost-effectiveness at a willingness to pay threshold of £30k/QALY of 98.9% and [redacted] at list and PAS price, respectively. In the DSA, the key driver of cost-effectiveness was the HR derived from the MAIC used to inform the OS extrapolation in the durvalumab arm. Otherwise, the ICER was relatively insensitive to variations in the model inputs, with no other input variations leading to an ICER exceeding £30k/QALY. Finally, serplulimab is dominant compared to durvalumab in all modelled scenarios at PAS price, as well as the majority of scenarios at list price, with none of the ICERs in the scenario analysis exceeding £30k/QALY.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

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) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1820 Advisory board Honoraria) - Roche (1 year funding of GLCC project; £10,000 for Lung cancer Awareness Month initiative) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Novocure (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project) - Astra Zeneca (£30,000 for 1 year funding of GLCC project; £500 for Meeting Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker honorarium) - Regeneron (£30,000 for 1 year funding of GLCC project) - Gilead (£30,000 for 1 year funding of GLCC project; £460 speaker honorarium) - Merck (£30,000 for 1 year funding of GLCC project) - J &J (£20,000 for Lung Cancer Awareness Month initiative)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
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. Durvalumab in combination with etoposide and platinum based chemotherapy in this indication is currently being appraised in NICE [TA662]). We understand that there are no direct comparisons of Serplulimab with either of these immunotherapy drugs in this 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 do not have any information or data, specific to this technology, beyond that which is already publicly available. Amongst patients with previously untreated extensive stage small cell lung cancer, Serplulimab plus chemotherapy significantly improved overall survival compared with chemotherapy alone.

Disadvantages of the technology

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

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 relatively few advances in treatment over decades. • The outcome from current standard treatment, for this patient group, is poor. There is massive unmet need. • •

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

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

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of Respiratory Nurses
3. Job title or position	Lung Cancer Specialist Nurse
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of Respiratory Nurses (ARNS) was established in 1997 as a nursing forum to champion the specialty respiratory nursing community, promote excellence in practice, and influence respiratory health policy. ARNS also works to influence the direction of respiratory nursing care.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Stop further progression of disease, improve functional status, improve quality of life, improve symptoms.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction of disease burden, no further progression of disease following commencement of treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Small cell lung cancer patients have limited treatment options. The more treatments available for patients, the better.

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

9. How is the condition currently treated in the NHS?	Platinum based chemo, atezolizumab with carboplatin and etoposide
9a. Are any clinical guidelines used in the	683

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.)	Currently well defined. Some patients receive alternative treatments due to fitness.
9c. What impact would the technology have on the current pathway of care?	Provide alternative treatment options.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	It will provide alternative treatment options but will be given in a similar way
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics only.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of oncology nurses to administer the drug. Education to oncologists and pharmacists to understand the regime and protocol. Resource in pharmacy to produce the correct drug mix for patients.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	May depend on performance status and comorbidities

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Should be comparable to administering current medications, will involve additional trips to hospital and additional appts in chemo clinic.

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?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Progression free survival may also bring increased quality of life
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	yes
16a. Is the technology a 'step-change' in the management of the condition?	No

16b. Does the use of the technology address any particular unmet need of the patient population?	No
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?	Side effects can be difficult for patients but can be managed with support.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival, life expectancy, quality of life.
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	Not currently used so not sure

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. How do data on real-world experience compare with the trial data?	n/a

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	No

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Small cell lung cancer is hard to treat so more treatment options are needed • • • •

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

Clinical expert statement

Information on completing this form

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

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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

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

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Thursday 12 June 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

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

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

1. Your name	Dr Shobhit Baijal
2. Name of organisation	University Hospitals Birmingham NHS Trust
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with extensive-stage small-cell lung cancer? ☒ A specialist in the clinical evidence base for extensive-stage small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
8. What is the main aim of treatment for extensive-stage small-cell lung cancer?	Prolong survival and improve quality of life

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in OS of greater than 3 months compared with soc
10. In your view, is there an unmet need for patients and healthcare professionals in extensive-stage small-cell lung cancer?	Yes – significant unmet need to improve survival outcomes
11. How is untreated extensive-stage small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Atezolizumab or Durvalumab plus platinum / etoposide chemotherapy Current technology would be an alternative treatment option
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	-would be used withing the same healthcare resources -SACT delivery units -no added investment required

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Within the limitations of cross trial comparisons the OS benefit is more pronounced than that seen with Atezolizumab or Durvalumab
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	n/a
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The same as current soc
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment to continue till loss of clinical benefit
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	n/a

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	It is a step change compared to carboplatin and etoposide which were the the comparator in the clinical trial
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	n/a
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	OS was the most important outcome measure

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	n/a
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA638, TA1041]?	n/a
23. How do data on real-world experience compare with the trial data?	n/a
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	n/a

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

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

Click or tap here to enter text.

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Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

Produced by Newcastle University

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Contributions of authors: Katie Thomson led the clinical effectiveness team and together with Julia Whitehall and Aalya Al-Assaf carried

	out the assessment of clinical effectiveness and wrote the first draft of the clinical effectiveness sections of the report; Madeleine Still and Sonia Garcia Gonzalez-Moral assessed the literature searches and wrote the critique of these; Gill Norman edited and commented on the clinical effectiveness and information sections. Stephen Rice led the health economics team and together with Lakshmi Jayachandran carried out the assessment of cost effectiveness wrote the critique of these and carried out the economic modelling, supported by Najmeh Moradi and Tumi Sotire. Gurdeep S Sagoo edited and commented on the report and was overall project lead.
Acknowledgements:	The authors are grateful to Dr Tim Benepal for clinical advice and to Dr Nick Meader for advice on the MAICs.
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Report key:	Confidential data are redacted ([redacted]) throughout the report.

Abbreviations

AE	Adverse events
AUC	Area under the curve
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BSA	Body surface area
CAV	Combination chemotherapy regimen comprising, cyclophosphamide plus doxorubicin plus vincristine
CEM	Cost-effectiveness model
CI	Confidence interval
CNS	Central nervous system
CPS	Combined positive score
CS	Company submission
CSR	Clinical study report
CUA	Cost-utility analysis
D	Day
DOR	Duration of response
DSA	Deterministic Sensitivity Analysis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG PS	European Cooperative Oncology Group performance status
ECOG	Eastern Cooperative Oncology Group
EEPRU	Policy Research Unit in Economic Methods of evaluation in Health and Social Care Interventions
EMA	European Medicines Agency
eMIT	Electronic Marketing Information Tool
EORTC QLQ	European Organisation for Research and Treatment Quality of Life questionnaire
EOT	End of treatment
EP	Etoposide plus either cisplatin or carboplatin
ESMO	European Society of Medical Oncology
ESS	Effective sample size
ES-SCLC	Extensive Stage-Small Cell Lung Cancer
EuroQOL	EuroQol group
HCHS	Hospital and Community Health Services
HLX10	Serplulimab
HR	Hazard ratio

HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
iRECIST	Immune-based Response Evaluation Criteria in Solid Tumors
IRRC	Independent Radiology Review Committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IxRS	Interactive Voice/Web Response System
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
Mb	Megabase
mDoR	Median duration of response
MeSH	Medical subject headings
ML-NMR	Multilevel-network meta regression
N	Sample size
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not recorded
OLE	Open-label extension
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
P	Probability value
PAS	Patient access scheme
PCI	Prophylactic cranial irradiation
PD	Progressed disease
PD1	Programmed cell death protein 1
PDL1	Programmed Death-Ligand 1
PfC	Points for clarification

PFS	Progression-free survival
PFS2	Progression free survival-2
PICOS	Population, Intervention, Comparator, Outcome, and Study type
PPS	Per protocol set
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient reported outcomes
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Every three weeks
QALY	Quality adjusted life year
QLQ-LC13	Quality of Life Questionnaire Lung Cancer 13
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse events
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOD	Sum of diameters
TA	Technology Assessment
TEAE	Treatment emergent adverse events
TPS	Tumour proportion score
TTD	Time to death
TTOT	Time-to-off treatment
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

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1 EXECUTIVE SUMMARY

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

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 presents the model outcomes. Section 1.3 summarises all key issues identified by the EAG relating to clinical effectiveness and cost-effectiveness. Section 1.4 summarises the EAG's preferred assumptions and ICERs.

Further detail regarding key and non-key issues are described in the main EAG Report (Sections 2 to 6).

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

1.1 Overview of the EAG's key issues

Table 1.1: Summary of EAG's key issues

Issue number	Brief summary of issue	Report section(s)
1	Company's trial and indirect treatment comparison (ITC) results may not be generalisable to the National Health Service (NHS) patient population.	3.6.1, 3.7.1, 3.7.2
2	Poor fit of progression-free survival (PFS) and overall survival (OS) parametric models for serplulimab and carboplatin + etoposide to the Kaplan-Meier data.	4.2.3.1
3	Assuming constant hazard ratios for OS for atezolizumab versus serplulimab and for durvalumab versus serplulimab over the duration of the model.	4.2.3.2
4	Poor fit of time-to-off treatment (TTOT) parametric model for serplulimab and carboplatin + etoposide to the Kaplan-Meier curves well.	4.2.6.1.1
5	Lower average body weight and height in ASTRUM-005 in comparison with England clinical practice.	4.2.6.3
Abbreviations: EAG = Evidence Assessment Group; ITC = indirect treatment comparison; NHS = National Health Service; OS = overall survival; PFS = progression-free survival; TOTT = time-to-off treatment		

1.2 Overview of key model outcomes

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

Overall, the technology is modelled to affect QALYs by:

- Increasing median life years;
- Increasing time in the PFS and progressed disease (PD) states;
- Increasing the adverse events due to longer time on treatment.

Overall, the technology is modelled to affect costs by:

- The time on treatment (acquisition and admin);
- Increasing the adverse events due to longer time on treatment;
- The number of patients receiving subsequent treatment;
- The delayed occurrence of palliative care costs.

Based on the EAG's assessment, the modelling assumptions that have the greatest effect on the ICER are:

- The parametric curves selected for OS for serplulimab and carboplatin + etoposide;
- The parametric curve selected for TTOT for serplulimab;
- The assumption that the OS HRs serplulimab vs atezolizumab, and for serplulimab vs. durvalumab derived from MAICs are constant for the duration of the model;
- The average weight and height of patients with ES-SCLC in England matches the average weight and height in England of 65-74 year olds;
- The EQ-5D utility estimates for PD and PFS from ASTRUM-005 are generalisable to the England ES-SCLC population.

1.3 Description of the EAG's key clinical and economic issues

Table 1.2: Key issue [1] Background characteristics of trial participants may not reflect characteristics of those that would be seen in English clinical practice

Report section	3.6.1, 3.7.1, 3.7.2
Description of issue and why the EAG has identified it as important	The clinical effectiveness evidence for serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (ES-SCLC) is derived from the ASTRUM-005, IMpower133, and CASPIAN trials. While the trials used similar designs and a common comparator, permitting the generation of two separate matching-adjusted indirect comparisons (MAICs), there are differences within and between trial settings. These differences are reflected in the included patient demographics and subsequent treatment after disease progression, which differs from the NHS patient population and United Kingdom (UK) clinical practice. There is some supportive evidence indicating different disease trajectories and outcomes for a subgroup of the Asian patient population, however, robust evidence directly ascertaining treatment effect modifiers is lacking. Therefore, the translatability of the evidence presented in this submission remains uncertain in relation to the NHS patient population.
What alternative approach has the EAG suggested?	Generation of a multilevel-network meta regression (ML-NMR) targeted towards the NHS patient population.
What is the expected effect on the cost effectiveness estimates?	It is unclear if the estimates of clinical benefit are likely to be applicable to a UK clinical setting. The expected impact on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	Some of the uncertainties surrounding the within and between-study variation and the precision of relative effect estimates between treatments may have been addressed through the application of a ML-NMR.
Abbreviations: EAG = Evidence Assessment Group; ES-SCLC = extensive stage-small cell lung cancer; MAIC = matching-adjusted treatment comparison; ML-NMR = Multilevel-network meta regression; UK = United Kingdom	

Table 1.3: Key issue [2] PFS and OS parametric models for serplulimab and carboplatin + etoposide did not fit the Kaplan-Meier curves well

Report section	4.2.3.1
Description of issue and why the EAG has identified it as important	The visual inspection of log-cumulative hazard plots produced by the Company were not straight and indicated that the proportional hazards assumption for PFS or OS could be rejected while the company selected the log-logistic parametric model fitted independently for PFS and OS for both serplulimab and carboplatin + etoposide. In response to the EAG concerns and in line with the NICE TSD14 guidance[1] recommending flexible modeling when the proportional hazards assumption is in doubt, the company presented spline models. The 2/3 knot were most

Report section	4.2.3.1
	closely fitted to the Kaplan-Meier curves. However, the company stated that, according to the clinical experts, who had been consulted on standard parametric extrapolations, long-term OS predictions appeared to be overestimated.
What alternative approach has the EAG suggested?	Due to uncertainty in long-term extrapolation, the EAG used the Company's 3 knot spline (flexible) model in the base case analysis with some adjustments in the OS and PFS for serplulimab and carboplatin + etoposide. For instance, for serplulimab, the EAG modelled a linear change in the HR for serplulimab vs carboplatin + etoposide from the HR at 3.5 years to 1 at 6.5 years to account for the Company clinical expert opinion of lower overall survival in the long-term. The EAG also conducted additional scenario analysis by applying an exponential curve in the OS for serplulimab after 3.5 years following the 3 knot spline model so that the model OS prediction at 10 years matched the company 10-year OS loglogistic model prediction. For carboplatin + etoposide, the 3 knot spline modelled was used until 18 months and then an exponential curve was fit to match the 10 year prediction. See Sections 4.2.3.1 and 6.1.1.4.
What is the expected effect on the cost effectiveness estimates?	The EAG combined the approach of fitting the 3 knot spline model to both TTOT, PFS and OS. In addition, the 3-year waning assumption applied from 3.5 years to 6.5 years was made for the HR for serplulimab vs carboplatin + etoposide, for serplulimab vs durvalumab and for serplulimab vs atezolizumab. Altogether, the result of these combined alternative (but related) assumptions was to change the ICER versus carboplatin + etoposide from [redacted] to [redacted]
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up evidence on PFS, OS and TTOT for serplulimab and carboplatin + etoposide would reduce uncertainty in the model predictions. Alternatively, PFS and OS specific mortality hazard rates could be estimated and a semi-Markov model developed, but the individual patient data for atezolizumab and durvalumab may not be available to conduct this analysis.
Abbreviations: EAG = Evidence Assessment Group; HR = hazard ratio; OS= overall survival; PFS = progression free survival; NICE = National Institute for Health and Care Excellence; TSD = technical support document; TTOT = Time-to-off treatment	

Table 1.4: Key issue [3] Constant hazard ratios for OS for atezolizumab versus serplulimab and for durvalumab versus serplulimab were assumed for the duration of the model

Report section	4.2.3.2
Description of issue and why the EAG has identified it as important	The OS hazard ratios (HRs) for atezolizumab and durvalumab versus serplulimab were assumed constant over the duration of the model.

Report section	4.2.3.2
	The EAG believes that this assumption may not reflect the real clinical context, and it is unlikely that it would remain constant as patients eventually experience disease progression and come off treatment. The EAG believes that, while the implicit HR from the 3 knot spline models was fairly constant over the first 18 months, the HR may get closer to 1 over time.
What alternative approach has the EAG suggested?	In line with the assumption the EAG made about the HR for serplulimab vs carboplatin + etoposide, the HRs for OS for atezolizumab and durvalumab versus serplulimab were assumed to go from the MAIC HR at 3.5 years to 1 at 6.5 years.
What is the expected effect on the cost effectiveness estimates?	The EAG combined the approach of fitting the 3 knot spline model to both TTOT, PFS and OS. In addition, the 3-year waning assumption applied from 3.5 years to 6.5 years was made for the HR for serplulimab vs carboplatin + etoposide, for serplulimab vs durvalumab, and for serplulimab vs atezolizumab. Altogether, the result of these combined alternative (but related) assumptions was to change the ICER versus carboplatin + etoposide from [redacted] to [redacted]
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up data for OS for each treatment would provide more data on survival in the long-term. Alternatively, PFS and OS specific mortality hazard rates could be estimated and a semi-Markov model developed, but the individual patient data for atezolizumab and durvalumab may not be available to conduct this analysis.
Abbreviations: EAG = Evidence Assessment Group; OS= overall survival; PFS = progression free survival; HR = hazard ratio; MAIC = matching-adjusted treatment comparison; TOTT = time-to-off treatment	

Table 1.5: Key issue [4] TTOT parametric model for serplulimab and carboplatin + etoposide did not fit the Kaplan-Meier curves well

Report section	4.2.6.1.1
Description of issue and why the EAG has identified it as important	The TTOT curve did not fit the Kaplan-Meier curve well for serplulimab. Consequently, the percentage on treatment may be overestimated earlier in the model and underestimated later in the model. Where possible, the association between treatment cost and effectiveness from the clinical trials should be retained in the economic model.
What alternative approach has the EAG suggested?	As for OS, the EAG used the 3 knot spline model for serplulimab until 3.5 years, and after 3.5 years the percentage on treatment was limited to the percentage on treatment in each of the PFS and PD states in the previous cycle and the PFS and PD numbers in the current cycle.
What is the expected effect on the cost effectiveness estimates?	The EAG combined the approach of fitting the 3 knot spline model to both TTOT, PFS and OS. In addition, the 3-year waning assumption applied from 3.5 years to 6.5 years was made for the HR for serplulimab vs carboplatin + etoposide, for serplulimab vs durvalumab and for serplulimab vs atezolizumab. Altogether, the result of these combined alternative (but related) assumptions was to change the ICER versus carboplatin + etoposide from [redacted] to [redacted]
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up data would provide additional information on longer-term time on treatment.
Abbreviations: EAG = Evidence Assessment Group; TTOT = time-to-off treatment; OS= overall survival; PFS = progression free survival; PD = progressed disease;	

Table 1.6: Key issue [5] The average body weight and height in ASTRUM-005 was lower than in UK clinical practice

Report section	4.2.6.3
Description of issue and why the EAG has identified it as important	For serplulimab and chemotherapy drugs which are based on weight and body surface area (BSA), the company used a mean body weight of 68.4 kg and height of 167 cm in the model informed by ASTRUM-005. The percentage of the ASTRUM-005 population that was Asian was 67.4%. Working counter to this, 80% of the ASTRUM-005 population were male, whereas according to the National Lung cancer audit report, from 36,886 patients diagnosed with lung cancer in England during 2022, about 49.8% of patients with SCLC in England are women.[2]. The EAG acknowledges that this proportion is not specific to ES-SCLC; however it reflects the proportion of female patients in SCLC group across England. Additionally, the National Lung cancer audit repoted that the median age at diagnosis for SCLC was 70 years and according to the Health Survey for England[3], individuals aged 69–74 years have the average weight of 79.3 kg and height of 166.8 cm. To counteract that, it is possible that patients lose weight when they have this stage of cancer. The average weight for non-Asians listed in the company model was 78.84 kg and the average height for non-Asians was 171.29 cm. Treatment effectiveness is independent of dose per unit of patient size. Consequently, if lower height and weight are used then drug costs may be underestimated in UK clinical practice for the same expected effectiveness.
What alternative approach has the EAG suggested?	The EAG use the average height and weight in England (age group 65–74 years) in the EAG base case, and use the average ASTRUM-005 height and weight and ASTRUM-005 trial non-Asian height and weight in scenario analyses.
What is the expected effect on the cost effectiveness estimates?	Changing the average weight and height from the ASTRUM-005 averages to the England averages changes the ICER vs carboplatin + etoposide from [redacted] to [redacted]
What additional evidence or analyses might help to resolve this key issue?	Data on the weight and height of patients with ES-SCLC in England would provide the necessary information to determine the impact on drug costs.
Abbreviations: BSA = body surface area; EAG = Evidence Assessment Group; SCLC = small-cell lung cancer	

1.4 Summary of the EAG's preferred assumptions and ICER

Error! Reference source not found. shows the probabilistic results of the Company base-case and Table 1.8 shows the results of the EAG base-case. Five changes were made in the Company base-case to produce the EAG base-case.

The first change was to fit a flexible joint spline model to the OS and PFS curves. The EAG considered that fitting a more flexible model to better represent the KM curves from ASTRUM-005 and then model a declining HR would more closely reflect the trial evidence and the company clinical expert opinion.

The second change was to assume that the HR for OS for serplulimab versus atezolizumab and for serplulimab versus durvalumab would trend to 1 from 3.5 years to 6.5 years to match the same assumption in the first change in the EAG base case.

The third change was to fit a flexible joint spline model to the TTOT curve, and assume that the percentage on treatment in the PFS and PD states was no greater than the proportions in those states from a timepoint near the end of the Kaplan-Meier curve.

The fourth change was to change the distribution of patients receiving treatments among PFS and PD states so that a larger portion of the patients in the PFS would receive treatment rather than assuming an equal distribution among the health states (company base-case). In the EAG base-case, the percentage of PD patient receiving serplulimab was capped at an arbitrary percentage (20%).

The fifth change was to incorporate the weight and height of patients according to the England population. This would change the treatment doses and thereby, the acquisition costs. In the EAG base-case, Weight = 79.3 kg, Height = 168.4 m^2.

Table 1.9, Table 1.10 and

Table 1.11 reports the results of selected scenarios.

Table 1.7 Probabilistic results of the company base case

Technology	Total costs (£)	Total QALYs x1.2	Incremental		ICER (£) x1.2
			costs (£)	QALYs x1.2	
serplulimab + carboplatin + etoposide	[redacted]	2.10			
atezolizumab + carboplatin + etoposide	[redacted]	1.55	[redacted]	0.55	[redacted]

serplulimab + carboplatin + etoposide	[redacted]	2.10			
durvalumab + carboplatin + etoposide	[redacted]	1.68	[redacted]	0.42	[redacted]
serplulimab + carboplatin + etoposide	[redacted]	2.10			
carboplatin + etoposide	[redacted]	1.21	[redacted]	0.89	[redacted]
Source: CS and CS PofC Response[4] Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year					

Table 1.8: Probabilistic results of the EAG base case

Technology	Total costs (£)	Total QALYs x1.2	Incremental			ICER (£) x1	ICER (£) x1.2
			costs (£)	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.06					
durvalumab + carboplatin + etoposide	[redacted]	1.72	[redacted]	0.29	0.35	[redacted]	[redacted]

serplulimab + carboplatin + etoposide	[redacted]	2.07		0			
atezolizumab + carboplatin + etoposide	[redacted]	1.60	[redacted]	0.383	0.46	[redacted]	[redacted]
serplulimab + carboplatin + etoposide	[redacted]	2.06					
carboplatin + etoposide	[redacted]	1.23	[redacted]	0.7	0.84	[redacted]	[redacted]

Source: EAG model

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Table 1.9: Selected results from company after PfC and EAG's deterministic scenario analysis – atezolizumab as comparator

Scenario	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1 (£/QALY)	ICER x1.2 (£/QALY)
	EAG base-case	**N/A**	[redacted]	0.41	0.50	[redacted]	[redacted]
CS 6-2	Utility derivation method: Scenarios using the time to death approach and progression status by treatment status are presented. Scenarios using the time to death approach and progression status by treatment status are presented. Progression status without on/off treatment	Progression status by on/off treatment	[redacted]	0.4	0.48	[redacted]	[redacted]
CS 7-1	Adverse events: Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented. AE disutilities for all patients included	Exclude AE disutilities	[redacted]	0.41	0.50	[redacted]	[redacted]
EAG 1	Survival Curve. Curve 2 in the Scenario tab: 3 knot + 3 years treatment waning effect	Curve 1 in the Scenario tab: 3 knot + exponential	[redacted]	0.45	0.53	[redacted]	[redacted]
EAG 2	TTOT in PFS and PD states. TTOT in PFS and PD states assumption: maximum of 20% in PD	TTOT in PFS and PD states assumption: maximum of	[redacted]	0.41	0.50	[redacted]	[redacted]

	state are assumed to be on treatment	10% in PD state are assumed to be on treatment					
EAG 4	Utility. Utility values from ASTRUM-005 trial were mapped to EQ-5D-3L	Utility values published in the study conducted by Nafees et al. (2008):[5] PFS = 0.673, PD = 0.473	[redacted]	0.32	0.38	[redacted]	[redacted]

Source: EAG economic model
Abbreviations: CS = Company Submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year; CPRD = Clinical Practice Research Datalink; Adelphi DSP = Adelphi Disease Specific Programmes; PfC = points for clarification; SoC = standard of care; OCS = oral corticosteroids

Table 1.10: Selected results from company after clarification and EAG's deterministic scenario analysis – carboplatin + etoposide as comparator

Scenario	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1 (£/QALY)	ICER x1.2 (£/QALY)
	EAG base-case	**N/A**	[redacted]	0.70	0.85	[redacted]	[redacted]
CS 6-2	Utility derivation method: Scenarios using the time to death approach and progression status by treatment status are presented. Scenarios using the time to death approach and progression status by treatment status are presented. Progression status without on/off treatment	Progression status by on/off treatment	[redacted]	0.67	0.81	[redacted]	[redacted]
CS 7-1	Adverse events: Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented. AE disutilities for all patients included	Exclude AE disutilities	[redacted]	0.73	0.87	[redacted]	[redacted]
EAG 1	Survival Curve. Curve 2 in the Scenario tab: 3 knot + 3 years treatment waning effect	Curve 1 in the Scenario tab: 3 knot + exponential	[redacted]	0.78	0.93	[redacted]	[redacted]
EAG 2	TTOT in PFS and PD states. TTOT in PFS and	TTOT in PFS and PD	[redacted]	0.70	0.85	[redacted]	[redacted]

	PD states assumption: maximum of 20% in PD state are assumed to be on treatment	states assumption: maximum of 10% in PD state are assumed to be on treatment					
EAG 4	Utility. Utility values from ASTRUM-005 trial were mapped to EQ-5D-3L	Utility values published in the study conducted by Nafees et al. (2008):[5] PFS = 0.673, PD = 0.473	[redacted]	0.54	0.65	[redacted]	[redacted]

Source: EAG economic model

Abbreviations: CS = Company Submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year; CPRD = Clinical Practice Research Datalink; Adelphi DSP = Adelphi Disease Specific Programmes; SoC = standard of care; OCS = oral corticosteroids

Footnote: *indicates that this result is the full incremental ICER result for serplulimab

Table 1.11: Selected results from company after clarification and EAG's deterministic scenario analysis – durvalumab as comparator

Scenario	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1 (£/QALY)	ICER x1.2 (£/QALY)
	EAG base-case	**N/A**	[redacted]	0.31	0.37	[redacted]	[redacted]
CS 6-2	Utility derivation method: Scenarios using the time to death approach and progression status by	Progression status by on/off treatment	[redacted]	0.29	0.35	[redacted]	[redacted]

	treatment status are presented. Scenarios using the time to death approach and progression status by treatment status are presented. Progression status without on/off treatment						
CS 7-1	Adverse events: Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented. AE disutilities for all patients included	Exclude AE disutilities	[redacted]	0.33	0.40	[redacted]	[redacted]
EAG 1	Survival Curve. Curve 2 in the Scenario tab: 3 knot + 3 years treatment waning effect	Curve 1 in the Scenario tab: 3 knot + exponential	[redacted]	0.34	0.40	[redacted]	[redacted]
EAG 2	TTOT in PFS and PD states. TTOT in PFS and PD states assumption: maximum of 20% in PD state are assumed to be on treatment	TTOT in PFS and PD states assumption: maximum of 10% in PD state	[redacted]	0.31	0.37	[redacted]	[redacted]

		are assumed to be on treatment					
EAG 4	Utility. Utility values from ASTRUM-005 trial were mapped to EQ-5D-3L	Utility values published in the study conducted by Nafees et al. (2008):[5] PFS = 0.673, PD = 0.473	[redacted]	0.26	0.31	[redacted]	[redacted]

Source: EAG economic model

Abbreviations: CS = Company Submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year; CPRD = Clinical Practice Research Datalink; Adelphi DSP = Adelphi Disease Specific Programmes; SoC = standard of care; OCS = oral corticosteroids

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with untreated ES-SCLC	Adults with untreated ES-SCLC	Not applicable (NA)	In line with scope.
Intervention	Serplulimab with carboplatin and etoposide	Serplulimab with carboplatin and etoposide	NA	In line with scope.
Comparator(s)	Platinum-based combination chemotherapy Atezolizumab with carboplatin and etoposide (for people with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1) Durvalumab (subject to NICE appraisal)‡	Platinum-based combination chemotherapy Atezolizumab with carboplatin and etoposide (for people with ECOG PS of 0 or 1)	In the original Company submission (CS), it was stated:[6] "Durvalumab has not been included in this appraisal as it is not recommended at the time of submission, although a NICE recommendation is expected on 19th February 2025. At the time of the decision problem meeting, Accord were informed that durvalumab was not	NICE technology guidance is available for atezolizumab (with carboplatin and etoposide) and durvalumab.[7,8] Durvalumab was recommended by NICE in February 2025, and the original Company submission (CS)[6] was dated prior to this recommendation and only included an ITC/MAIC with atezolizumab. Following the approval, and in response to the EAG's Points for Clarification (PfC), the Company included an additional ITC/MAIC with durvalumab. Further details are provided in Section 2.1.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			a relevant comparator". (p. 10) Following the approval of durvalumab (TA1041),[7] the Points for Clarification (PfC) response included an additional ITC with durvalumab.[4]	
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life	NA	The outcomes reported in ASTRUM-005 match those reported in the scope. Overall survival (OS) was the primary outcome, with a range of secondary outcomes also presented including all those mentioned in the scope: Progression-free survival (PFS), response outcomes (objective response rate (ORR) and duration of response (DOR)), incidence rates of adverse events (AE) and serious adverse events (SAE), and quality of life). The submission uses an ITC and MAIC to assess effectiveness and only two outcomes (OS and PFS) were presented for the Bucher ITC/MAIC (and directly used in the cost-effectiveness modelling). This narrowing of outcomes, whilst understandable, is of some concern. Further details are provided in Section 2.2.
Economic analysis	The reference case stipulates that the cost effectiveness of	The measure of benefit was QALYs.	The Company economic analysis	Given that durvalumab was added as a comparator in response to the clarification letter, the Company model was not developed to efficiently allow for a full

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	The base case time horizon was 20 years. The NHS and Personal Social Services perspective was adopted for costs. The cPAS price for serplulimab was included.	matched the NICE reference case.	incremental cost-effectiveness analysis including all 4 comparators.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	technologies will be taken into account.			

Source: Document B[6]
Abbreviations: AE = adverse events; CS = company submission; DOR = duration of response; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NA = Not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; ORR = objective response rate; OS = overall survival; PfC = Points for Clarification; PFS = progression free survival; SAE = serious adverse events
Footnote: ‡Durvalumab received approval from NICE in February 2025.

2.1 Comparators

Treatment guidance for ES-SCLC by the European Society for Medical Oncology (ESMO) highlights that treatment choice is linked to a patients' PS and contraindications for immunotherapy.[9] If there are no contraindications for immunotherapy and the patients' PS is 0 or 1, either four cycles of carboplatin-etoposide-atezolizumab and maintenance atezolizumab, or four cycles of platinum-etoposide-durvalumab and maintenance durvalumab are suggested. Alternatively (for patients with contraindications for immunotherapy), a regimen of carboplatin-etoposide, (4-6 cycles) or carboplatin-oral topotecan or cisplatin-irinotecan is suggested. If a patients' PS is 2 or more, carboplatin-etoposide/carboplatin-gemcitabine (4-6 cycles) or best supportive care is suggested.[9] This proposed treatment pathway is broadly comparable with that outlined in the NICE guidelines for the first-line treatment for ES-SCLC:[10]

- Offer platinum-based combination chemotherapy to people with extensive-stage disease small-cell lung cancer (SCLC) (broadly corresponding to T1–4, N0–3, M1a/b – including cerebral metastases) if they are fit enough;
- Assess the person's condition before each cycle of chemotherapy for extensive-stage disease SCLC (broadly corresponding to T1–4, N0–3, M1a/b) and offer up to a maximum of 6 cycles, depending on response and toxicity;
- Consider thoracic radiotherapy with prophylactic cranial irradiation (PCI) for people with extensive-stage disease SCLC who have had a partial or complete response to chemotherapy within the thorax and at distant site;
- Consider PCI for people with extensive-stage disease SCLC and World Health Organization (WHO) PS 0 to 2, if their disease has responded to first-line treatment.

Additional NICE technology guidance outlines immunotherapy options alongside platinum-based chemotherapy, including atezolizumab with carboplatin and etoposide (TA638)[8] and durvalumab (TA1041).[7] Clinical advice to the EAG has confirmed PCI and thoracic radiotherapy are used sparingly in clinical practice. Other treatments which are used in this population include stereotactic radiosurgery/radiotherapy for cerebral metastases, however there are strict criteria which patients must meet to be eligible for these treatments.[11] Clinical advice to the EAG also indicated that use of topotecan in the UK is limited.

The comparators detailed in the NICE scope for this technology appraisal include:[12]

- Platinum-based chemotherapy;
- Atezolizumab with carboplatin and etoposide (for people with ECOG PS of 0 or 1) and;
- Durvalumab (subject to NICE appraisal at the time of scope development).

Durvalumab with etoposide and either carboplatin or cisplatin was recommended as of 19th February 2025 (after the company submission (CS)) as an option for untreated ES-SCLC, only if patients have an ECOG PS of 0 or 1 and the Company provides durvalumab according to the commercial agreement.[7] In the original CS,[6] durvalumab was not included in the appraisal as it was not recommended at the time of submission. The Company indicated that "at the time of the decision problem meeting, Accord [the company] were informed that durvalumab was not a relevant comparator" (p.10).[6] In the PfC (Question A1),[4] the EAG asked the Company to conduct further analyses including durvalumab as a comparator in both their clinical and cost effectiveness analyses. The Company included the

additional analysis in the PfC response, and provided indirect efficacy estimates of comparative efficacy between serplulimab/durvalumab derived from a MAIC. The EAG's preferred approach was a ML-NMA,[13] which has been used in previous NICE technology appraisals.[14] However, the Company instead used a second MAIC by matching and reweighting of the ASTRUM-005 individual patient data (IPD) to the baseline characteristics of the aggregate CASPIAN data.[4] This approach is critiqued in Section 0. A head-to-head comparison evaluating the safety and efficacy of serplulimab plus chemotherapy (carboplatin-etoposide) in comparison with atezolizumab plus chemotherapy for this indication is currently in progress (NCT05468489), with an estimated primary completion date of September 2025.[15]

Tislelizumab with platinum-based chemotherapy and etoposide for untreated ES-SCLC (ID6158) is also under NICE development,[16] therefore there is the possibility of an additional comparator which may receive NICE guidance in the medium term.

2.2 Outcomes

The NICE scope includes outcomes related to OS, PFS, response rates, adverse effects of treatment and health-related quality of life (HRQoL).[12] Whilst the company states that the outcomes reported in the CS are in line with this scope, it is important to highlight that this reporting refers only to the ASTRUM-005 trial. The submission uses an ITC to assess effectiveness, in which two outcomes were considered – OS and investigator assessed PFS.[6] These two outcomes were modelled for the Bucher ITC and the MAIC (see Table 2.2 for a comparison of the outcomes reported for ASTRUM-005, IMpower133, CASPIAN and the ITC/MAIC) and were subsequently used in the cost-effectiveness modelling.

The other outcomes reported in the scope were described in the ASTRUM-005 trial and are reported in the CS.[6] As the analysis used two MAICs, these outcomes are not directly comparable across all treatment arms. However, the EAG is satisfied that the most important outcomes used for cost-effectiveness modelling are available for the two comparator technologies (serplulimab versus atezolizumab and serplulimab versus durvalumab).

Table 2.2: Outcomes detailed in ASTRUM-005, IMpower133 and CASPIAN against NICE scope outcomes for serplulimab

Outcome type	NICE Scope	ASTRUM-005[a]	IMpower133[a]	CASPIAN[a]	Butcher ITC[a]	MAIC
Survival	OS	OS (primary outcome)	OS (primary outcome) OS rates at 1 year and at 2 years	OS (primary outcome)	OS	OS
	PFS	PFS (assessed by independent radiology review committee (IRRC) based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1) PFS, assessed by investigator based on RECIST 1.1 and the modified RECIST 1.1 for immune -based therapeutics (iRECIST) PFS2 (assessed by investigator based on RECIST 1.1)	PFS (assessed by investigator using RECIST v1.1) (primary outcome) PFS rates at 6 months and at 1 year)	PFS using investigators assessments according to RECIST 1.1	PFS (investigator assessed)	PFS (investigator assessed)
Response rates		ORR, assessed by IRRC and investigator based on RECIST 1.1 DOR, assessed by IRRC and investigator based on RECIST1.1	Objective response, defined by partial response and complete response as determined by the investigator according to RECIST 1.1 Time in response, defined as the same as	Objective response using investigator assessments according to RECIST 1.1 progression		

			DOR for responders (for non-responders time in response is defined as date of randomisation plus 1 day)			
Adverse effects of treatment		AE (including SAE)	Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Technology Criteria for Adverse Events v4.0	The safety and tolerability profile of durvalumab +/- tremelimumab in combination with platinum-based chemotherapy treatment compared with platinum-based chemotherapy		
HRQoL		EQ-5D-5L, European Organisation for Research and Treatment of Cancer Quality of Life Scale (EOQLQ) (C30) scale and EORTC Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13) scale.	Changes in baseline patient reported outcomes (PROs) of health-related quality of life, lung cancer-related symptoms, physical (functioning, and health status as assessed by the EORTC QLQ-C30 and QLQ-LC13.	Time to deterioration of HRQoL and PRO symptoms using EORTC QLQ-C30 Time to deterioration of PRO symptoms, assessed using EORTC QLQ-LC13 Change from baseline in primary PRO symptoms as assessed by EORTC QLQ-C30 and QLQ-LC13 Change from baseline in primary symptoms, assessed using EORTC QLQ-C30 and EORTC QLQ-LC13.		

Source: ASTRUM-005 CSR.[17] IMPower133 protocol[18], and CASPIAN[19-21]
Abbreviations: AE = adverse events; BICR = blinded independent central review; DOR = duration of response; EORTC QLQ-C30 = EORTC Core Quality of Life questionnaire (30 items); EORTC QLQ-LC13 = EORTC Core Quality of Life questionnaire (lung cancer module); iRECIST = immune-based response evaluation criteria in solid tumours; IRRC = immune-related response criteria; ORR = objective response rate; OS = overall survival; PFS = progression free

survival; PFS-2 = progression free survival-2, defined as time from randomisation to progression on second-line therapy; RECIST = response evaluation criteria in solid tumours; PRO = Patient-reported outcomes; SEA = serious adverse events.
Footnote: [a] Only those trial outcomes in ASTRUM-005, IMPower133 or CASPIAN that map directly to the NICE Scope reported.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS describes a systematic literature review (SLR) conducted to identify Randomised Controlled Trial (RCT) and open-label extension (OLE) studies comparing the efficacy and safety of serplulimab compared to other treatments recommended by European clinical guidelines (ESMO and NICE)[9,10] for treatment naïve adult patients with ES-SCLC. The methods of the SLR are detailed in Appendix D of the CS.[22]

A summary of the EAG's critique is presented in Table 3.1 below. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 3.1: Summary of the EAG's critique of the systematic literature review

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Section 2.4 Appendix D[22]	**Appropriate** The Company report a good range of bibliographic and non-bibliographic sources for the retrieval of published and grey literature studies.
Search strategies	Section 6.2 Appendix D[22]	**Some concerns** Only bibliographic database search strategies had been reported. The EAG has some concerns around the sensitivity and specificity of the searches, with regards the population and the comparators searches. Additionally, on request, the Company provided additional details of hand searching results of grey literature sources.[4] Systematic reviews and ITCs were additionally identified for cross-referencing purposes which is also good practice (however as an RCT filter was used to find studies, it is unlikely that this search was comprehensive, or whether an additional search was undertaken to find relevant reviews). This is further described in Section 3.2 below.
Search filters	Section 2.1 Appendix D[22]	**Some concerns** Scottish Intercollegiate Guidelines Network (SIGN) study type filters were used however these were adapted by the Company. It is unclear if the performance of this filter would have been compromised by these adaptations. Further detail can be found in Section 3.3 below.
Eligibility criteria	Table 1, Appendix D[22]	**Appropriate** The study question covered by the SLR matched the NICE scope,[12] namely to synthesise the available comparative evidence (safety and efficacy) of serplulimab + carboplatin and etoposide in the treatment of untreated ES-SCLC. The EAG are satisfied with the predefined eligibility criteria. Only RCTs or OLE studies were sought, which is understandable given the maturity of the evidence

		base. However, other single-arm studies are available which may inform real-world clinical practice. For example, LUMINANCE (NCT04774380) is a single-arm study in patients with previously untreated ES-SCLC. In this trial, patients with a WHO PS score of 0-2 were eligible, and PCI was given at the investigator's choice.[23,24] Non-English language studies were excluded. This may introduce bias and limit the generalisability of findings, potentially missing key evidence and hindering a comprehensive understanding of a topic. However, given the topic and the likelihood that international trials would be published in English, the EAG is broadly satisfied with this approach.
Screening	Appendix D, Section 2.5 p.16-17; 3.1 p.20-21[22]	**Some concerns** Screening was undertaken in duplicate, with disagreements resolved through discussion. The flow of records through the SLR was provided in the accompanying Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart, detailed in Figure 1 in Appendix D.[22] In total, 32 individual reports, representing 16 unique studies were included in the review. The EAG have some concerns with whether the eligibility criteria stated in the Table 1 were appropriately applied,[22] particularly whether the regimens/targeted therapies identified were recommended for the treatment of ES-SCLC by ESMO and NICE guidelines. Further information is presented in Section 3.4.
Data extraction	Appendix D, Section 2.6 (p.17-19)[22]	**Appropriate** Data extraction was performed by a single reviewer and a subset (20%) of the extracted data was checked against the original articles. Any discrepancies were resolved by consulting a third reviewer.[22] The Company are the sponsor of the only clinical trial from the SLR (ASTRUM-005) which assessed serplulimab, and therefore the Company have direct access to the clinical trial data. The original data extraction file submitted by the Company comprised only three publications from the CASPIAN trial.[19,20,25] Although the EAG asked for the complete data extraction sheet to be provided at PfC (Question B6),[4] the Company instead commented on the quality appraisal data. IMPower133 and CASPIAN which are used in the ITC are however reported in the CS,[6,22] so the EAG accept that this omission was an oversight. The EAG agree the data extraction methods used were largely appropriate.
Quality appraisal	Appendix D, Section 2.7 (p. 19, 20)[22]; Excel Quality	**Some concerns** All included studies were assessed using Cochrane Risk of Bias for randomised trials (version 2.0).[27] The quality appraisal was completed by one reviewer and checked by a second. Discrepancies were resolved

	appraisal spreadsheet[26]	through discussion, or if necessary, with a third reviewer.[22] There is discrepancy between the data reported in the 'summary' sheet and that reported in the 'Figure (ITT) tab'.[26] This is reported in Section 3.5. Aside from the discrepancies with regards ratings for domains within Cochrane Risk of Bias 2, the EAG are satisfied with the approaches taken.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ES-SCLC = extensive stage-small cell lung cancer; ITC = indirect treatment comparison; NICE: National Institute for Health and Care Excellence; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; PS = Performance Status; SIGN = Scottish Intercollegiate Guidelines Network; SLR = systematic literature review; WHO = World Health Organization		

3.2 Search strategies

Searches were conducted for clinical effectiveness (reported in Appendix D),[22] and for economic and humanistic burden (Appendix H).[28] Searches were appraised by the EAG using the Peer Review of Electronic Search Strategies (PRESS) checklist.[29] A critique of the search strategies for economic and humanistic burden can be found in Section 4.1. Searches were conducted on 5th April 2024, from the inception date of each database onwards. The EAG has concerns regarding the sensitivity of the searches, and the comparator search terms.

3.2.1 Sensitivity of searches

The NOT operator was used to systematically exclude Non-Small Cell Lung Cancer (NSCLC) from both the clinical SLR and the economic and humanistic burden SLR. This approach is not appropriate nor best practice in systematic literature reviewing and is not recommended as it effectively excludes any record in which the NSCLC terms would be present including those records where both SCLC and NSCLC are present. According to the Cochrane handbook Chapter 4, Section 4.4.2 Structure of a search strategy "The 'NOT' operator should be avoided where possible to avoid the danger of inadvertently removing records that are relevant from the search set".[30] This approach automatically reduces the sensitivity of the search to retrieve all possible evidence.

The EAG raised this issue in the PfC letter (Question B1).[4] In their response, the company reaffirmed their confidence in the robustness of their approach. Nevertheless, the company provided further searches removing the exclusion of the NSCLC. The comparison of number of results retrieved with the use of exclusion (5th April 2024) and without (11th March 2025) is illustrated in Table 3.2. The EAG are unable to say whether the second search contains duplicate records already identified in the original search results. Further the EAG cannot state whether or not the additional records indicated in column 4 ('Difference') are indicative of additional relevant information being missed by the original searches conducted on 5th April 2024.

Table 3.2: Comparison of two different search approaches

Database	Original search results (5th April 2024)	Search without NOT operator (11th March 2025)	Difference in N of records retrieved
Cochrane Clinical Search	1,328	8,872	7,544
Cochrane Economic & Humanistic Search	31	3,593	3,562
Embase Clinical Search	1,288	8,953	7665
Embase Economic & Humanistic Search	216	3,808	3,592
PubMed Clinical Search	1,032	5,676	4,644
PubMed Economic & Humanistic Search	193	2,659	2,466
Total	4,088	33,561	29,473

Source: Appendix D;[22] Appendix H;[28] Company response to PfC letter[4]

Additionally, in several search strings, it was not clear whether terms used were controlled vocabulary or text word searches, nor which fields were searched in text word strings (e.g., Clinical SLR, Section 6.2.1, Table 13 lines #7 to #16).[22] The EAG raised this point in the PfC letter (Question B4),[4] however, given the Company's response the EAG have not been able to ascertain whether title, abstract and keyword fields were used in combination with equivalent controlled vocabulary terms systematically for all databases and all search concepts. There also appear to be contradictions within the Company's response which states that 'In case of PubMed, free terms (no Medical Subject Headings (MeSH)) were used for search strategies.'[4] It is common practice for the title, abstract, and keywords fields to be searched as a minimum; the lack of clarity in the reporting of the searches impacts the EAG's ability to assess the sensitivity of the search.

3.2.2 Comparators search terms

Across databases, the terms used for comparators were not applied consistently. Four terms related to carboplatin, namely "carplan", "erbakar", "ercar" and "ifacap" were included in the Cochrane database, but not in Embase.com or PubMed (Medline) database searches (Clinical SLR, Section 6.2.1). The term 'sch900475' was used in the pembrolizumab search in Cochrane and Embase.com but was missed out from the PubMed (Medline) search. The search term 'strentarga' was used in the Cochrane and Embase searches for 'ipilimumab' alternative names but was missed from the PubMed (Medline) search. The Cochrane and Embase search strings for atezolizumab includes a misspelt term 'tecntriq' as well as 'tecentriq'. These issues may negatively affect the retrieval of relevant records for comparator technologies.

3.3 Search filters

Search filters are developed to systematically retrieve certain study designs. The use of search filters for study design is common practice in systematic reviewing. The Company

state in the SLR (Appendix D)[22] that the SIGN search filters were applied and extra terms added to these, however it is unclear why some of the terms in the SIGN search filters are not present in the reported search strategies.

The EAG considers that a satisfactory search of grey literature sources was performed in conjunction with the database searches. These searches included health technology assessment (HTA) bodies, conference proceedings, cost effectiveness registries, Google Scholar, Sheffield Centre for Health and Related Research Health Utilities Database and EuroQol group.

In summary, without comprehensive testing, it is difficult for the EAG to quantify the effects that all the issues mentioned may have had on search results, but it seems likely the effects would be relatively minor. Overall, the EAG has some concerns but is generally satisfied that the search for clinical effectiveness studies was conducted appropriately.

3.4 Screening

As detailed in Table 1 in Appendix D of the CS (p.13),[22] which records the Population, Intervention, Comparator, Outcome, and Study type (PICOS) framework for the clinical SLR, the comparator for the SLR includes ‘any regimens and/or targeted therapies recommended for the treatment of ES-SCLC by European Guidelines (ESMO and NICE guidelines)’.[9,10] Of the 16 unique trials recorded in the SLR, seven unique treatment regimens were detailed (

Table 3.3). Whilst most regimens were included in either ESMO or NICE guidance, irinotecan with carboplatin and topotecan with cisplatin cannot be found in either guidance. Both irinotecan and topotecan are topoisomerase I inhibitors.[31,32] The combination of carboplatin-topotecan or cisplatin-irinotecan is indicated for patients with a PS of 0 or 1 who show contradictions for immunotherapy.[9] However, two of the treatment combinations highlighted in the SLR (highlighted in italics in

Table 3.3) have a different platinum-based chemotherapy regimen. Four studies (from five articles) reported irinotecan with carboplatin as the intervention,[33-37] with a further three studies listing the topotecan-cisplatin combination.[38-40]

Table 3.3: Comparator treatment regimens included in SLR

SLR treatments	ESMO guidance	NICE guidance
serplulimab + carboplatin + etoposide	-	This appraisal
durvalumab + platinum-etoposide	For patients with PS 0-1 with no contraindications for immunotherapy	TA1041[7]
atezolizumab + carboplatin + etoposide	For patients with PS 0-1 with no contraindications for immunotherapy	TA638[8]
irinotecan + cisplatin	For patients with PS 0-1 with contraindications for immunotherapy	-
irinotecan + carboplatin	-	-
topotecan + cisplatin	-	-
etoposide + carboplatin	For patients with PS 0-1 with contraindications for immunotherapy (carboplatin may be replaced by cisplatin in patients <70 years of age or based on the toxicity profile)	NG122[10]

Source: Treatment regimens listed in the SLR (Table 3)[22]
Abbreviations: ESMO =European Society for Medical Oncology; NICE = National Institute for Health and Care Excellence; PS = performance status; SLR = Systematic literature review; TA = technology appraisal.

The EAG note that the prespecified eligibility criteria were not followed. However, previous research has confirmed no difference in efficacy between carboplatin- and cisplatin-based chemotherapy in the first-line treatment of SCLC, although notably differences in the toxicity profiles are evident.[41] Furthermore, as only serplulimab, durvalumab, and atezolizumab (with platinum chemotherapy[1]) were taken forward to derive effectiveness and cost-effectiveness estimates, the EAG are satisfied that the screening was undertaken satisfactorily.

[1] Chemotherapy regimen differs between treatments: Serplulimab is used in combination with carboplatin and etoposide; durvalumab is used in combination with etoposide and either carboplatin or cisplatin; and atezolizumab in used in combination with carboplatin and etoposide

3.5 Quality appraisal

All included studies assessed were critically appraised using the Cochrane Risk of Bias 2.[42] There is discrepancy between the data reported in the 'summary' sheet and that reported in the 'Figure (ITT)' tab in the accompanying Excel spreadsheet in the CS (Table 3.4).[26] The 'summary' sheet details textual levels of bias by domain (e.g., low, some concerns) whereas the 'Figure (ITT)' sheet reports the information graphically. For four of the studies,[34,40,43,44] there are discrepancies between the two sources. Most often the assignment of bias with regards to the randomisation process differs (more often labelled as 'low' in the figure' and of 'some concerns' in the sheet). The EAG cannot account for this discrepancy.

The results in the figure sheet ('Figure (ITT)') were confirmed in Question B6 in the PfC.[4] The randomisation method raised 'some concerns' in eight of the studies, and treatment allocation blinding was unclear in 11 of the 16.[4] Whilst issues of consistency amongst the sources is unfortunate, considering only the ASTRUM-005, IMpower133, and CASPIAN are used for effectiveness and cost-effectiveness estimates, and these are consistently recorded, the EAG are not unduly concerned with this oversight.

Table 3.4: SLR Risk of Bias (discrepancies between Excel sheet summary and figure)

Study	Randomisation process		Deviations from intended interventions		Missing outcome data		Measurement of the outcome		Selection of the reported result		Overall bias	
	Figure	Sheet	Figure	Sheet	Figure	Sheet	Figure	Sheet	Figure	Sheet	Figure	Sheet
Noda et al. 2002[43]												
Quoix et al. 2005[38]												
Schmittel et al. 2006[33]												
Eckardt et al. 2006[39]												
Hanna et al. 2006[44]												
Okamoto et al. 2007[45]												
Hermes et al. 2008[34]												
Lara et al. 2009 (SWOG S0124)[46]												
Zatloukal et al. 2010[47]												
Schmittel et al. 2011[35]												
Fink et al. 2012[40]												
Kim et al. 2019[48]												

Shimokawa et al. 2021, 2023[36,37]												
ASTRUM-005[49]												
IMpower133[18]												
CASPIAN[25]												

Source: Excel spreadsheet detailing quality appraisal for SLR.[26]
Notes: green colouring refers to low risk of bias; yellow colouring refers to 'some concerns'. Bold highlighting refers to where there is discrepancy.

3.6 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Three RCTs - ASTRUM-005,[49] IMpower133,[18] and CASPIAN,[19] were included in the SLR as part of the CS (CS Appendix D)[22] and are summarised below. All were international phase III, RCTs, however, ASTRUM-005 was the only RCT investigating the safety and efficacy of serplulimab compared to any comparator (carboplatin and etoposide chemotherapy) in adults with untreated ES-SCLC in line with the NICE scope.[12] As detailed in Section 2.1, NICE's recommendation for durvalumab for adults with untreated ES-SCLC, was still under development at the time of the decision problem meeting, therefore the Company deemed durvalumab not to be a relevant comparator in this submission. Furthermore, the Company reasoned carboplatin-etoposide to be the only platinum-based regimen with relevance to UK practice, presenting standard of care in the NHS.[6] Subsequently, the Company used IPD data from ASTRUM-005 and aggregate data from IMpower133 to generate a MAIC between serplulimab and atezolizumab, both in combination with carboplatin and etoposide, in the absence of head-to-head trial evidence (CS Section B.2.8).[6]

On 19th February 2025 durvalumab with etoposide and either carboplatin or cisplatin, was recommended by NICE for patients with untreated ES-SCLC.[7] Consequently, the EAG in the PfC (Question A1)[4] asked the Company to conduct further analyses including durvalumab as a comparator in both their clinical and cost effectiveness analyses. As part of the response to the PfC, the Company conducted a second MAIC using aggregate data from CASPIAN, to generate efficacy estimates between serplulimab and durvalumab.[4] The critique of the design, conduct, and analysis of each of these trials is provided below in the Sections 3.6.1, 3.6.2, and 3.6.3, respectively.

3.6.1 ASTRUM-005

ASTRUM-005 assessed the clinical efficacy and safety of serplulimab in combination with carboplatin and etoposide versus placebo with carboplatin and etoposide, in previously untreated patients with ES-SCLC (NCT04063163).[49-51] This trial was an international, phase III, randomised, double-blind, multicentre, placebo-controlled study. ASTRUM-005 was conducted at 114 hospital sites in six countries (China, Georgia, Poland, Russian Federation, Turkey, Ukraine).[49] A total of 585 patients were randomised in 2:1 ratio to receive either 4.5 mg/kg of serplulimab with chemotherapy (n=389) or placebo with chemotherapy (n=196) every 3 weeks.(B.2.3.1, p.35)[6] Serplulimab treatment was given by intravenous (IV) infusion continued until disease progression, death, intolerable toxicity, withdrawal of consent, or due to other reasons mentioned in the study protocol.[6,51] "All patients received 100 mg/m^2 of etoposide on days 1, 2, and 3, and carboplatin within the area under the serum drug concentration time curve of 5 mg (mL/min (up to 750 mg) on day 1 of each cycle for up to four cycles via IV infusions (every 3 weeks for up to 12 weeks)."(CS B.2.3.1, p.35)[6] A summary of the EAG's critique of the design, conduct, and analysis of ASTRUM-005 is presented in Table 3.5, with key points expanded upon in the following sections.

Table 3.5: Summary of EAG's critique on the design, conduct and analysis of the ASTRUM-005 trial

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Treatment	B.2.3.1, Figure 6, p.35;[6] B.2.3.4, p.38;[6] B.2.7, p.59-60;[6] Cheng, et al. (2022);[49] Cheng, et al. (2022)[51]	**Some concerns** Participants were randomised to receive: serplulimab 4.5 mg/kg, by IV infusion for 30 to 90 minutes, or placebo by IV infusion, on day 1 of each 3 week (21 days) cycle, until disease progression, death, unacceptable toxicity, withdrawal of consent, or other reasons specified in the trial protocol.[49,51] All patients received carboplatin (area under the curve (AUC)=5 mg/mL/min, up to 750 mg) on day 1 and etoposide 100 mg/m^2, on days 1, 2, and 3 of each cycle by IV,' for up to a maximum of 4 cycles.[49,51] The dosage and method of administration of serplulimab is the same to that approved by the European Medicines Agency (EMA),[52] and the platinum-based combination chemotherapy, administered alone, or in combination with either atezolizumab or durvalumab, is recommended by NICE and ESMO as a first line treatment for ES-SCLC.[7-9] Clinical advice to the EAG confirmed the dosage and number of chemotherapy cycles reflects current UK practice. The EAG believes that the first line treatment aligns with the decision problem. However, the EAG has some concerns surrounding subsequent treatments administered to patients the point of disease progression. See Section 3.6.1.1 for further comment.
Randomisation	B.2.3.1 p.34-35; [6] Cheng, et al. (2022);[49]Cheng, et al. (2022)a[51]	**Appropriate** During the trial 585 participants in China, Georgia, Poland, Russian Federation, Turkey, and Ukraine, were randomised 2:1 to receive serplulimab or placebo, both in addition to chemotherapy. Participants were randomly assigned centrally, using an interactive web/voice response system with randomly selected block sizes of 3, 6, 9, stratified by Programmed Death-Ligand 1 (PDL1) expression, brain metastases and age.[49,51] The EAG believes that the randomisation process was appropriate.

Allocation concealment	B.2.3, p.34-40;[6] Cheng, et al. (2022);[49] Cheng, et al. (2022)a[51]	**Appropriate** In ASTRUM-005 the subjects, investigator, sponsor, and designated personnel were reported to be unaware of the randomisation and treatment allocation.[6,51] Participants were randomly allocated to treatment arms using an interactive web/voice response system and the administration of placebo/serplulimab was blinded.[49,51,53] Concealment allocation methods used are in alignment with those recommended by Cochrane Risk of Bias 2.[27] Therefore the EAG agrees that the allocation concealment was appropriate.
Eligibility criteria	B.2.3.2, p.36;[6] B.1.1, p.10;[6] Cheng, et al (2022);[49] Cheng, et al. (2022)a,[51]	**Appropriate** Adult patients with histologically and cytologically confirmed ES-SCLC who have not received prior therapy for ES-SCLC were eligible,[49,51] which is in line with the NICE scope.[12] Participants were required to have an ECOG PS score of 0 or 1, which matches the NICE recommendations for treatment comparators atezolizumab and durvalumab.[7,8] Overall, the EAG agree that the eligibility criteria are appropriate.
Blinding	B.2.3.1, p.34[6]	**Appropriate** The subjects, investigator, sponsor, and designated personnel were unaware of the randomisation and treatment allocation.[6] Administration of placebo/serplulimab was blinded, while chemotherapy was openly administered.[49,51,53] The study was unblinded after the last subject completed the end of the study visit or under the condition of the interim analysis as determined by the Independent Data Monitoring Committee.[6] Unblinding during the study was only allowed in case of emergency or as required by the regulatory authorities.[53] In addition to the allocation concealment methods described above, the EAG believes that blinding in this study to be appropriate.
Baseline characteristics	B.2.3.5, p.40-41;[6] Cheng, et al. (2022)[49]	**Key issue** Patient characteristics were balanced across both treatment and control arms. However, patients were enrolled across six countries, not including the UK, and were [redacted] and Asian (68.5%, n=401/585).[49] Additionally, compared to that seen in English practice, a relatively high proportion of patients were never smokers, and were more likely to be male.[49] The EAG have therefore raised the generalisability of the study population to the NHS patient population as a key issue. See Section 3.6.1.2 for further comment.

Dropout rate	B.2.4.2, p.46-48[6]	**Appropriate** As of the cutoff date of 7th May 2024, [redacted] participants randomised had discontinued the study treatment, which was most commonly due to progressive disease and occurred in a higher proportion of patients receiving placebo [redacted]The rates of participants who withdrew from study treatment or discontinued study treatment due to AEs, was lower in the placebo group [redacted]respectively) compared to those receiving serplulimab [redacted] respectively).[4] While [redacted]patients had discontinued the study, predominantly due to death, which was higher in the placebo group [redacted][6] Overall, the EAG have no concerns over the retention rate in this patient population.
Statistical analyses	B.2.4, Table 9, p.44-46[6] Cheng et al. (2022)[49]	**Appropriate** Sample size calculations were based on the assumption that the median OS for treatment with placebo with chemotherapy (carboplatin and etoposide) was 10 months and the hazard ratio (HR) of the serplulimab with chemotherapy group versus the placebo group was 0.7.[6] A HR of 0.7 was inferred from the results of the IMpower133 study.[49] Given an enrolment period of 24 months and a whole study period of 34 months, at least 342 OS events were required to achieve a confidence level of 85% at an overall significance level of α = 0.05 (two-sided).[6] Assuming a 20% drop out rate a total of 567 subjects (378 in the serplulimab arm and 189 in the placebo arm) were required.[6,49] Efficacy analyses were performed on the intention-to-treat (ITT) population, comprising all randomised patients.[6,49] The safety endpoint analysis comprised all subjects who received at least one dose of study intervention.[6] Statistical analysis was also conducted in Asian and non-Asian countries separately.[17] Accordingly, the EAG considers the statistical analysis approach appropriate.

Outcome measures	B.1.1, Table 1, p.10[6] B.2.1, Table 4, p.33-34[6] B.2.3.7, Table 8, p.42[6] B.2.4, Table 9, p.44[6] B.2.1.1.2, p.52[6]	**Appropriate** The outcome measures and definitions, in addition to instruments used align with the NICE scope.[12] The primary endpoint was OS, while key secondary efficacy endpoints included PFS, PFS2, ORR, and DoR, which were assessed by the IRRC and investigator based on RECIST 1.1 or the modified RECIST 1.1 for immune based therapeutics.[6] Secondary endpoints included safety outcomes (including AEs, SAEs), pharmacokinetics, immunogenicity and biomarker analysis. Additionally, quality of life (QoL) was assessed using EQ-5D-5L, along with the cancer and lung cancer-specific instruments EORTC QLQC30, and EORTC QLQ-LC13.[6] QoL was captured prior to the first dose and every other subsequent dosing cycle until the end of treatment. In the CS, least squares mean changes from baseline to week 18, [redacted] were presented. Accordingly, the EAG consider the outcomes measures appropriate.
Results: Efficacy outcomes	B.2.6, p.48 – 60;[6] Clinical Study Report (CSR), p.130-132;[17] PfC response, p.28[4]	**Appropriate** Treatment with serplulimab plus carboplatin and etoposide demonstrated an overall OS benefit compared to placebo at the end of study data cutoff (median follow-up: [redacted]months), indicated by an OS of [redacted]months in serplulimab arm compared to [redacted]months in placebo arm (HR=[redacted] [95% confidence interval (CI): [redacted], [redacted]).[6] The median OS benefit observed with the addition of serplulimab was also reported within [redacted] In the total study population improvements in PFS, PFS2, confirmed ORR, and DoR, were also observed in the serplulimab group compared to placebo.[6] Patient reported outcomes indicated similar improvements in QoL between serplulimab and placebo treatment groups, with significant improvement at week 18 in the 'pain in other parts' symptom domain of QLQ-LC13, in those receiving serplulimab.[6] The key survival outcomes were assessed and subsequently used for cost effectiveness analysis. Overall, the EAG are satisfied with the results of efficacy outcomes.

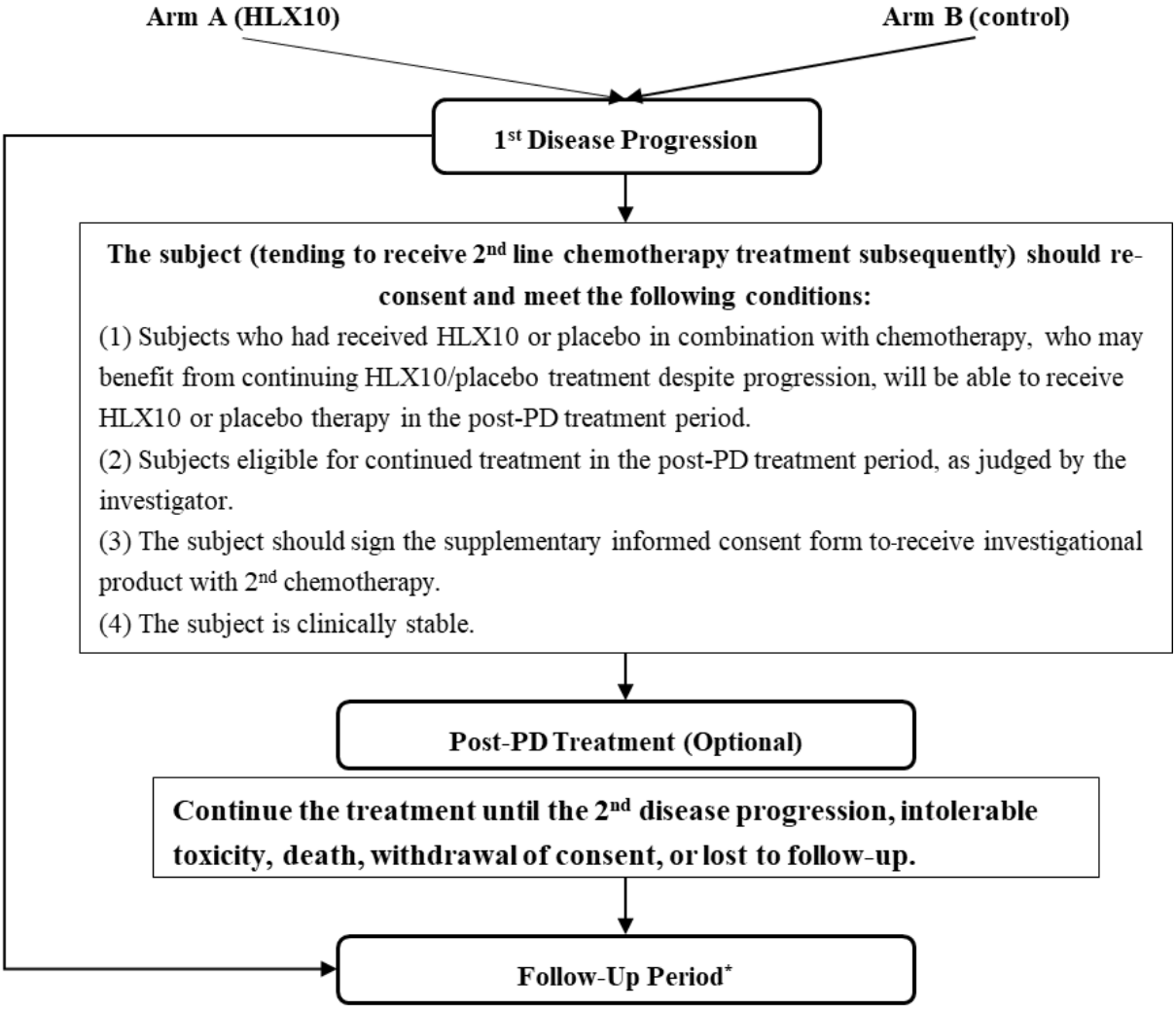
Results: Adverse events	B.2.9, p.72-76;[6] CS Appendix G, p.158-165[6]	**Appropriate** Overall serplulimab was well tolerated with a similar rate of treatment emergent adverse events (TEAEs) compared to placebo ([redacted]).[6] Although the incidence of SAEs ([redacted]).and drug related TEAEs ([redacted]).was higher in those receiving serplulimab compared to placebo, the number of patients that discontinued serplulimab/placebo due to TEAEs was overall similar ([redacted]).[6] The incidence of TEAEs leading to death was higher in the placebo arm than serplulimab arm ([redacted]).[6] Immune-related TEAEs occurred in a higher proportion of patients receiving serplulimab compared to placebo [redacted] Overall, the EAG are satisfied with the safety profile of serplulimab.
Results: Subgroup analyses	B.2.8, p.60-62[6]	**Appropriate** No subgroup analysis was specified in the NICE scope.[12] However, prespecified subgroup analyses were presented in the CS for the following subgroups: age, sex, race, ethnicity, baseline ECOG PS score, baseline smoking status, baseline brain metastasis, and baseline PD-L1 expression levels. The subgroup analyses, inferred using ITT and per protocol set (PPS), generated HRs for OS, PFS, and PFS2, favouring serplulimab over placebo across all subgroups.[6] Although the analyses provide supportive evidence for an overall benefit of serplulimab over placebo regardless of the covariates tested, the small sample sizes of these subgroups reduce the power of these analyses and therefore warrants caution in their interpretation.

Abbreviations: AE = Adverse events; AUC = area under the concentration-time curve; CI = Confidence Interval; CNS = central nervous system; CPS = Combined positive score; CS = company submission; CSR = Clinical study report; D = Day; DOR = Duration of response; EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EMA = European Medicines Agency; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Scale; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13; EOT = End of treatment; ES-SCLC = extensive stage – small cell lung cancer; HR = Hazard Ratio; iRECIST = Immune-based Response Evaluation Criteria in Solid Tumours; IRRC = Independent Radiology Review Committee; ITC = Indirect treatment comparison; ITT = Intent-To-Treat Population; IV = intravenous infusion; IWRS/IVRS = interactive web/voice response system; mDoR = median duration of response; NA; Not applicable; NICE = National Institute for Health and Care Excellence; ORR = Objective response rate; OS = Overall survival; p = probability value; PD-L1 = Programmed cell death-ligand 1; PFS = Progression Free Survival; PFS2 = Progression Free Survival 2; PPS = Per protocol set; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; SmPC = summary of product characteristics; TEAE = Treatment-emergent adverse event; TPS = tumour proportion score; UK = United Kingdom; vs. = versus.

3.6.1.1 Treatment

In ASTRUM-005 [redacted] and [redacted] of participants had subsequent treatment after first disease progression in the serplulimab and placebo arms, respectively.[4] However, clinical advice to the EAG was that in UK clinical practice, very few patients will get to second line treatment. Additionally, cyclophosphamide plus doxorubicin plus vincristine (CAV), was indicated be a global standard option, however this is considered very toxic and difficult to deliver. While topotecan is also considered to be very difficult treatment to deliver; the advice received by the EAG is that it also has very modest benefits and unconvincing response rates. Clinical expert advice that supported the appraisal of atezolizumab with carboplatin and etoposide for untreated ES-SCLC (NICE TA638),[8] also referred to in the CS (B.3.5.2; p.121),[6] indicated that only 10 – 20% of patients move to second line treatment after the relapse of their disease and that in the UK general practice, patients will either be re-challenged with first-line chemotherapy, treated with topotecan or treated with CAV.[8]

Figure 3.1: Schematic of study treatment



Source: Figure 4, PfC Question B9.b[4], Figure 1, p.89[51]
Abbreviations: HLX10 = serplulimab; PD= progressed disease.
Footnotes: * Follow-Up Period includes safety follow-up and survival follow-up. Patients who are not eligible for post-PD treatment will be followed up for safety and survival status

In response to PfC (Question B9) the Company confirmed if a subject had first disease progression, was clinically stable, and intended to receive second-line chemotherapy treatment subsequently (the selection of second-line chemotherapy may refer to the National Comprehensive Cancer Network (NCCN) guidelines or the ESMO guidelines), it was at the discretion of the investigator to continue treating the subject with blinded serplulimab or placebo assignment per protocol in addition to the second-line chemotherapy, until the second disease progression, intolerable toxicity, death, withdrawal of consent, or loss to follow-up (Figure 3.1).[4,49,51] Any other anti-PD-1 and anti-PD-L1 therapy were not allowed.{ Cheng, 2022 #32;Cheng, 2022 #135} However, out of the total study population (N=585), [redacted] patients were also documented to receive atezolizumab and [redacted] received durvalumab as a subsequent line of treatment, which are not recommended second-line treatments in UK clinical practice.[8,17]

In the PfC response (Question B9), the Company summarises the subsequent anticancer treatments after first disease progression stratified by Asian and non-Asian subgroups (Table 3.6).[4]

[redacted] Additionally, [redacted] and [redacted] of the Asian subgroup in the serplulimab arm received targeted therapies, or other therapies which included herbal or Traditional Chinese Medicine, immunomodulator, antineoplastic agent and other clinical trial therapies, respectively.

[redacted] These data therefore highlight differences in subsequent treatments administered and treatment pathways between Asian and non-Asian groups, as well as countries in the trial. As these may not reflect standard clinical practice in England the EAG have therefore identified this as some concern.

Table 3.6: Summary of subsequent anticancer treatment after first disease progression in ASTRUM-005 (cutoff date: 7th May 2024)

	Serplulimab group			Placebo group		
	All serplulimab arm	Asian	Non-Asian	All placebo arm	Asian	Non-Asian
	N=389	N=262	N=127	N=196	N=139	N=57
Number of patients with ≥1 treatment after first disease progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Line of therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 and other[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Therapy type	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Target Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 16, PfC Question B9[4]
Footnotes: [a] Other lines of therapy included herbal or Traditional Chinese Medicine, thermo-chemotherapy perfusion, and non-systemic treatment, among others.
[b] Other therapies include herbal or Traditional Chinese Medicine, immunomodulator (lentinan, thalidomide, spleen amino peptide oral lyophilized powder, thymopolypeptides for injection, etc), antineoplastic agent (unknown) and other clinical trial.

3.6.1.2 Baseline characteristics

The baseline characteristics of participants in the trial are summarised in Table 3.7. In the CS and PfC response (Question B7) the company stated baseline characteristics [redacted].[4,6,54] However, the EAG note, the trial did not take place in the UK, enrolling patients predominantly from China (n=400/585) in addition to Russia (n=42/585), Georgia (n=50/585), Poland (n=7/585), Ukraine (n=41/585) and Turkey (n=45/585)[4] Subsequently key differences in baseline characteristics compared to the UK patients population can be observed, particularly with regards to sex, race and never smokers, raising concerns regarding the generalisability of the study population to the that in the UK. In the UK, the rates of lung cancer incidence are very similar among males and female (48% in females and 52% in males).[55] However, the vast majority of the participants in both arms of ASTRUM-005 are males (81.5% in the serplulimab arm and 83.7% in the placebo arm).[49] With the majority of patients being enrolled from China, about two thirds (401/585, 68.5%) of the total trial population are Asian.[49] Notably, Asian ethnicity has been

indicated to be a favourable prognostic factor for ES-SCLC, with differences in treatment responses, being observed between different ethnicities/race due to genetic variation.[56]

Table 3.7: Summary of baseline characteristics of patients who participated in the ASTRUM-005 trial

Characteristics	Serplulimab group (n=389)	Placebo group (n=196)
Age at screening (years)		
Min, max	28, 76	31, 83
Mean (standard deviation, SD)	61.0 (8.64)	61.1 (8.75)
Median (Q1, Q3)	63.0 (56.0, 67.0)	62.0 (55.0, 68.0)
<65 years	235 (60.4)	119 (60.7)
Gender, n (%)		
Male, n (%)	317 (81.5)	164 (83.7)
Female, n (%)	72 (18.5)	32 (16.3)
Race,[a] n (%)		
Asian	262 (67.4)	139 (70.9)
Non-Asian[b]	127 (32.6)	57 (29.1)
Ethnicity, n (%)		
Hispanic or Latino	0	0
Not Hispanic or Latino	366 (94.1)	184 (93.9)
Other	23 (5.9)	12 (6.1)
Smoking status, n (%)		
Current	102 (26.2)	48 (24.5)
Former	206 (53.0)	113 (57.7)
Never	81 (20.8)	35 (17.9)
Baseline ECOG Performance Status Scale score[c]		
0	71 (18.3)	32 (16.3)
1	318 (81.7)	164 (83.7)
Prior anti-cancer therapy, n (%)		
Chemotherapy[d]	9 (2.3)	3 (1.5)
Other[e]	1 (0.3)	2 (1.0)
PD-L1 expression levels, n (%)		
Negative, TPS<1%	317/379 (83.6)	152/186 (81.7)
Positive, TPS≥1%	62/379 (16.4)	34/186 (18.3)
Brain metastases, n (%)	50 (12.9)	28 (14.3)
Liver metastasis, n (%)	99 (25.4)	51 (26.0)

Characteristics	Serplulimab group (n=389)	Placebo group (n=196)
Source: Table 6, Document B[6]; Table 1, Cheng et al. (2022)[49] Abbreviations: CPS = continued positive score; ECOG PS = Eastern Cooperative Oncology Group performance status; PD-L1 = programmed death-ligand 1; SOD = sum of diameters; TPS = tumour proportion score. Footnotes: **a Self-reported by the patients by selecting 1 or more racial designations (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, White, or Other) or based on identity information provided by the patients; b All patients were White** **c Scores range from 0 to 5 (higher scores indicate greater disability)**; **d There were 11 patients who had received treatment for limited-stage small cell lung cancer (treatment-free interval ≥6 months). One patient in the placebo group had received treatment for gastric cancer (>5 years ago)** ; **e Herbal or traditional Chinese medicine (2 in the placebo group) and the immunostimulant lentinan (1 in the serplulimab group).**		

Clinical advice to EAG stated it was very rare for never smokers to present as patients with SCLC in UK clinical practice, smoking being a well-known risk factor for SCLC.[57] Meanwhile in ASTRUM-005, 19.8% (116/585) of the total study population were never smokers.[49] Additionally an imbalance in the proportion of Asian to non-Asian never smokers can be seen in the ASTRUM-005 trial; of the total Asian study population [redacted] were never smokers, whilst in the total non-Asian study population only [redacted] were never smokers.[17] This corresponds to [redacted] and [redacted] of the Asian, and non-Asian never smoking study subgroups respectively.[17] In corroboration, epidemiological studies report there to be a greater proportion of never smokers in East Asian patients with SCLC compared to Caucasian patients.[58] In ASTRUM-005 the authors,[49] proposed second-hand smoke exposure to be causal to the development of SCLC in Asian never smokers. However, clinical advice to EAG highlighted the incidence of a subgroup of the never smoking Asian population with adenocarcinoma (a type of NSCLC), which harbours oncogenic mutations,[58,59] and may transform into SCLC.[60] Clinical advice to the EAG stated that this association was only theoretical and the genetic profiling of oncogenic mutations in ASTRUM-005 trial is not available to explore this further. Independently, there has been some speculation as to whether the Asian population in the ASTRUM-005 trial may include mixed histology or other tumours, such as NSCLC, which have more favourable responses to chemotherapy combined with immunotherapy.[61] Overall, this suggests there may be different disease trajectories and treatment responses for the Asian population, particularly never smokers, however, how this translates to the NHS patient population is not known.

3.6.2 IMpower133

IMpower133 (NCT02763579), is a multicentre, phase I/III, double-blind, placebo-controlled trial that evaluated the safety and efficacy of atezolizumab in combination with carboplatin and etoposide versus placebo with carboplatin and etoposide in the treatment of ES-SCLC in previously untreated patients.[18] A total of 403 participants were randomly assigned in 1:1 ratio to receive, in the induction phase, four 21-day cycles of carboplatin (AUC 5 mg /ml/min, IV on day 1 of each cycle) and etoposide (100 mg/m^2 of body-surface area, IV on days 1 through 3 of each cycle) with either atezolizumab (at a dose of 1200 mg, IV on day 1 of each cycle) or placebo.[18] A maintenance phase followed the induction phase, in which the participants received either atezolizumab or placebo (based on their previous random allocation) until disease progression or the occurrence of unacceptable toxicity.[18] A total of 201 patients received atezolizumab with carboplatin and etoposide; and 202 patients received placebo with carboplatin and etoposide.[18] The trial had 106 sites in 21 countries (Australia, Austria, Brazil, Chile, China, Czechia, France, Germany, Greece, Hungary, Italy,

Japan, Republic of Korea, Mexico, Poland, Russian Federation, Serbia, Spain, Taiwan, United Kingdom, United States).[18,62,63]

A summary of the EAG's critique of the design, conduct and analysis of IMpower133 is presented in Table 3.8.

Table 3.8: Summary of EAG's critique on the design, conduct and analysis of the IMpower133 trial

Trial design or conduct concept	Section in CS (or other sources) where methods are reported	EAG's assessment
Treatment	Liu, et al. (2021);[63] Horn, et al. (2018);B.2.8, p.63-67[6]	**Some concerns** Participants were randomised to receive four 21-day cycles of carboplatin (AUC 5 mg /ml/min, IV on day 1 of each cycle) and etoposide (100 mg/m^2 of body-surface area, IV on days 1 through 3 of each cycle) with either atezolizumab (at a dose of 1200 mg, IV on day 1 of each cycle) or placebo (induction phase) followed by a maintenance phase.[18,63] During the latter PCI was allowed and patients could continue to receive their assigned treatment until they had unacceptable toxic effects, disease progression or no additional clinical benefit.[18,63] Being in line with that, recommended treatment dosage of atezolizumab[8,64] and the NICE scope,[12] the EAG believes that the first-line treatment is appropriate. However, there are some concerns surrounding the subsequent treatments administered to patients which may not align with that seen in English clinical practice. See Section 3.6.2.1 for further comment.
Randomisation	Horn, et al. (2018); B.2.8, p.63-67[6]	**Appropriate** During the trial 403 participants were randomised from 106 sites in 21 countries in a 1:1 ratio to atezolizumab (n=201) or placebo (n=202), using stratified permuted-block randomisation.[18] The randomisation was stratified following the stratification factors: sex, ECOG PS, and the presence of brain metastasis.[18] The EAG believes that the randomisation method used in the trial was appropriate.
Allocation concealment	Horn, et al. (2018); B.2.8, p.63-67[6]	**Appropriate** Patients were randomised using stratified permuted-block randomisation, performed using an interactive voice or web response system (IxRS).[18]Overall, the EAG believe that the allocation concealment was appropriate, meeting recognised standards. T
Eligibility criteria	Horn, et al. (2018); B.1.1,	**Appropriate**

	p.10;[6] B.2.8, p.63-67[6]	Eligible participants were patients with cytologically and histologically confirmed ES-SCLC who had a ECOG status score of 0 or 1, and who had not received a previous systemic treatment for ES-SCLC. Patients who had treated or asymptomatic central nervous system (CNS) metastases were eligible. These eligibility criteria are in line with the scope,[12] and therefore, the EAG believes that the eligibility criteria are appropriate.
Blinding	Horn, et al. (2018); B.2.8, p.63-67[6]	**Appropriate** IMpower133 was reported to be double-blinded; the Sponsor and its agents (except the IxRS service provider, pharmacokinetics/pharmacodynamic laboratory personnel, and the independent Data Monitoring Committee members); the study site personnel, including the investigator; and the patients were blinded to treatment allocation. Unblinding was permitted at the patient and study level in case of emergency or as required by local health authorities.[65] Thus, the EAG considers the blinding approach in this clinical trial appropriate.
Baseline characteristics	B.2.8, p.63-67[6]	**Some concerns** The trial was global enrolling patients from 106 sites in 21 countries including the UK.However, as only summary level published data of IMPower133 are available, the exact number of patients recruited from the UK is unknown. Compared to the incidence in the UK,[55] a higher proportion of male patients were enrolled. Therefore, the EAG have raised some concerns. See Section 3.6.2.2 for further comment.
Dropout rate	Horn, et al. (2018) ClinicalTrials.gov, (2017);[66] Reck, et al. (2024);[67] Liu, et al. (2021)[63]	**Appropriate** At data cutoff of 24th January 2019, 161 patients randomised to the atezolizumab arm (n=201) discontinued the trial (138 due to death; 3 lost to follow-up; 2 withdrawal by physician; 18 withdrew).[63] In the placebo arm (n=202), 172 discontinued the study (158 due to death; 2 lost to follow-up; 12 withdrawals).[63] Additionally patients in the atezolizumab arm were eligible to rollover to an extension trial (IMbrella A; NCT03148418), if they continued to receive atezolizumab at the time of trial closure or were in survival follow-up after atezolizumab discontinuation.[66,67] The EAG is satisfied with the overall retention rate reported.
Statistical analyses	Horn, et al. (2018); Liu, et al. (2021)[63]	**Appropriate** The sample size was calculated based on OS. It was estimated that 306 deaths in the ITT population would be required in order to provide 91% power at a two-sided significance level of 0.045 to detect a

		HR for death with atezolizumab vs. placebo of 0.68, with the use of a log-rank test.[18] The primary end points were assessed in the ITT population.[18] Safety analyses included all patients who had received at least one dose of atezolizumab (n=198) or placebo (n=196).[18,63] Accordingly, the EAG considers the statistical analyses appropriate.
Outcome measures	Horn, et al. (2018); Liu, et al. (2021);[63] B.2.8, p.63-67;[6] Mansfield et al. (2020)[68]	**Appropriate** The primary endpoints were OS and investigator assessed PFS per RECIST 1.1.[18,63] Key secondary endpoints included investigator assess ORR (according to RECIST) and DOR.[18,63] Additional endpoints and measurements included safety (including AEs assessed according to National Cancer Institute Common Terminology Criteria for AEs v4.0), HRQoL (using QLQ-C30 and QLQ-LC13 instruments), and exploratory biomarker analyses.[63,65,68] HRQoL was assessed on day 1 of each 21-day treatment cycle at scheduled study visits during treatment, and at 3 months and 6 months after treatment discontinuation.[68] The key survival outcomes were assessed and subsequently used for cost effectiveness analysis and, as these outcomes match those listed in the scope,[12] the EAG consider the outcomes measured appropriate.
Results: Efficacy outcomes	Horn, et al. (2018); Liu, et al. (2021);[63] B.2.8, p.63-67;[6] Mansfield et al. (2020)[68]	**Appropriate** Treatment with atezolizumab plus carboplatin and etoposide resulted in improvement in OS and PFS compared to placebo carboplatin, and etoposide. At the data cutoff date of 24th January 2019 (OS median follow-up 22.9 months), median OS was 12.3 months (95% CI: 10.8 to 15.8) in the atezolizumab arm compared to 10.3 months (95% CI, 9.3 to 11.3) in the placebo arm (HR: 0.76; 95% CI: 0.60 to 0.95; p = 0.0154).[63] The median PFS was 5.2 months in the atezolizumab arm and 4.3 months in the placebo arm (HR=0.77; 95% CI: 0.62 to 0.96; p= 0.02).[63] ORR and DoR were reported to be similar between treatment groups.[63] Patient reported outcomes indicated HRQoL to improve in both arms after initiating treatment and during the maintenance phase.[68] The EAG believe that the results of the efficacy outcomes presented in IMPower133 are appropriate.
Results: Adverse events	Horn, et al. (2018); Liu, et al. (2021)[63]	**Appropriate** At data cutoff points (24th April 2018 and 24th January 2019) the AEs were comparable. At data cutoff 24th April 2018, the most common grade 3 or 4 AEs were neutropenia, anaemia, and decreased neutrophil count.[18,63]At the data cutoff 24th January

		2019 all participants in atezolizumab arm (100%) had any grade AEs versus 96.4% in the placebo arm. SAEs occurred in 38.9% in the atezolizumab arm vs. 35.2% in the placebo arm. Grade 3 or 4 AEs occurred in 67.7% and 63.3% in patients in the atezolizumab and placebo arms respectively. The most common immune related AEs reported in the atezolizumab arm vs. placebo arm were rash (20.2% vs. 10.7%), hypothyroidism (12.6% vs 0.5%) and hepatitis (7.6% vs 4.6%).[63] The EAG agree that the safety profile presented is acceptable.
Results: Subgroup analyses	Horn, et al. (2018); Liu, et al. (2021)[63]	**Appropriate** No subgroup analysis was specified in the NICE scope.[12] However, pre-specified subgroup analyses were conducted for OS and PFS, stratified by sex, age, ECOG score, brain metastasis, liver metastasis, tumour mutational burden and PD-L1 expression.[18,63] Overall, no difference in benefit for OS or PFS with atezolizumab was observed across these subgroups, however, owing to the sample sizes the EAG considers these results are supportive but warrant caution in their interpretation.
Abbreviations: AE = Adverse events; AUC = area under the concentration-time curve; CI = Confidence Interval; CNS = central nervous system; DOR = Duration of Response; EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = Hazard Ratio; IxRS = interactive voice/web response system; ITC = Indirect treatment comparison; ITT = Intent-To-Treat Population; Mb = megabase; OS = Overall survival; p = probability value; PD-L1 = Programmed cell death-ligand 1; PFS = Progression Free Survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; SmPC = summary of product characteristics; vs. = versus		

3.6.2.1 Treatment

At the primary data cut off (24th April 2018) of IMpower133, 51.7% (104/201) and 57.4% (116/202) patients in the atezolizumab and placebo group, respectively were reported to receive at least one subsequent therapy.[18,65] The EAG are unaware of such data in later study cut off dates.[63] Furthermore, 22 patients in each treatment group of IMPower133 were reported to receive PCI which was permitted during the maintenance phase of the trial.[18] A summary of subsequent anticancer treatments are presented in Table 3.9. Understandably, as 21 countries were involved in IMpower133,[18] treatment patterns observed will not specifically represent clinical practice in any one country. However, it remains unknown if these subsequent treatments confounded outcomes in the trial and what the estimates of the effectiveness would be expected to be observed if treatment pathways used in English standard clinical practice were followed, as is recommended by the DSU.[69,70] Furthermore, clinical advice to the EAG confirmed very few patients in English clinical practice receive further lines of treatment, or PCI. Thus, the EAG have some concerns over subsequent treatment received, and how this translates to the standard treatment pathway in English practice.

Table 3.9: Summary of subsequent anticancer treatment in IMPower133

	Atezolizumab Group (N=201)	Placebo Group (N=202)
Line of therapy		
Second	101 (50.2)	116 (57.4)
Third	29 (14.4)	38 (18.8)
Fourth	3 (1.5)	15 (7.4)
Therapy type		
Total number of patients with at least one treatment	104 (51.7)	116 (57.4)
Total number of treatments — no.	138	176
Chemotherapy/non-anthracycline	81 (40.3)	88 (43.6)
Chemotherapy/anthracycline	31 (15.4)	46 (22.8)
Immunotherapy	6 (3.0)	15 (7.4)
Other	2 (1.0)	2 (1.0)
Targeted therapy	2 (1.0)	1 (0.5)

Source: Table S4 Horn et al. (2018)[65]
Note: Data are no. of patients with at least one treatment (%) unless otherwise specified. Multiple cases within a specific line of therapy and regimen for a patient were counted once for the frequency of line of therapy or regimen name. A patient was counted more than once if that patient received more than one therapy type under each line and regimen. The data cutoff date was 24th April 2018.

3.6.2.2 Baseline characteristics

IMpower133 was a global study including 106 sites across 21 countries (Australia, Austria, Brazil, Chile, China, Czechia, France, Germany, Greece, Hungary, Italy, Japan, Republic of Korea, Mexico, Poland, Russian Federation, Serbia, Spain, Taiwan, United Kingdom, United States).[18,62,63] However, as only summary level published data of IMPower133 is available, the exact number of patients recruited from the UK is unknown. Thus, the EAG have some concerns regarding the generalisability of the population in the IMpower133 to the UK patient population. For example, across the total study population approximately two thirds of the participants were males (64.2 % in atezolizumab arm and 65.3% in the placebo group). Lung cancer incidence rates in males and females in the UK are overall reported to be similar (including NSCLC) (Cancer Research, UK, 2017-2019).[55]

The proportion of participants reported as never smokers and patients with brain metastasis in IMpower133 is similar to that seen in UK clinical practice as confirmed by a clinical advisor and reported in a retrospective cohort study by Blackhall et al. (2023).[71] Data derived from patient's medical records between October 2013 – October 2015, indicated that among patients with untreated ES-SCLC who were diagnosed in the UK (n=103), 8.7% had brain metastasis and 3.9% were never-smokers at the time of diagnosis.[71]

3.6.3 CASPIAN

The CASPIAN trial (AstraZeneca) is an international, multicentre phase III, open-label study to investigate the efficacy and safety of combining durvalumab with or without tremelimumab with platinum-based chemotherapy followed by durvalumab with or without tremelimumab

maintenance therapy versus platinum-based chemotherapy alone as first-line treatment in patients with ES-SCLC (NCT03043872).[19-21,25] Durvalumab was identified as a relevant comparator in the NICE Scope,[12] and received NICE guidance (TA1041) in February 2025. Data on the durvalumab plus platinum-based chemotherapy (carboplatin or cisplatin + etoposide) arm was included in the PfC response,[4] and was used by the Company to form a connected network with serplulimab (using the ASTRUM-005 trial) using a Bucher ITC and MAIC (see Section 3.7.2 for further details).

Durvalumab was administered as an IV infusion every three weeks for 12 weeks (4 cycles) and every three weeks thereafter until progressive disease or other discontinuation criteria.[21] The trial was conducted in 209 sites in 23 countries (Argentina, Austria, Brazil, Bulgaria, China, Czechia, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Netherlands, Poland, Romania, Russian Federation, Slovakia, Spain, Taiwan, Turkey, Ukraine, United States).[19,21] No participants were drawn from the UK. A summary of the EAG's critique of the design, conduct and analysis of CASPIAN is presented in Table 3.10.

Table 3.10: Summary of EAG's critique on the design, conduct and analysis of the CASPIAN trial

Trial design or conduct concept	Section in CS (or other sources) where methods are reported	EAG's assessment
Treatment	Paz-Ares et al. (2019)[19]	**Some concerns** CASPIAN comprised two experimental arms and an active comparator arm: • Durvalumab with tremelimumab and platinum-based chemotherapy (carboplatin or cisplatin + etoposide) • Durvalumab with platinum-based chemotherapy (carboplatin or cisplatin + etoposide) • Platinum-based chemotherapy (carboplatin or cisplatin + etoposide) + PCI (investigator's discretion) Patients in the immunotherapy groups received up to four cycles of platinum–etoposide plus durvalumab 1,500 mg with or without tremelimumab 75 mg every three weeks followed by maintenance durvalumab 1,500 mg every four weeks.[19] Patients continued treatment until disease progression per investigator assessment, unacceptable toxicity, or other discontinuation criteria were met.[19] This aligns with the dosage (1,500 mg) and administration of durvalumab by the emc,[72] The EAG are satisfied that the first line treatment dosage matches that recommended by regulatory authorities. However, the EAG has some concerns surrounding subsequent treatments administered to patients. See Section 3.6.2.1 for further comment.
Randomisation	Paz-Ares et al. (2019)[19]	**Appropriate**

		Randomisation was performed using an interactive voice-response or web-response system. This centralised system effectively manages the randomisation process, and the EAG are satisfied that this was performed adequately.
Allocation concealment	Paz-Ares et al. (2019)[19]	in a 1:1:1 ratio to receive durvalumab plus platinum-etoposide, durvalumab plus tremelimumab plus platinum-etoposide, or platinum-etoposide alone.[19].[19]
Eligibility criteria	Paz-Ares et al. (2019)[19]	**Appropriate** The trial assessed 972 patients for eligibility, of which 805 underwent randomisation.[19] Trial eligibility for CASPIAN matched the NICE scope for serplulimab, namely treatment-naïve ES-SCLC patients.[12] Eligible patients were aged at least 18 years (20 years in Japan) with treatment-naive ES-SCLC, a WHO PS score of 0 or 1, with suitability for first-line platinum-based chemotherapy.[19] Patients with brain metastases were eligible provided they were asymptomatic or treated and stable off steroids and anticonvulsants for at least one month before study entry.[19] The EAG believes the eligibility criteria to be appropriate.
Blinding	Paz-Ares et al. (2019)[19]	**Some concerns** CASPIAN was open-label and allocation was unmasked to investigators and patients.[19] The sponsor was however masked to all aggregated efficacy and safety data.[19] Open-label studies lack the rigor of blinded studies and can introduce significant bias, although as the primary outcome is OS this is less of a concern and is further explored in Section 3.6.3.23.6.3.1.
Baseline characteristics	Paz-Ares et al. (2019),[19] Paz-Ares et al. (2022)[25]	**Some concerns** The trial was conducted in 209 sites across 23 countries in Europe, Asia, and South and North America.[19] No trial participants were drawn from the UK, and therefore the EAG have some concerns regarding the generalisability of the population in CASPIAN to that seen in UK clinical practice. Whilst the baseline characteristics are comparable across trial arms, the trial population may not be reflective of patients seen in UK. [19]This is discussed further in Section 3.6.3.3.
Dropout rate	Paz-Ares et al. (2019)[19]	**Appropriate** From the 805 patients who underwent randomisation, three patients did not receive treatment in the durvalumab plus platinum-etoposide arm, with a further three in the platinum-etoposide arm. Amongst those patients who received durvalumab plus platinum-etoposide, 42 discontinued platinum-etoposide and 222 discontinued durvalumab, the majority of which

		(n=177) were for reasons of disease progression.[19] In the platinum-etoposide arm, 76 discontinued platinum-etoposide.[19] The EAG are satisfied that dropout was comparable between treatment arms, was not excessive and that reasons for attrition were reported.
Statistical analyses	Paz-Ares et al. (2019)[19]	**Appropriate** Efficacy data were analysed on an 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.[19] The EAG are satisfied that the statistical analyses are appropriate
Outcome measures	NICE, (2025)[12] Paz-Ares et al. (2019),[19] ClinicalTrials.gov, (2017)[21]	**Appropriate** The NICE scope includes outcomes related to OS, PFS, response rates, HRQoL and safety.[12] The CASPIAN trial encompassed outcomes related to OS, PFS, ORR, the percentage of patients alive (and/or progression free) at 6, 12, and 18 months, pharmacokinetics of durvalumab/ tremelimumab, patients with anti-drug antibodies, HRQoL.[21,19] OS and PFS were analysed in the ITC. The EAG considers the outcomes to be appropriate, and the key survival outcomes were assessed and subsequently used for cost effectiveness analysis.
Results: Efficacy outcomes	Paz-Ares et al. (2019),[19] Goldman et al. (2021),[74] Paz-Ares et al. (2022),[25] ClinicalTrials.gov (2017)[21]	**Appropriate** The trial met the primary endpoint. At data cutoff 11th March 2019, OS was significantly longer in the durvalumab plus platinum-etoposide arm than the platinum-etoposide arm (HR = 0·73; 95% C I= 0·59 - 0·91; p=0·0047). Median OS was 13·0 months (95% CI= 11·5 – 14·8) for the durvalumab plus platinum-etoposide arm vs. 10·3 months (95% CI= 9·3 – 11·2) for the platinum-etoposide arm. The benefit of OS was sustained (at median follow-up of 25.1 and 39.4 months (data cutoff 27th January 2020 and 22nd March 2021, respectively). At data cutoff 11th March 2019, PFS HR was 0·78 (95% CI 0·65 – 0·94). Median PFS was 5·1 months (95% CI = 4·7 – 6·2) for the durvalumab plus platinum–etoposide arm vs. 5·4 months (95% CI = 4·8 – 6·2) for the platinum–etoposide arm.[19] Confirmed OR (analysed post-hoc) was 182 (68%) for the durvalumab plus platinum–etoposide arm vs. 155 (58%) for the platinum–etoposide arm; OR =1·56 (95% CI = 1·10 – 2·22).[19] Overall, the EAG agrees that the efficacy results presented are appropriate.

Results: Adverse events	Paz-Ares, et al. (2019),[19] Goldman, et al. (2021)[74]	**Appropriate** AEs of any cause and grade and of grade 3 or 4 occurred in 98% and 62% of patients treated with durvalumab plus platinum–etoposide respectively vs. 97% and 62% of patients treated with platinum–etoposide respectively. SAEs occurred in 31% of patients in the durvalumab plus platinum–etoposide arm vs. 36% in the platinum–etoposide arm. Any AE leading to death occurred in 5% of patients in durvalumab plus platinum–etoposide arm vs. 6% in the platinum–etoposide arm. 9% in each arm had adverse events that led to discontinuation. The most common AEs were neutropenia, anaemia, nausea, and alopecia.[19,74] The EAG agree that the safety profile presented is acceptable.
Results: Subgroup analyses	NICE, (2025)[12] Paz-Ares, et al. (2019),[19]	**Appropriate** No subgroup analysis was specified in the NICE scope.[12] Pre-specified sub-group analysis of overall survival was done to establish the consistency of the treatment effect according to baseline characteristics of planned platinum (carboplatin vs. cisplatin), age (<65 years vs ≥65 years), sex (women vs men), WHO PS (0 vs 1), smoking status (smoker vs. non-smoker), brain or CNS metastases (yes vs. no), disease stage at diagnosis (stage 3 vs. stage 4), race (Asian vs. non-Asian), and region (Asia vs. Europe vs. North and South America).[19] The HRs for OS consistently favoured durvalumab plus platinum–etoposide versus platinum–etoposide across all prespecified patient subgroups.[19] The EAG consider the subgroup analyses in this clinical trial appropriate.
Abbreviations: AE = Adverse events; CI = Confidence Interval; CNS = central nervous system; EAG = Evidence Assessment Group; emc = electronic medicines compendium; ES-SCLC = extensive stage – small cell lung cancer; HR = Hazard Ratio; HRQoL = Health-related quality of life; ITC = Indirect treatment comparison; ITT = Intent-To-Treat Population; N = sample size; NICE = National Institute for Health and Care Excellence; OR = Odds Ratio; ORR = Objective response rate; OS = Overall survival; PFS = Progression Free Survival; SAE = serious adverse event; UK = United Kingdom; vs. = versus; WHO = World Health Organization.		

3.6.3.1 Treatment

At the data cut off (24th March 2019) 42% (113/268) of patients receiving durvalumab plus platinum etoposide and 44% (119/269) of patients in the control arm were reported to receive at least one subsequent therapy.[19] Furthermore, 21 patients in the control arm were reported to receive PCI.[19] A summary of subsequent anticancer treatments received are presented in Table 3.11. As 23 countries were involved across Europe, Asia, North America and South America,[18] treatment pathways will not specifically represent clinical practice of any one country. Additionally, it remains unknown if these subsequent treatments confounded outcomes in the trial. Clinical advice to the EAG confirmed very few patients in English clinical practice receive further lines of treatment, or PCI. Regarding PCI specifically, Roche Products Limited noted in their PfC response for atezolizumab (TA638), that an

advisory board of practicing NHS oncologists suggested (as of 2019), the proportion of patients receiving PCI is highly variable across the UK, and the rate is falling due to uncertainty in survival benefits.[75] Thus, the EAG have some concerns over subsequent treatment received, and how this translates to the clinical pathway in the England.

Table 3.11: Summary of subsequent anticancer treatment in CASPIAN

	Durvalumab + EP (n = 268)	**EP (n = 269)**
Patients who received study treatment, *n* (%)	265 (98.9)	266 (98.9)
Patients ongoing study treatment	27 (10.1)	0
Patients receiving any subsequent therapy, *n* (%)	125 (46.6)	126 (46.8)
Chemotherapy	123 (45.9)	119 (44.2)
Single agent	67 (25.0)	72 (26.8)
Platinum doublet	61 (22.8)	51 (19.0)
Other	31 (11.6)	33 (12.3)
Immunotherapy	6 (2.2)	18 (6.7)
Single agent	1 (0.4)	5 (1.9)
Immunotherapy + immunotherapy	2 (0.7)	3 (1.1)
Immunotherapy + chemotherapy	1 (0.4)	4 (1.5)
Immunotherapy + other	0	0
Investigational agent	3 (1.1)	7 (2.6)
Other systemic therapies	3 (1.1)	5 (1.9)
Patients receiving ≥1 subsequent line of treatment, *n* (%)	125 (46.6)	126 (46.8)
Patients receiving ≥2 subsequent lines of treatment, *n* (%)	52 (19.4)	51 (19.0)
Patients receiving >2 subsequent lines of treatment, *n* (%)	17 (6.3)	16 (5.9)

Source: CASPIAN research papers[19,76]
Abbreviations: EP = etoposide plus either cisplatin or carboplatin

3.6.3.2 Blinding

The study was open label, although the sponsor was masked to all aggregated efficacy and safety data.[19] Open-label studies are less rigorous than blinded studies due to the potential for significant bias introduced by the absence of blinding. As such, they are generally only employed when blinding is impractical or unethical, or when the outcome being measured is entirely objective, like survival rates.[77] The two experimental arms in the trial (durvalumab + tremelimumab + platinum-based chemotherapy and durvalumab with platinum-based chemotherapy) have identical administration routes for the immunotherapy treatments. The active comparator arm has only platinum-based chemotherapy. Whilst this is worth consideration, as the primary outcomes relate to survival rates, the EAG are not unduly concerned. As of 22nd March 2021, the CASPIAN trial comprised a follow-up of 39.4 months, and the trial maturity was 86%.[25] Given the maturity of the data arising from the poor prognosis of patients, the open-label nature of the trial is largely acceptable. Whilst blinding

would have led to a lower risk of bias, the key outcomes derived from the ITC encompassed OS and PFS (investigator assessed). As CASPIAN used blinded independent central review (BICR) in addition to investigator-assessed, the study results are as robust as possible given the open-label design. As such, the EAG is satisfied that the approach was largely adequate.

3.6.3.3 Baseline characteristics

CASPIAN was a global trial recruiting patients from 209 sites in 23 countries (Argentina, Austria, Brazil, Bulgaria, China, Czechia, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Netherlands, Poland, Romania, Russian Federation, Slovakia, Spain, Taiwan, Turkey, Ukraine, United States).[19,21] No patients were drawn from the UK, although the highest proportion of patients by region were from Europe (199 patients out of a total of 268 (74.2%) for durvalumab with platinum-based chemotherapy and 205 patients out of a total of 269 (76.2%) for platinum-based chemotherapy alone).[25] However, the EAG has some concerns about the generalisability of the population in the CASPIAN trial to the UK patient population, particularly in relation to the proportion of males/females, and the high proportion of patients who were 'never smokers'. For example, across the total study population over two thirds of the participants were males (71% in the durvalumab plus platinum-etoposide and 68% in the platinum-etoposide group) and8% and 6% of trial participants (for the durvalumab with platinum-based chemotherapy and platinum-based chemotherapy arms respectively) were 'never smokers'.[19] In the UK, lung cancer incidence rates (including NSCLC) (Cancer Research, UK, 2017-2019) are comparable amongst males and females.[55]Furthermore, in CASPIAN, [19]A retrospective cohort study by Blackhall et al. (2023)[71] indicated that among patients with untreated ES-SCLC who were diagnosed in the UK (n=103), 54.4% were male and 3.9% were never-smokers at the time of diagnosis. Clinical advice to EAG further iterated that it was rare for patients reporting as never smokers to be seen in clinical practice. The EAG therefore has some concerns whether the population of CASPIAN is reflective of the patient population seen in the UK.

3.7 Critique of trials identified and included in the indirect comparison

In the final scope issued by NICE, platinum-based combination chemotherapy, durvalumab with platinum-based combination chemotherapy, and atezolizumab with carboplatin and etoposide, were considered relevant comparators.[12] The company reasoned carboplatin-etoposide to be the only platinum-based regimen with relevance to UK practice, presenting standard of care in the NHS, thus precluding the need to construct an network meta-analysis (NMA) with other platinum-based treatment regimens.[6] This was further validated in a modified Delphi panel conducted by the company and verified to the EAG by a clinical advisor.[54] Furthermore, as detailed in Section 2.1, NICE's recommendation for durvalumab for adults with untreated ES-SCLC, was still under development at the time of the decision problem meeting. Subsequently, the Company initially deemed durvalumab not to be a relevant comparator. In the absence of head-to-head trial evidence, the company carried out an ITC in the form of a MAIC to compare serplulimab with atezolizumab, both in combination with carboplatin and etoposide treatment (CS Section B.2.8).[6]

On 19th February 2025 durvalumab with etoposide and either carboplatin or cisplatin, was recommended by NICE for patients with untreated ES-SCLC.[7] Consequently the EAG in the PfC (Question A1)[4] asked the Company to conduct further analyses, preferably a ML-NMR, including durvalumab as a comparator.[13] In response the Company included durvalumab in this submission by conducting a second MAIC using aggregate data from CASPIAN to

generate efficacy estimates between serplulimab and durvalumab.[4] The EAG's critique of the two MAICs are given below in Sections 3.7.1 and 3.7.2.

3.7.1 ASTRUM-005 vs. IMpower133

A summary of the EAG's comments regarding the methodology of the MAIC using IPD from ASTRUM-005 and published aggregate data from IMpower133 are presented in Table 3.12, with key points expanded upon in the following sections below.

Table 3.12: Summary of the EAG's critique of the MAIC methods

Aspect of MAIC design or conduct	Section in CS where methods are reported	EAG's assessment
Statistical methods	B.2.8.4, p68-69[6]	**Some concerns** The company performed a MAIC using guidance from the NICE decision support unit (DSU)[78] and methods described by Signorovitch et al. (2010)[79] Baseline characteristics of the ASTRUM-005 ITT population were adjusted to that of the aggregate summary data of IMpower133. Cox proportional hazards were applied to estimate the relative efficacy between serplulimab treatment and atezolizumab for OS and PFS. An unadjusted ITC was also provided using the Bucher method for reference. The treatment comparator durvalumab for patients with untreated ES-SCLC, included in the final scope[12] and recently approved by NICE,[7] was not included in the CS. See Section 3.7.1.1 for further comment.
Included study characteristics and demographics	B.2.8.1, B.2.8.2 p65-68[6]	**Key issue** Both ASTRUM-005 and IMpower113 trials were overall similar in design, including patients with untreated ES-SCLC. However, the EAG note that ASTRUM-005 was conducted outside the UK, while IMpower133 was carried out across 21 countries including the UK. Subsequently differences in patient and disease characteristics (see Sections 3.6.1 and 3.6.2), and subsequent treatments to that observed in UK clinical practice, raises some concerns over the generalisability and transportability of the trial populations and outcomes to the NHS patient population. See Section 3.6.1.2 for further comment.
Covariates included in the MAIC	B.2.8.2, p66-68[6]	**Some concerns** The company included five covariates within the MAIC: age, ECOG, smoking status, brain metastases, liver metastases. Other variables with evident imbalances between ASTRUM-005 and IMpower133 were not adjusted for; this was stated to be due to lowering of the effective sample size (ESS), availability of data from IMpower133, or there being no significant difference in subgroup analyses of ASTRUM-005. The EAG have some concerns surrounding the identification and uncertainties of potential treatment effect modifiers and impact on the results.

		See Section 3.7.1.3 for further comment.
Results	B.2.8.5- 2.8.7, p69-72[6]	**Some concerns** The company stated [redacted] However, the EAG note the analyses are dependent on the proportional hazards assumption, which there exists to be some level of uncertainty. See Section 3.7.1.4 for further comment.
Sensitivity analyses	B.2.8.5- 2.8.7, p69-72[6]	**Appropriate** In the CS, an unadjusted ITC was provided using the Bucher method. Additionally, the company reported sensitivity analyses in the PfC, which explored the impact of incorporating different covariates (Question B8) and trial cut-off points (Question B11).[4] The results of the sensitivity analyses are consistent, which suggests the impact of the different variables measured was minimal and, therefore the primary analysis conducted in the CS is considered appropriate.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ECOG = Eastern Cooperative Oncology Group; ES-SCLC = extensive stage-small cell lung cancer; ITC = indirect-treatment comparison; ITT = intention-to-treat; MAIC = matching adjusted indirect treatment comparison; ML-NMR = multilevel network meta-regression; NICE DSU = National Institute for Health and Care Excellence Decision Support Unit; OS = overall survival; PfC = points for clarification; PFS = progression free survival		

3.7.1.1 Statistical methods

The treatment comparator durvalumab for untreated ES-SCLC, included in the final scope[12] was also recently approved by NICE.[7] As discussed in Section 2.1 durvalumab was not included in the CS. In the PfC (Question 1)[4] the EAG requested the company to conduct a ML-NMR using individual patient level data from ASTRUM-005 with aggregate data from IMpower133 and CASPIAN, to determine the relative efficacy of serplulimab in comparison to durvalumab and atezolizumab (and chemotherapy). ML-NMR, recommended by the NICE DSU,[80] allows flexibility to generate population-adjusted ITC estimates from any number of treatments and studies, which are applicable to any specified target population.[13] While the EAG agrees MAICs are an acceptable statistical approach to population adjustment, MAICs are only appropriate for simple-two-study scenario and are not generalisable to larger treatment networks.[13] Furthermore MAICs are limited to providing a comparison that is adjusted to the population of the trial for which only aggregate data are available.[13] and can only adjust for differences in observed covariates distributions and not for differences in treatment switching.[78]

The differences in countries involved in ASTRUM-005, IMpower133 and CASPIAN, raises some concern to the EAG over the generalisability and transportability of the trial outcomes to the NHS population. In particular, study population characteristics and subsequent treatment patterns may not be relevant to those seen in UK clinical practice; this is discussed in more detail in Sections 3.6.1 and 3.6.2. Thus, instead of generating another MAIC using the ASTRUM-005 and CASPIAN trials, a ML-NMR would enable the integration of individual patient level data from ASTRUM-005 with aggregate data from IMpower133 and CASPIAN, to determine the relative efficacy of serplulimab in comparison to durvalumab and atezolizumab (and platinum-based chemotherapy alone).

3.7.1.2 Included study characteristics and demographics

In CS Section 2.8.1 the Company state the ASTRUM-005 and IMpower133 are comparable in design and eligibility criteria.[6,18,49] As discussed in Sections 2.1 and 3.6.1.1, clinical advice to the EAG confirmed immunotherapy treatment with atezolizumab and chemotherapy regimens offered in the two studies, reflected that given in UK practice. However, the EAG note there are substantial differences in the trial settings; ASTRUM-005 enrolled patients from China (n=400/585), Russia (n=42/585), Georgia (n=50/585), Poland (n=7/585), Ukraine (n=41/585), and Turkey (n=45/585),[4] whilst IMpower133 enrolled patients from sites in 21 countries including the UK (number enrolled not available) and China (N=110/403).[18,62] These differences are reflected in the variation in the study population demographics and baseline characteristics between the two trials presented in

Table 3.13. The EAG therefore have some concerns surrounding the relative overlap of the two trial populations and transportability to the NHS patient population.

During the modified Delphi study conducted by the company it was agreed that baseline patient characteristics and results of the ASTRUM-005 were broadly comparable to those expected for the first-line UK population.[54] However, as discussed in Sections 3.6.1.2 and 3.6.2.2, both trials included a higher proportion of males than females, while in the UK incidence rates for lung cancer are relatively similar for males and females.[55] Moreover, compared to patients enrolled in IMpower133, patients in ASTRUM-005 were more likely to be younger, male, Asian, and less likely to be smokers.[6,18,49] In ASTRUM-005 68.5% (401/585) of patients were Asian, and 31.5% (184/585) were non-Asian (all reported as White), whilst in IMPower133 only 17.1% (69/403) were Asian and 79.9% (322/403) of patients were White.[62] Additionally, in ASTRUM-005 19.8% (116/585) of patients across both treatment arms were never smokers,[49] compared to 3% (12/403) of all patients enrolled in IMpower133.[18] The clinical advisor to EAG highlighted that there is some theoretical evidence that suggests there may be different disease trajectories and treatment responses for the Asian population, particularly those reporting as never smokers; however, how this translates to the NHS patient population is not known. Overall, IMPower133 may more closely algin to the UK population with regard to smoking status and race than ASTRUM-005.

Table 3.13: Patient characteristics in matched analysis

Baseline Variables	ASTRUM-005		ASTRUM-005 Adjusted		IMpower133	
	Serplulimab (N = 389)	Placebo (N = 196)	Serplulimab (ESS = 240)	Placebo (ESS = 126)	Atezolizumab (N = 201)	Placebo (N = 202)
Age Group, n (%)						
≥ 65 years	154 (39.6)	77 (39.3)	**108 (44.8)**	**60 (47.5)**	**90 (44.8)**	**96 (47.5)**
< 65 years	235 (60.4)	119 (60.7)	**132 (55.2)**	**66 (52.5)**	**111 (55.2)**	**106 (52.5)**
Sex, n (%)						
Male	317 (81.5)	164 (83.7)	216 (90.2)	117 (92.9)	129 (64.2)	132 (65.3)
Female	72 (18.5)	32 (16.3)	24 (9.8)	9 (7.1)	72 (35.8)	70 (34.7)
Race, n (%)						
Asian	262 (67.4)	139 (70.9)	150 (62.6)	84 (66.4)	33 (16.4)	36 (17.8)
Non-Asian	127 (32.6)	57 (29.1)	90 (37.4)	42 (33.6)	168 (83.6)	166 (82.2)
Disease Stage, n (%)						
IV	318 (81.7)	155 (79.1)	204 (84.8)	100 (79.3)	NR	NR
III or other	71 (18.3)	41 (20.9)	36 (15.2)	26 (20.7)	NR	NR
ECOG, n (%)						
PS 1	318 (81.7)	164 (83.7)	**153 (63.7)**	**84 (66.8)**	**128 (63.7)**	**135 (66.8)**
PS 0	71 (18.3)	32 (16.3)	**87 (36.3)**	**42 (33.2)**	**73 (36.3)**	**67 (33.2)**
Smoking Status, n (%)						
Current/former smoker	308 (79.2)	161 (82.1)	**229 (95.5)**	**124 (98.5)**	**192 (95.5)**	**199 (98.5)**
Never	81 (20.8)	35 (17.9)	**11 (4.5)**	**2 (1.5)**	**9 (4.5)**	**3 (1.5)**
Brain Metastasis, n (%)						
Yes	50 (12.9)	28 (14.3)	**20 (8.5)**	**11 (8.9)**	**17 (8.5)**	**18 (8.9)**
No	339 (87.1)	168 (85.7)	**220 (91.5)**	**115 (91.1)**	**184 (91.5)**	**184 (91.1)**
Liver Metastasis, n (%)						
Yes	99 (25.4)	51 (26.0)	**92 (38.3)**	**45 (35.6)**	**77 (38.3)**	**72 (35.6)**
No	290 (74.6)	145 (74.0)	**148 (61.7)**	**81 (64.4)**	**124 (61.7)**	**130 (64.4)**
Tumor Mutational Burden, n (%)						
≥10 mutations/Mb	22/195 (11.3)	4/110 (3.6)	13/120 (10.5)	2/71 (2.7)	102/173 (59.0)	110/178 (61.8)
<10 mutations/Mb	173/195 (88.7)	106/110 (96.4)	107/120 (89.5)	69/71 (97.3)	71/173 (41.0)	68/178 (38.2)
Previous Anticancer Treatments, n (%)						
Yes	10 (2.6)	5 (2.6)	6 (2.4)	3 (2.0)	66 (32.8)	65 (32.2)
No	379 (97.4)	191 (97.4)	234 (97.6)	123 (98.0)	135 (67.2)	137 (67.8)

Source: CS Section 2.8.5 Table 24[6]; Lui et al. 2021[63]
Bold data indicate matching variables.
Abbreviations: ECOG PS = European Cooperative Oncology Group performance status; NR = not recorded.

As discussed in Section 3.6.1.1, the EAG raised concerns over subsequent treatments received after disease progression in ASTRUM-005 that are not routinely used in the UK. In response to PfC Question B9,[4] the company indicated a [redacted]

At the primary analysis cut-off of IMpower133 (April 24, 2018), 51.7% (104/201) patients receiving atezolizumab received at least one line of subsequent therapy.[18,65] However, subsequent treatment by country or race is not available from IMpower133, thus no direct comparisons can be made for this trial. As 21 countries were involved in IMpower133,[18] it may be assumed that treatment patterns observed will not specifically represent clinical practice of any one country. However, the proportion of patients receiving subsequent treatment lines in either treatment arm of IMpower133, can be seen to be [redacted].[4,65] Furthermore, the EAG note that in IMPower133, PCI was permitted in either treatment arm at the discretion of the investigator during the maintenance period; in total 22 patients in each treatment group of IMPower133 were reported to receive PCI.[18] Conversely in ASTRUM-005 radiotherapy was prohibited.[49] Clinical advice to the EAG confirmed very few patients in UK clinical practice receive further lines of treatment or PCI. Overall, the EAG have some concerns over subsequent treatment patterns and impact this had on patients in these trials and how this translates to the NHS population.

Furthermore, compared to the baseline disease characteristics presented in IMpower133, patients in ASTRUM-005 were more likely to present with an ECOG PS of 1 versus 0, more likely to have existing brain metastases, but less likely to have liver metastases or have received previous anticancer treatments.[6,18,49] A recent retrospective analysis conducted at a Cancer Centre in Ontario, Canada, indicated only 12.1% patients with ES-SCLC, would have met the eligibility criteria for IMpower133 or CASPIAN.[81] The main reasons for ineligibility would have been an ECOG greater than or equal to 2, inadequate organ function and brain metastases.[81] Utilising the UK retrospective chart review by Blackhall et al,[71] 42.7% patients with ES-SCLC had an ECOG performance status score of 0 or 1, while 32% had an ECOG PS score greater than or equal to 2, which would have made them ineligible to enrol in ASTRUM-005[53] or IMpower133[65] (ECOG PS score was unknown for 25.2% patients[71]). Adequate organ function (defined by measurements of the haematologic system, hepatic function, renal function, and coagulation function) was also stipulated for inclusion in either ASTRUM-005[53] or IMpower133.[65] However, the mean average number of organ systems affected (including cardiovascular, respiratory, hepatic, neurological systems, infections, diabetes) was 1.2 in the UK cohort,[71] indicating that most real-world patients had comorbidities affecting one or more organ systems, which may have prevented them from enrolling in the latter two trials. However, this remains uncertain. Overall, the lack of, or unclear UK patient representation and treatment pattern reflective of UK clinical practice in ASTRUM-005 and IMpower133 raises some concerns to the EAG as to their translatability to the NHS patient population, and clinical practice.

3.7.1.3 Covariates included in the MAIC

In the CS Section B.2.8.2, baseline patient characteristics with notable imbalances between ASTRUM-005 and IMpower133 were highlighted.[6] These included age, ethnicity, ECOG

performance, smoking status, the presence of brain metastases or liver metastases, mutational tumour burden, and previous anticancer treatments (

Table 3.13).[6] To account for these imbalances, the company assessed these characteristics for population adjustment based on four factors: 1) availability of data or aggregated results; 2) significant impact on the treatment effect; 3) imbalance in distribution across studies; and 4) the number of cases with a particular characteristic is at least 10% of the total cases, without leading to an excessively low ESS.[6] The company adjusted for age, ECOG performance, brain metastasis, liver metastasis, smoking status; outcomes generated from the MAIC were shown to be similar to that of an unadjusted ITC.[6]

The EAG acknowledge there is a lack of trial data available for three variables (disease stage, PDL1 expression levels, and blood-based tumour mutational burden), leading to some uncertainty of any confounding impacts these may have on the treatment effect estimates. Moreover, the Company's rationale for or against the adjustment of variables measured, appeared to be purely number driven and lacked supporting evidence that engagement with clinical experts had influenced their methodology (Table 3.14).[6] Adjustment for race and previous cancer treatment was deemed to lead to excessively low ESS,[6] indicating a relatively small overlap between trial populations. The EAG also note the Company do not provide justification for judgement of what would be an ESS sufficient to test the treatment effect of serplulimab compared to atezolizumab. Furthermore, the rationale provided by the Company for not adjusting for sex or race in the MAIC, was based on the subgroup analysis of OS from ASTRUM-005. As no significant difference in OS was observed for patients based on sex (p-value=0.65) or race (p-value=0.58) (Figure 3 in Cheng et al. 2022[49]), these variables were deemed not to impact treatment effect. However, while these subgroup analyses provide supportive information to identify potential treatment effect modifiers, interpretation of lack of significant differences warrants caution as they are not powered to detect significant differences.

Table 3.14: Rationale for variable selection for population adjustment

	Adjusted	Rationale
Age group (≥65 yr)	Yes	Imbalance in patient age between ASTRUM-005 and IMpower133.
Sex	No	Subgroup analysis in ASTRUM-005 showed no impact of sex on treatment effect.
Race	No	Adjustment would lead to excessively low ESS resulting in unreliable outcomes, furthermore subgroup analysis in ASTRUM-005 showed no impact of race on treatment effect.
Disease stage	No	Not reported in IMpower133.
ECOG	Yes	Imbalance in patient ECOG status between ASTRUM-005 and IMpower133.
Smoking status	Yes	Imbalance in patient smoking status between ASTRUM-005 and IMpower133.
Brain metastases	Yes	Imbalance in the presence of brain metastases between ASTRUM-005 and IMpower133.
Liver Metastases	Yes	Imbalance in the presence of liver metastases between ASTRUM-005 and IMpower133.
Blood-based tumor mutational burden	No	Not tested in all participants.
PD-L1	No	Not reported in IMpower133.
Previous anticancer treatments	No	Adjustment would lead to excessively low ESS resulting in unreliable outcomes.

Source: CS Section 2.8.2 Table 22[6]
Abbreviations: ECOG PS = European Cooperative Oncology Group performance status; PD-L1 = programmed death-ligand 1

As recommended by the NICE DSU, each variable used in population adjustment must be justified.[78] This requires that (i) its status as an effect modifier needs to be supported by external quantitative evidence, expert opinion, or systematic review and (ii) the degree of imbalance needs to be made explicit.[78] The EAG therefore asked the Company in the PfC (Question B8)[4] to provide further justification for how they derived their final list of adjusted variables. In response the Company provided a rationale for selection of key prognostic variables, based on their impact on OS and confounders identified through a SLR, with advice from clinical and statistical experts. In addition, the Company provided a sensitivity analysis which incorporated various combinations of matching variables for MAIC analyses for OS (Table 3.15 and Figure 3.2: Forest plots for MAIC results of OS in ASTRUM-005 vs. IMpower133).[4]

The EAG note that whilst all effect modifiers should be adjusted for, in an anchored MAIC it is recommended that purely prognostic variables should not be adjusted to avoid inflating standard error (SE) due to over-matching.[78] Clinical advice to the EAG stated that while many variables are known prognostic factors, smoking status was the most prominent treatment effect modifier but there is no robust evidence validating treatment effect modifiers in patients with SCLC. However, the sensitivity analysis

[redacted]

[redacted].[4] The EAG acknowledge these analyses do provide supportive evidence but are limited by the small sample sizes and the lack of robust evidence of treatment effect modifiers in this patient population.

Table 3.15: Results of MAIC Analyses for OS in ASTRUM-005 vs. IMpower133

Type	Matching Baseline Characteristics Variables	HR (95% CI)
Primary analysis	Age Group; ECOG; Smoking Status; Brain Metastases; Liver Metastases	[redacted]
Sensitivity analysis 1	Based on the list of variables used in the primary analysis, excluding ECOG	[redacted]
Sensitivity analysis 2	Based on the list of variables used in the primary analysis, including Sex	[redacted]
Sensitivity analysis 3	Based on the list of variables used in the primary analysis, including Disease Stage[1]	[redacted]
Sensitivity analysis 4	Based on the list of variables used in the primary analysis, including Disease Stage[1], excluding Brain Metastasis and Liver Metastasis	[redacted]
Sensitivity analysis 5	Based on the list of variables used in the primary analysis, excluding all never-smokers from ASTRUM-005	[redacted]
Sensitivity analysis 6	Based on the list of variables used in the primary analysis, including Baseline Tumour Burden[2]	[redacted]
Sensitivity analysis 7	Based on the list of variables used in the primary analysis, including Race	[redacted]
Sensitivity analysis 8	Based on the list of variables used in the primary analysis, only including non-Asians from ASTRUM-005	[redacted]
Sensitivity analysis 9	Include all baseline characteristic variables, but only retain cases with available TMB values[3]	[redacted]

Source: PfC (Question B8)[4]
Abbreviations: HR = Hazard Ratio; CI = Confidence Interval; NA = Not Available (unable to obtain a valid result).
Note: Since the 'Disease Stage' proportion was not reported in the IMpower133 study, it is assumed that the proportion of stage IV patients was to mimic the proportion seen in the CASPIAN study.
The mean and standard deviation (SD) of the sum of the longest diameters of target lesions at baseline in the ASTRUM-005 study were calculated using actual values. In the IMpower133 study, the mean value was replaced with the median, and the SD referred to the ASTRUM-005 study. The baseline tumour burden was not reported in the CASPIAN study.

Figure 3.2: Forest plots for MAIC results of OS in ASTRUM-005 vs. IMpower133

Source: PfC (Question B8)[4]
Abbreviations: ESS = effective sample size; HR = hazard ratio; IPD = individual patient data; MAIC = matched adjusted indirect comparison; NA = not available; OS = overall survival

3.7.1.4 Results

The company stated [redacted] (Table 3.16).[6] [redacted][6] However, the EAG note the analyses assume homogeneity across all patient subgroups and that all relevant confounding factors have been accounted for. In CS Section 3.3,[6] the Company have plotted the log cumulative hazard plots for ASTRUM-005 and also for IMpower133 (by reconstructing pseudo IPD for the latter trial). Although statistical tests do not suggest the proportional hazards assumption was violated,[49] a visual assessment suggests some uncertainties regarding the assumption. Therefore, it may have been better practice for the Company to conduct sensitivity analyses using models that relax the proportional hazards assumption.[82] This is discussed further in Section 4.2.3.

Table 3.16: Results of indirect treatment comparison between serplulimab plus carboplatin-etoposide compared to atezolizumab plus carboplatin-etoposide, based on ASTRUM-005 and IMpower133

	Bucher ITC, HR (95% CI)	MAIC, HR (95% CI)
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Source: Table 26, CS Section B.2.8.5[6]
Abbreviations: CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; PFS = progression free survival; OS = overall survival.

The EAG noted the ITC was carried out using a [redacted] follow-up for ASTRUM-005 (median follow-up: [redacted][6], but a 2-year follow-up for IMpower133 (median follow-up: 22.9 months).[63] Trials with a shorter duration of follow-up could be associated with fewer events and may not have the power to detect differences between interventions. However, at the two study cut-offs, [redacted] patients in ASTRUM-005[6] and 74.9% (302/403) patients in IMpower133 patients had died.[63] Furthermore in response to PfC (Question B11)[4] the Company provided analyses with ASTRUM-005 trial data censored at 24 months, which provided similar outcomes to that provided in the CS.[6] The nearly [redacted] in median follow-up may have been influenced by the longer recruitment period of ASTRUM-005 (September 12, 2019, and April 27, 2021) compared to IMpower133 (June 6, 2016, and May 31, 2017), however, the reasons for this remain unclear.

Table 3.17. Results of indirect treatment comparison between serplulimab plus carboplatin-etoposide compared to atezolizumab plus carboplatin-etoposide based on ASTRUM-005 and IMpower133, with ASTRUM-005 data censored at 24 months

	Bucher ITC, HR (95% CI)	MAIC, HR (95% CI)
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Source: PfC (Question B11)[4]
Abbreviations: CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; PFS = progression free survival; OS = overall survival

Finally, as discussed in Sections 3.6.1.1 and 3.7.1.2, patients in ASTRUM-005 and IMpower133 were permitted to receive subsequent treatments after disease progression at the discretion of the investigator. At the final data cut off for ASTRUM-005 [redacted] patients in the serplulimab treatment arm received subsequent therapies,[4] compared to 51.7% (104/201) of patients receiving atezolizumab at the primary cut off for IMpower133.[18,65] Clinical advice to the EAG, was that subsequent treatment provided in ASTRUM-005 did not reflect treatment pathways that would be expected in UK clinical practice. Estimates of the effectiveness that would be expected to be observed if treatment pathways used in English standard clinical practice were followed, as is recommended by the DSU,[69,70] are not provided in this submission. Therefore, it remains unknown as to whether any subsequent treatments received in either ASTRUM-005 or IMPower133 impacted OS and thus the HRs provided in this submission.

3.7.2 ASTRUM-005 vs. CASPIAN

A summary of the EAG's comments regarding the methodology of the MAIC using IPD from ASTRUM-005 and published aggregate data from CASPIAN, are presented in Table 3.18, with key points expanded upon in the following sections.

Table 3.18: Summary of the EAG's critique of the MAIC methods; ASTRUM-005 vs. CASPIAN

Aspect of MAIC design or conduct	Section in CS where methods are reported	EAG's assessment
Statistical methods	PfC[4]	**Some concerns**

		As detailed in Section 3.7.1.1, no treatment comparison with durvalumab, recently approved by NICE and included in the final scope, was included in the CS. At the request of the EAG, the Company generated comparative efficacy estimates for serplulimab versus durvalumab using a MAIC.[4] The EAG's preference was a ML-NMR using individual patient level data from ASTRUM-005 with aggregate data from IMpower133 and CASPIAN, to determine the relative efficacy of serplulimab in comparison to durvalumab and atezolizumab (and chemotherapy). See Section 3.7.2.1 3.7.1.1 for further comment.
Included study characteristics and demographics	PfC[4]	**Key issue** ASTRUM-005 and CASPIAN, both international, phase III RCTs, investigated the efficacy and safety of PDL1/PD1 inhibitors, serplulimab and durvalumab respectively, in adults with untreated ES-SCLC, in line with the NICE scope.[12] However, neither ASTRUM-005 or CASPIAN were conducted in the UK. Subsequently, uncertainties surrounding the transitivity and transportability of the trials to the NHS patient population and clinical practice are evident. Additionally, the EAG note the control arm of CASPIAN, whilst encompassing treatment with etoposide plus either cisplatin or carboplatin in line with the NICE scope, does not include a placebo. See Section 3.7.2.2 for further comment.

Covariates included in the MAIC	PfC[4]	**Some concerns** The company included four covariates within the MAIC: ECOG, smoking status, brain metastases, liver metastases. Other variables in ASTRUM-005 and CASPIAN were not adjusted for; this was stated to be due to the unavailability of data or there being no significant difference in subgroup analyses of ASTRUM-005. The EAG have some concerns surrounding the selection and uncertainties of potential treatment effect modifiers and impact on the results. See Section 3.7.2.3 for further comment.
Results	PfC[4]	**Some concerns** The company stated [redacted] However, the EAG note after disease progression, a lower proportion of patients in the durvalumab treatment arm received subsequent treatments compared to those receiving serplulimab; [4,25,76] this may impact OS. See Section 3.7.1.4 for further comment.
Sensitivity analyses	NA	**Some concerns** The EAG note that no sensitivity analyses were presented alongside the MAIC provided by the company in the PfC response,[4] to explore the impact of adjusting for different variables in in the primary analysis. Whilst these analyses do not robustly validate treatment effect modifiers, such analyses may have provided supportive evidence for this submission. See Section 3.7.2.5 for further comment.

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ECOG = Eastern Cooperative Oncology Group; ES-SCLC = extensive stage-small cell lung cancer; ITC = indirect-treatment comparison; ITT = intention-to-treat; MAIC = matching adjusted indirect treatment comparison; ML-NMR = multilevel network meta-regression; NA, not applicable; NICE DSU = National Institute for Health and Care Excellence Decision Support Unit OS = overall survival; PfC = points for clarification; PFS = progression free survival.

3.7.2.1 Statistical methods

In the CS no treatment comparison with durvalumab, recently approved by NICE and included in the final scope, was included. At the request of the EAG, the company generated comparative efficacy estimates for serplulimab versus durvalumab using a MAIC (PfC Question A1 and B8).[4] The statistical approach was the same as that applied to the first MAIC estimating efficacy estimates for serplulimab versus atezolizumab (CS Section B.2.8.4, p68-69[6]). Baseline characteristics of the ASTRUM-005 ITT population were adjusted to that of the aggregate summary data of CASPIAN. Cox proportional hazards were applied to estimate the relative efficacy between serplulimab treatment and atezolizumab for OS and PFS. An unadjusted ITC was also provided using the Bucher method for reference.

As discussed in Section 3.7.1.1, the EAG acknowledge MAICs are an acceptable statistical approach. However, the EAG's preference would have been a ML-NMR using individual patient level data from ASTRUM-005 with aggregate data from IMpower133 and CASPIAN, to determine the relative efficacy of serplulimab in comparison to durvalumab and

atezolizumab (and chemotherapy alone). ML-NMR, recommended by the NICE DSU,[80] allows flexibility to generate population-adjusted ITC estimates from any number of treatments and studies, which are applicable to any specified target population.[13]

3.7.2.2 Included study characteristics and demographics

ASTRUM-005 and CASPIAN, both phase III RCTs, investigated the efficacy and safety of the PDL1/programmed cell death protein (PD1) inhibitors, serplulimab and durvalumab respectively, in adults with untreated ES-SCLC, are in line with the NICE scope.[12] The EAG are satisfied that the trial eligibility criteria and outcomes were overall similar in design across ASTRUM-005 and CASPIAN. However, differences within and between trial settings, and subsequent patient demographics and characteristics presented in Table 3.19, generate uncertainties as to the transitivity and transportability of the included trials to the NHS patient population and clinical practice.

Moreover, to permit an anchored comparison the company assumed that placebo plus carboplatin and etoposide was equivalent to carboplatin and etoposide based on the similarity in absolute outcomes between the two studies.[4] However, the EAG note that, while the control arm of CASPIAN used treatment with etoposide plus either cisplatin or carboplatin in line with the NICE scope,[12] and dosage in ASTRUM-005,[49] up to six cycles of chemotherapy treatment was permitted every three weeks plus PCI, and no treatment with a placebo was given.[25] This contrasts with the control arm of ASTRUM-005, which used a placebo and permitted up to four cycles of etoposide plus carboplatin.[49] Thus, there is some concern as to whether equivalence of the open-label control arm of CASPIAN and the double-blind placebo-control arm of ASTRUM-009 can be reliably assumed.

CASPIAN enrolled patients from 23 countries across Asia, North and South America, and Europe, not including the UK.[25] However, in comparison to ASTRUM-005, most patients were white (85% versus 82% in the durvalumab plus platinum-etoposide arm versus the comparator) and the highest proportion of patients by region were from Europe (45%; 242 patients out of a total of 537 for durvalumab with platinum-based chemotherapy and platinum-based chemotherapy alone).[25] However, as discussed Section 3.6.1.2, in the UK incidence rates for lung cancer are relatively similar for males and females,[55] while across both ASTRUM-005 and CASPIAN more males were enrolled. Furthermore in the durvalumab treatment arm of CASPIAN, 42% (113/268) patients received subsequent treatment after progressive disease,[25] compared to [redacted] patients in the serplulimab arm of ASTRUM-005 (Table 3.6 in Section 3.6.1.1). As detailed in Section 3.6.1.1, there was [redacted][4] The proportion of patients that received subsequent treatments stratified by country or race are not available for CASPIAN. Similar to IMpower133 (Section 3.7.1.2), as CASPIAN took place in 23 countries, subsequent treatments and patterns observed, may not specifically represent clinical practice of any one country. However, the proportion of patients receiving subsequent treatment overall in CASPIAN, [redacted].[4,25] Clinical advice to the EAG confirmed that it is unlikely that most patients in the NHS go on to receive subsequent treatments. The EAG therefore have some concerns over the impact subsequent treatments had on patients in the included trials, and how this reflects the NHS population.

The EAG note that in CASPIAN 6.9% (37/537) of all patients enrolled were never smokers.[25] However, in ASTRUM-005, as discussed in Sections 3.6.1.2 and 3.7.1.2, 19.8% (116/585) of patients across both treatment arms in ASTRUM-005 were never smokers,[49] which is relatively higher than that seen in UK clinical practice as supported by clinical advice to the EAG, and a retrospective chart review reporting3.9% (4/103) of patients with ES-SCLC to be never smokers.[71] ([49]While robust evidence is lacking, there is some suggestion that there may be different disease trajectories and treatment responses for the never smoking Asian population, however, how this translates to the NHS patient population is not known.

As discussed in Section 3.7.1.2a recent retrospective analysis in Canada has suggested that only 12.1% of patients seen at a single centre with ES-SCLC, would have met the eligibility criteria for IMpower133 and CASPIAN trials.[81] The main reasons for ineligibility would have been an ECOG PS score greater than or equal to 2, inadequate organ function and brain metastases.[81] To provide context for real world patients in the UK, the retrospective chart review by Blackhall et al,[71] reported 42.7% patients with ES-SCLC in the UK had an ECOG performance status score of 0 or 1, while 32% had an ECOG PS score greater than or equal to 2, and therefore would have been ineligible to enrol in CASPIAN[76] or ASTRUM-005[53] (ECOG PS score was unknown for 25.2% patients[71]). Additionally, adequate organ function (defined by measurements of the haematologic system, hepatic function, renal function, and coagulation function) was also stipulated for inclusion in either CASPIAN[76] or ASTRUM-005{Cheng, 2022 #129}. However, in the UK cohort the mean average number of organ systems affected (including cardiovascular, respiratory, hepatic, neurological systems, infections, diabetes) was 1.2,[71] indicating that most patients had comorbidities affecting one or more organ systems, which may have prevented them from enrolling in the latter two trials. However, this remains uncertain. The EAG have therefore identified the uncertainties surrounding the translatability of the trials to the patient population, and clinical practice in the UK as a key issue.

Table 3.19: Patient characteristics in matched analysis

Baseline variables	ASTRUM-005		ASTRUM-005: Adjusted		CASPIAN	
	Serplulimab (n=389)	Placebo (n=196)	Serplulimab (ESS=256)	Placebo (ESS=134)	Control (n=269)	Durvalumab (n=268)
Age group, n (%)						
≥ 65 years	154 (39.6)	77 (39.3)	93 (36.5)	52 (38.5)	112(41.6)	101 (37.7)
< 65 years	235 (60.4)	119 (60.7)	163 (63.5)	82 (61.5)	157 (58.4)	167 (62.3)
Sex, n (%)						
Male	317 (81.5)	164 (83.7)	228 (89.1)	122 (91.0)	184 (68.4)	190 (70.9)
Female	72 (18.5)	32 (16.3)	28 (10.9)	12 (9.0)	85 (31.6)	78 (29.1)
Race, n (%)						
Asian	262 (67.4)	139 (70.9)	159 (62.1)	88 (65.9)	42 (15.6)	36 (13.4)
Non-Asian	127 (32.6)	57 (29.1)	97 (37.9)	46 (34.1)	227 (84.4)	232 (86.6)
Disease stage, n (%)						

Baseline variables	ASTRUM-005		ASTRUM-005: Adjusted		CASPIAN	
	Serplulimab (n=389)	Placebo (n=196)	Serplulimab (ESS=256)	Placebo (ESS=134)	Control (n=269)	Durvalumab (n=268)
IV	318 (81.7)	155 (79.1)	217 (84.9)	106 (79.4)	245 (91.1)	240 (89.6)
III or other	71 (18.3)	41 (20.9)	39 (15.1)	28 (20.6)	24 (8.9)	28 (10.4)
ECOG, n (%)						
PS 1	318 (81.7)	164 (83.7)	**162 (63.1)**	**89 (66.5)**	**179 (66.5)**	**169 (63.1)**
PS 0	71 (18.3)	32 (16.3)	**94 (36.9)**	**45 (33.5)**	**90 (33.5)**	**99 (36.9)**
Smoking status, n (%)						
Current/former smoker	308 (79.2)	161 (82.1)	**235 (91.8)**	**126 (94.4)**	**254 (94.4)**	**246 (91.8)**
Never	81 (20.8)	35 (17.9)	**21 (8.2)**	**8 (5.6)**	**15 (5.6)**	**22 (8.2)**
Brain metastasis, n (%)						
Yes	50 (12.9)	28 (14.3)	**27 (10.4)**	**13 (10.0)**	**27 (10.0)**	**28 (10.4)**
No	339 (87.1)	168 (85.7)	**229 (89.6)**	**121 (90.0)**	**242 (90.0)**	**240 (89.6)**
Liver metastasis, n (%)						
Yes	99 (25.4)	51 (26.0)	**103 (40.3)**	**52 (38.7)**	**104 (38.7)**	**108 (40.3)**
No	290 (74.6)	145 (74.0)	**153 (59.7)**	**82 (61.3)**	**165 (61.3)**	**160 (59.7)**
Tumour mutational burden, n (%)						
≥10 mutations/Mb	22/195 (11.3)	4/110 (3.6)	14/128 (10.8)	2/75 (3.0)	NR	NR
<10 mutations/Mb	173/195 (88.7)	106/110 (96.4)	114/128 (89.2)	73/75 (97.0)	NR	NR
Previous anticancer treatments, n (%)						
Yes	10 (2.6)	5 (2.6)	6 (2.5)	4 (2.8)	NR	NR
No	379 (97.4)	191 (97.4)	250 (97.5)	130 (97.2)	NR	NR

Bold data indicate matching variables.
Source: PfC Question B8[4]; Liu et al, 2021;[63]; CSR Henlius 2024[17]
Abbreviations: ECOG = European Cooperative Oncology Group; ESS = effective sample size; NR = not recorded; PS = performance status

3.7.2.3 Covariates included in the MAIC

The Company included four covariates within the MAIC: ECOG, smoking status, brain metastases, liver metastases (Table 3.19).[4] Other variables not adjusted for in this MAIC were stated to be due to availability of data, or there being no significant difference in subgroup analyses of ASTRUM-005 (Table 3.20).[4] As discussed in Section 3.7.1.3 the EAG

raised some concerns surrounding the selection and uncertainties of potential treatment effect modifiers. A lack of trial data available for three variables (PDL1 expression levels, blood-based tumour mutational burden and previous anticancer treatments), raises some uncertainty of any confounding impacts these may have on the treatment effect estimates. Furthermore, the rationale provided by the company for not adjusting for sex or race, was based on the evidence from subgroup analysis of OS from ASTRUM-005, which lacks power and reliability due to small sample sizes. Moreover, clinical advice to the EAG stated that while some many variables are known prognostic factors, smoking status was the most prominent treatment effect modifier but there is no robust evidence validating treatment effect modifiers in patients with SCLC.

Table 3.20: Rationale for variable selection for population adjustment

Variable	Adjusted	Rationale
Age group (≥65 yr)	No	Patient age in ASTRUM-005 and CASPIAN were balanced.
Sex	No	Subgroup analysis in ASTRUM-005 and CASPIAN showed no impact of sex on treatment effect.
Race	No	Adjustment would lead to excessively low ESS resulting in unreliable outcomes, furthermore subgroup analysis in ASTRUM-005 showed no impact of race on treatment effect.
Disease stage	No	Cases of stage III or others accounted for about 10% or less of the total cases in CASPIAN and nearly balanced across studies.
ECOG	Yes	Imbalance in patient ECOG status between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Smoking status	Yes	Imbalance in patient smoking status between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Brain metastases	Yes	Imbalance in the presence of brain metastases between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Liver Metastases	Yes	Imbalance in the presence of liver metastases between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Blood-based tumour mutational burden	No	Not reported in CASPIAN.
PD-L1	No	Not reported in CASPIAN.
Previous anticancer treatments	No	Not reported in CASPIAN.

Source: PfC (Question B8)[4]
Abbreviations: ECOG = European Cooperative Oncology Group; PD-L1 = programmed death-ligand 1

3.7.2.4 Results

The Company stated that serplulimab plus carboplatin-etoposide demonstrated [redacted]

[redacted] (Table 3.16).[6]
[redacted][6] However, as discussed in Sections 3.7.2.2 the EAG note that in the durvalumab treatment arm of CASPIAN, a lower proportion (42%) of patients received subsequent treatment after progressive disease compared to [redacted] patients in the serplulimab arm of ASTRUM-005.[4,25,76] Furthermore, clinical advice to the EAG, was that subsequent treatment provided in ASTRUM-005 did not reflect treatment pathways that would be expected in clinical practice. Estimates of the effectiveness that would be expected to be observed if treatment pathways used in English standard clinical practice were followed, as is recommended by the DSU,[69,70] are not provided in this submission. This therefore raises some uncertainty as to if, and how these subsequent treatments impacted OS in both trials, and thus the ITC estimates generated in this submission.

Furthermore, as discussed in Section 3.7.1.4, the EAG identified some concerns with regards to the proportional hazards assumption; the generation of sensitivity analyses using models that relax the proportional hazards assumption,[82] may have helped validate the MAIC results. This is discussed further in Section 4.2.3.

Table 3.21. Results of indirect treatment comparison between serplulimab plus carboplatin-etoposide compared to durvalumab plus etoposide-carboplatin based on ASTRUM-005 and CASPIAN

	Bucher ITC, HR (95% CI)	MAIC, HR (95% CI)
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Source: PfC (Question B8)[4]
Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; PFS = progression free survival; OS = overall survival

3.7.2.5 Sensitivity analyses

The EAG note that no sensitivity analyses were presented alongside the MAIC provided by the Company in response the PfC,[4] to explore the impact of adjusting for different covariates in the primary analysis. Whilst these analyses do not robustly validate treatment effect modifiers, such analyses may have provided supportive evidence for this submission.

3.8 Conclusions of the clinical effectiveness section

Relevant literature in line with the NICE scope was identified through conducting a SLR, with searches conducted on 5th April 2024. The EAG identified some concerns relating to the sensitivity and specificity of the searches, as well as in the application of search filters and screening performed. Despite these oversights, the EAG are not unduly concerned and are generally satisfied that the SLR for clinical effectiveness studies was conducted appropriately. In total 16 studies were included in the SLR; however, only ASTRUM-005 matched the NICE scope, which investigated the efficacy and safety of serplulimab plus carboplatin and etoposide compared to placebo plus carboplatin and etoposide, in previously untreated patients with ES-SCLC.

The ASTRUM-005 trial (NCT04063163) was an international, double-blind, phase 3, RCT, which randomised 585 patients 2:1 to receive serplulimab or placebo intravenously every three weeks. In both treatment arms, patients received IV carboplatin and etoposide every three weeks for up to 12 weeks. The primary outcome was OS and, with a median follow-up of [redacted] months at the end of study, a statistically significant OS benefit of serplulimab treatment ([redacted] months) compared to placebo ([redacted] months) was observed (HR=[redacted] [95% CI: [redacted]). Secondary outcomes, including PFS, ORR and DoR, indicated serplulimab treatment to reduce the risk of progressive disease, improvement in ORR and mDOR. Overall, patient quality of life was not adversely impacted, with some improvements in “pain in other parts” domain in the serplulimab treatment group being reported. Furthermore, TTD was found to be comparable between treatment arms.

The EAG are satisfied that etoposide with carboplatin best reflected the most widely used platinum-based therapy in ES-SCLC in the UK. However, the company reasoned the comparator durvalumab listed in the NICE scope, not to be a relevant comparator in this submission, as NICE’s recommendation for durvalumab for adults with untreated ES-SCLC, was still under development at the time of the decision problem meeting. Subsequently, in the absence of a head-to-head trial of serplulimab versus atezolizumab treatment, the company concluded that IMpower133 was the only RCT that would enable the generation of an anchored ITC with ASTRUM-005. IMpower133, an international phase 3 trial evaluated the safety and efficacy of atezolizumab plus carboplatin and etoposide in patients with ES-SCLC, who had not previously received treatment (NCT02763579).

In the CS, a Bucher ITC connected through the common comparator placebo plus carboplatin and etoposide was performed using data from ASTRUM-005 and IMpower133. However, due to notable imbalances in baseline characteristics between the two trials, selected variables (age, ECOG performance, brain metastasis, liver metastasis, smoking status) were adjusted for in a MAIC. The MAIC indicated [redacted], which corroborated the Bucher ITC results, and were subsequently used to inform the cost-effectiveness analysis. The EAG noted there was a lack of trial data available for three variables (PDL1 expression levels, blood-based tumour mutational burden and previous anticancer treatments), raising some uncertainty of any confounding impacts these may have on the treatment effect estimates. Sensitivity analysis provided supportive evidence for the adjustment of selected covariates; however, these are limited in sample size and therefore power. Furthermore, clinical advice indicated that while some prognostic factors are widely recognised, there is a lack of robust evidence of treatment effect modifiers in patients with SCLC.

On 19th February 2025 durvalumab with etoposide and either carboplatin or cisplatin, was recommended by NICE for patients with untreated ES-SCLC.[7] Consequently the EAG asked the company to conduct further analyses including durvalumab as a comparator in both their clinical effectiveness and cost effectiveness analyses. In response, the company conducted a second MAIC using aggregate data from CASPIAN to generate efficacy estimates between serplulimab and durvalumab. CASPIAN, was an international, randomised, open-label, phase 3 trial investigating the efficacy of durvalumab plus platinum-etoposide, durvalumab plus tremelimumab plus platinum-etoposide or platinum-etoposide alone, in patients with untreated ES-SCLC.

Imbalances in baseline patient characteristics between CASPIAN and ASTRUM-005 led to the adjustment of selected variables (ECOG, smoking status, brain metastases, liver metastases). Similarly to the first MAIC using IPD from ASTRUM-005 and published aggregate data from IMpower133, availability of trial data and a lack of robust direct evidence of treatment effect modifiers, raises some uncertainty as to any confounding impacts these may have on the treatment effect estimates. The results of the MAIC demonstrated serplulimab plus carboplatin-etoposide provided [redacted]

In general, the EAG are satisfied with the quality and rigor of all three trials included, however, the EAG have some concerns over the transitivity and transportability of the trials to the NHS population. Whilst the trial eligibility criteria and outcomes were overall similar in design across the three trials, the trial settings, and subsequent patient demographics and characteristics, as well as treatment offered after disease progression, may not match that observed in UK clinical practice. The EAG have therefore identified this as a key issue. Neither CASPIAN nor ASTRUM-005 included trial sites within the UK, the latter trial enrolling mostly Asian patients (68.5%). In IMPower133, for which the company only have access to published summary-level data, the proportion of patients from the UK (out of the 21 countries included) is unknown. Whilst certain prognostic factors have been identified with some supportive evidence indicating different disease trajectories and outcomes for a subgroup of the Asian patient population, robust evidence directly ascertaining treatment effect modifiers is lacking. Therefore, the translatability of the evidence presented in this submission remains uncertain in relation to the NHS patient population.

In conclusion, the EAG accept that the company's treatment of the evidence available was broadly appropriate and in line with the NICE scope. The EAG agree MAICs present a reputable method, however, some of the uncertainties surrounding the within and between-study variation and the precision of relative effect estimates between treatments may have been addressed through application of a ML-NMR. ML-NMR has enabled recent technology appraisals utilising trials with considerable differences in study populations and not generalisable to the NHS patient population to generate comparative efficacy estimates for key outcomes including OS.[14] Thus, instead of performing a MAIC, the EAG's preferred approach would be a ML-NMR using individual patient level data from ASTRUM-005 with aggregate data from IMpower133 and CASPIAN, as it allows flexibility to generate population-adjusted ITC estimates from any number of treatments and studies, which are applicable to any specified target population.[13]

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

The Company conducted an SLR to identify and synthesise evidence on economic evaluations, healthcare resource use and associated costs related to the treatment of untreated ES-SCLC, and the impact of HRQoL in patients with ES-SCLC. Table 4.1 presents an overview of the EAG's critique of the methods used to identify studies for the review of cost-effectiveness, with key points expanded upon in the following sections below. The EAG's critique on the sensitivity of the searches is discussed in further detail alongside the clinical SLR in Section 3.1.

Table 4.1: Summary of the EAG's critique of the methods for the review of cost-effectiveness

Aspect of cost-effectiveness SLR	Section in CS where methods are reported	EAG's assessment
Data sources for cost-effectiveness analysis review	Section 6.1 Appendix H[28]	**Appropriate** The Company searched an appropriate range of bibliographic and non-bibliographic and grey literature sources for the cost-effectiveness review.
Data sources for model input	Section 6.1 Appendix H[28]	**Appropriate** The Company do not explicitly report searching for model input separately, however they report a comprehensive and appropriate range of bibliographic and non-bibliographic and grey literature sources for humanistic and cost-effectiveness studies from which this information could have been derived. They also provided a rationale for widening the time limits for the searches of health-state utility values and quality of life data.
Eligibility criteria for inclusion of economic evaluations	Section 6.1 Appendix H[28]	**Some concerns** The Company's eligibility criteria broadly mapped to the NICE scope. Some exclusion criteria may have impacted eligibility decisions: these are discussed in Section 4.1.3. However, the EAG are broadly satisfied that these were unlikely to have substantive impact.
Eligibility criteria for inclusion of health state utility value studies	Section 6.1 Appendix H[28]	**Some concerns** The Company's eligibility criteria broadly mapped to the NICE scope. Some exclusion criteria may have impacted eligibility decisions: these are discussed in Section 4.1.3. However, the EAG are broadly satisfied that these were unlikely to have substantive impact.
Eligibility criteria for inclusion of resource use and cost studies	Section 6.1 Appendix H[28]	**Some concerns** Some exclusion criteria may have impacted eligibility decisions: these are discussed in Section 4.1.3. However, the EAG are broadly satisfied that these were unlikely to have substantive impact.

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; National Institute for Health and Care Excellence; SLR = Systematic literature review

4.1.1 Sensitivity of searches

Similar to the clinical search as discussed in Section 3.2.1, the economic search used the NOT function to reduce sensitivity and exclude NSCLC populations, which is not best practice. The difference in number of search results between the initial searches and the clarification search is more pronounced in the economic searches (Table 3.2). It is likely that further relevant information would have been identified by this more sensitive search.

The use of controlled vocabularies and field searching (title, abstract and keywords) was also unclear throughout which may impact on retrieval of relevant results.

4.1.2 Use of search filters

The use of search filters for study design is common practice in systematic reviewing. The Company state in the Economic and Humanistic Burden SLR (Appendix H)[28] that the SIGN search filters were applied however as with the Clinical SLR, not all the terms have been incorporated in the Company's search. In the SIGN filter for economics in EMBASE, line #12 is (fiscal or financial or finance or funding).tw however this line does not appear in the SLR search (Appendix H, Section 6.1, Table 16). Similarly, lines #14, #15 and #16 of this filter, (cost adj estimate$).mp; (cost adj variable$).mp and (unit adj cost$).mp were also not used in the search.

There was no reported use of an appropriate search filter for quality of life which reduces the sensitivity of the search. This in turn raises the possibility of missing potentially relevant studies.

4.1.3 Eligibility criteria for inclusion of economic evaluations, Health state utility value studies and resource use and cost studies

Studies which did not report separate results by line of treatment were excluded as were studies which did not report stratification of squamous ES-SCLC patients. The EAG are satisfied that the restriction by line of treatment is appropriate to the scope. The restriction based on reporting of squamous ES-SCLC patients may have some impact on study inclusion but since these cases are reported to make up a low percentage of ES-SCLC the EAG believe that the impact is likely minimal. Restriction to English language studies and exclusion of conference abstracts with a narrower date window than full texts may also have had some impact on inclusion of relevant studies but the EAG do not believe that this is likely to be substantive given the dates involved and the development status of the technologies; date limits for full text publications appear appropriate for the economic and humanistic burden elements.

4.1.4 Conclusions of the cost effectiveness review

It is difficult for the EAG to quantify the effects of the issues with the search strategies described above in the absence of comprehensive testing. It seems likely however that these effects would be relatively minor, though more impactful than on the clinical SLR. Overall, the EAG is satisfied that the economic and humanistic burden SLR searches were conducted appropriately and that the inclusion criteria for the review were appropriate.

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

4.2.1 NICE reference case checklist

Table 4.2 summarises the NICE reference case checklist and the EAG's assessment on the company's submission in relation to their base-case analysis.

Table 4.2: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	Serplulimab with carboplatin and etoposide are used to treat adults with untreated ES-SCLC.	**Appropriate** Adults with untreated ES-SCLC were considered for the treatment with serplulimab, along with carboplatin and etoposide. See Section 2 and 4.2.2 for details.
Comparators	The comparators for the treatment of untreated ES-SCLC are • Platinum-based combination chemotherapy, • Atezolizumab with carboplatin and etoposide (for people with ECOG PS of 0 or 1), and • Durvalumab (subject to NICE appraisal).[‡]	**Appropriate** Durvalumab had not been included in the initial company submission to NICE because it was not yet recommended for the treatment of untreated extensive-stage small cell lung cancer. Following the approval on 19th February 2025, the EAG requested the company to include Durvalumab in the analysis, which the company subsequently did. Sections 2.1 and 4.2.2 provides more information on this.
Perspective on outcomes	The outcome measures to be considered include: • OS • PFS • Response rates • AE of treatment • HRQoL	**Appropriate** The EAG considers the perspective on outcomes to be appropriate. See Section 2.2
Perspective on costs	NHS and personal social services (PSS).	**Appropriate** The NHS and PSS perspectives on cost, which aligned with the NICE reference case, was adequately captured and deemed appropriate by EAG. See Section 4.2.6

Element of health technology assessment	Reference case	EAG comment on company's submission
Type of economic evaluation	Cost-utility analysis with a full incremental analysis.	**Appropriate** The company conducted a cost-utility analysis (CUA) with both pair-wise and deterministic full incremental cost-effectiveness analysis. See Sections 4.2.2. **Some Concerns** The company has adopted MAIC as a method for indirect treatment comparison, to incorporate into the cost-effectiveness analysis. See Section 0 for more information on this. Despite this, a full incremental cost-effectiveness analysis could potentially have been conducted, but the company model was not developed to efficiently evaluate 4 comparators in the full incremental analysis given the late addition of durvaluamb as a comparator.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	**Appropriate** A lifetime horizon of 20 years was considered in the CS model, which is in line with the previous NICE submission TA638 and NICE reference case.[8] The EAG believes that this adequately reflects the costs and outcomes of technologies under consideration. See Section 4.2.2
Synthesis of evidence on health effects	Based on SLR.	**Some concerns** The EAG is broadly satisfied that the SLR was appropriately conducted although some concerns were identified with the approach to search strategies. See Section 4.1

Element of health technology assessment	Reference case	EAG comment on company's submission
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Appropriate** The HRQoL measures was obtained from ASTRUM-005. The EQ-5D-5L was used to measure the health effects of treatments in patients in QALYs. Later, the values were mapped to EQ-5D-3L, to align with NICE reference case, using the mapping algorithm developed by Hernández-Alava and Pudney 2017 for the NICE DSU.[83] See Section 4.2.5
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	**Appropriate** The HRQoL data was reported by the patients in the ASTRUM-005 trial, which included Asian and non-Asian patients. See Section 4.2.5
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	**Appropriate** The HRQoL measures were informed by the ASTRUM-005 trial which used EQ-5D-5L for evaluating the health-related quality of life in patients. These scores were mapped to the NICE recommended EQ-5D-3L value set using the mapping function developed by Hernández-Alava and Pudney 2017 for DSU, using the 'EEPRU dataset' Hernández-Alava et al. 2023.[83,84] See Section 4.2.5
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	**Appropriate** Untreated ES-SCLC is considered as a severe condition and could be considered as an end-of-life disease. A severity modifier weight of 1.2 was applied to the QALY to account for serplulimab being a life-extending treatment. See Section 4.2.5

Element of health technology assessment	Reference case	EAG comment on company's submission
Evidence on resource use and costs	Costs should relate to NHS and personal social services (PSS) resources and should be valued using the prices relevant to the NHS and PSS	**Appropriate** Unit costs were appropriately obtained from eMIT, NHS reference costs, Personal Social Services Research Unit (PSSRU) unit costs and BNF. See Section 4.2.6
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	**Appropriate** An annual rate of 3.5% discount was applied to both costs and health effects. This adheres to the NICE reference case stipulation and is found to be appropriate by the EAG. See Section 4.2.5 and 4.2.6

Source: CS document[6]
Abbreviation: AE = Adverse events; BNF = British National Formulary; CS = company submission; CUA = cost-utility analysis; DSU= Decision Support Unit; EAG = Evidence Assessment Group; ECOG PS = European Cooperative Oncology Group performance status; ES-SCLC = Extensive Stage-Small Cell Lung Cancer; HRQoL = health-related quality of life; MAIC = matching-adjusted indirect comparison; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression free survival; PSS = personal social services; PSSRU = Personal Social Services Research Unit; QALY = quality-adjusted life year; SLR = systematic literature review
Footnotes: ǂDurvalumab received approval from NICE in February 2025.

4.2.2 Model structure

Table 4.2 below summarises the EAG's critique on the model structure and inputs adopted by the Company.

Table 4.3: Summary of EAG's critique on the design of the economic model

Aspect of model	Section in CS where methods are reported	EAG's assessment
Model structure/ health states	B.3.2.2[6]	**Some concerns** A partitioned survival model (PSM) was used, with PFS and OS curves obtained from the ASTRUM-005 trial, and HR for comparators obtained from MAICs. A Markov model is generally preferred over a PSM as better survival predictions may be obtained. When comparing serplulimab versus carboplatin + etoposide, the high percentage of patients who died by the end of follow-up means that uncertainty in survival predictions is not significant. However, the situation is different

		when modelling the outcomes of both atezolizumab and durvalumab. See Section 4.2.2.1.
Baseline population characteristics	B.3.2.1[6]	**Appropriate** The baseline characteristics of population were informed by the ASTRUM-005 trial. Refer to Section 3.6.1.2
OS and PFS survival modelling	B.3.3.2 to B.3.3.6[6]	**Key Issue [2]** The company fitted independent and joint models using the six most common parametric models to the Kaplan-Meier curves for serplulimab and carboplatin + etoposide. However, it was not clear if the log-cumulative hazard plots were parallel, and whether a more flexible model would be a better fit to the Kaplan-Meier data. **Key issue [3]** The PFS and OS hazard rates for atezolizumab and durvalumab were derived from HR estimates from the MAICs and the serplulimab PFS and OS curves derived from ASTRUM-005. See Section 3.7for the critique of these analyses. The HRs are assumed to be constant for the duration of the model. See Section 4.2.3
Adverse events/ complications	B.3.3.9[6]	**Some concerns** A continuous risk of adverse events was modelled over time. The actual risk of adverse events over time was not reported. See Section 4.2.4.
Internal and external validity	B.3.12[6]	**Appropriate** Internal validity: there was no commentary on internal validation methods, but the EAG only found errors in the time to death (TTD) population proportion calculations. External validity: because most patients had experienced disease progression by end of follow-up, the ASTRUM trial PFS outcomes for the carboplatin + etoposide served well as the evidence for baseline outcomes. OS model predictions were validated by clinical experts and by comparison with a USA registry data set on OS. It is not clear if subsequent treatment and therefore OS is likely to differ between England and the United States of America (USA). See Section 5.4.2

Source: Company submission document B[6]; clarification letter[4]
Abbreviations: PSM = partitioned survival model; MAICs = matching-adjusted indirect comparison; PFS = progression free survival; OS = overall survival; EAG = Evidence Assessment Group; TTOT = time to off treatment; USA = United States of America

4.2.2.1 Model structure/design

The model had three states: PFS, PD and death. The type of model was a PSM where the patients who were alive over time and the patients who were alive and progression-free over time were determined by survival curves. The number of patients who were alive and had disease progression were determined by subtracting the number of PFS patients from the number of OS patients. A Markov model is generally preferred over a PSM as better survival predictions may be obtained; however, a high percentage of patients had died by the end of follow-up (the OS rate at 4 years was [redacted]% in the serplulimab arm of ASTRUM-005) and the consequence is that uncertainty in survival predictions for serplulimab and carboplatin + etoposide is not significant. Variation in the ICER associated with change in survival predictions is illustrated in EAG analyses in Section 6.

However, a constant HR for PFS and OS is assumed in the model for atezolizumab versus serplulimab and for durvalumab versus serplulimab, estimated from the MAIC analyses (see Section 3.7). It is unlikely that it would remain constant as patients experience disease progression and come off treatment, although some patients continue to receive each of these treatments post-progression. It is possible that the HRs may be smaller (greater distance from 1) earlier in the model and greater (smaller distance from 1) later in the model.

4.2.3 Survival analysis and treatment waning

4.2.3.1 Serplulimab and carboplatin + etoposide

The company produced log-cumulative hazard plots to test whether the proportional hazards assumption could be rejected. The assumption of proportional hazards could not be rejected for PFS or OS. The company appropriately proceeded to test six common parametric models that may or may not be consistent with a proportional hazard assumption. This is consistent with NICE TSD14 guidance. The company selected the log-logistic parametric model fitted independently for PFS and OS for both serplulimab and carboplatin + etoposide. The company plots for the selected models and the Kaplan-Meier curves for PFS and OS are reproduced in Figure 4.1 and Figure 4.2.

The EAG also asked the company to provide the implicit HR plots for serplulimab versus carboplatin + etoposide for OS and PFS, which the company did in the clarification response. For the loglogistic model, the hazard ratio varies over time because this is an accelerated failure time model, which does not assume proportional hazards.

TSD14 also recommends testing the fit of models more flexible than the six common parametric models if the lines in the log-cumulative hazard plots are not straight. The EAG considers that it was not clear whether a more flexible model would be a better fit. On the one hand, there is a visual suggestion that the log-cumulative hazard plots are not straight, and it appears that the fitted curves may slightly underestimate outcomes early in the curves and overestimate outcomes later in the curves. On the other hand, the significant censoring, particularly in the control arm after 18 months for PFS and after 42 months for OS, may mean that a more flexible model is not a better fit. Consequently, the EAG requested more flexible joint models to be fitted and for the company to comment in the clarification letter.

In the company's response to the clarification letter, the company presented spline models with 1, 2 and 3 knots. The company plots for the spline models and the Kaplan-Meier curves for OS and PFS are reproduced in Figure 4.1 and Figure 4.2. The company noted that while

spline models with 2/3 knots most closely fitted the Kaplan-Meier curves, the long-term overall survival predictions appeared to be overestimated according to clinical expert opinion, particularly for serplulimab. Furthermore, even the spline model with 1 knot for PFS resulted in PFS estimates greater than OS in the long-term. The EAG considers these observations to be important and they suggest that if longer-term and larger sample sizes were available then Kaplan-Meier curves may lower or take a downturn after a point in time.

Over the Kaplan-Meier time period for carboplatin + etoposide, the implicit hazard ratio for serplulimab vs carboplatin + etoposide from the 3 knot spline model was roughly constant at [redacted].

Consequently, in the EAG base case for OS, the 3 knot spline model is fitted for serplulimab and for carboplatin + etoposide until the latest timepoint at which the number of patients still at risk was at least 10 (42 months and 18 months, respectively). For serplulimab, after 42 months, despite a fairly constant hazard ratio of [redacted] over the first 18 months, the EAG modelled an alternative survival curve to account for company clinical expert opinion of lower overall survival in the long-term. The company clinical experts considered the loglogistic model to provide more plausible OS predictions than the 3 knot spline OS predictions. In the EAG base case, the hazard ratio was assumed to linearly increase from 0.6 to 1 from 3.5 years to 6.5 years, which is a significant time period given the median survival for this population with carboplatin + etoposide treatment. In a scenario analysis an exponential curve was fitted so that the predicted OS at 10 years was the same as the predicted OS in the company base case. For carboplatin + etoposide, the 3 knot spline model is fitted until 18 months and then an exponential curve is fitted so that the OS at 10 years is similar to the logistic model prediction.

For PFS for serplulimab, the 3 knot spline model was selected for the EAG base case until 42 months and a 3 year waning assumption (until 6.5 years) was assumed. For carboplatin + etoposide, the 3 knot spline model was selected for the EAG base case until 12 months and then an exponential curve was fitted to match the loglogistic model prediction at 5 years.

The OS and PFS plots for the EAG analyses are presented in Figure 4.3 and Figure 4.4.

Both of these long-term approaches (3-year waning and fitting to 10-year loglogistic prediction) produce OS predictions within plausible ranges of the company clinical experts, and the difference in ICERs between the two is small as shown in EAG analyses. However, ultimately, survival may be greater or smaller over the long-term.

Figure 4.1: Overall survival curves modelled for serplulimab and carboplatin + etoposide

Source: Produced by EAG from the company economic model
Abbreviations: Carboplatin + E: carboplatin +etoposide; Serplulimab: serplulimab + carboplatin +etoposide; KM: Kaplan-Meier; 3knot spline + exp: initially a 3 knot spline modelled, followed by an exponential model

Figure 4.2: Progression-free survival curves modelled for serplulimab and carboplatin + etoposide

Source: Produced by EAG from the company economic model
Abbreviations: Carboplatin + E: carboplatin +etoposide; Serplulimab: serplulimab + carboplatin +etoposide; KM: Kaplan-Meier; 3knot spline + exp: initially a 3 knot spline modelled, followed by an exponential model

Figure 4.3: Overall survival curves modelled in the EAG base case

Source: Produced by EAG from the company economic model
Abbreviations: Carboplatin + E: carboplatin +etoposide; Serplulimab: serplulimab + carboplatin +etoposide; 3knot spline + exp: initially a 3 knot spline modelled, followed by an exponential model

Figure 4.4: Progression-free survival curves modelled in the EAG base case

Source: Produced by EAG from the company economic model
Abbreviations: Carboplatin + E: carboplatin +etoposide; Serplulimab: serplulimab + carboplatin +etoposide; 3knot spline + exp: initially a 3 knot spline modelled, followed by an exponential model

4.2.3.2 Atezolizumab and durvalumab

Constant HRs for OS and PFS for atezolizumab versus serplulimab and for durvalumab versus serplulimab were both estimated from MAICs. See Section 3.7and the critique of the analyses. The HR for OS may possibly be constant over the short-term; the implicit HR derived from the 3 knot spline models suggest a fairly constant HR for OS of around [redacted] over the first 18 months. For OS, in the EAG base case, the assumption is made that the OS HRs for atezolizumab vs serplulimab and for durvalumab vs serplulimab linearly tends towards 1 from 3.5 years to 6.5 years. For PFS, the atezolizumab vs serplulimab and for durvalumab vs serplulimab HRs are assumed to remain constant for the duration of the model in the EAG base case.

The OS and PFS curves for the EAG analyses for all comparators are presented in Figure 4.3 and Figure 4.4.

4.2.4 Adverse events

AEs were modelled on a weekly basis. Many more events occurred in the serplulimab trial arm than in the carboplatin + etoposide trial arm, but patients were also alive for longer. The Company calculated the total weeks at risk and divided the number of events by the total number of weeks at risk to get the rate of adverse events per week. It was not clear how the number of weeks at risk was calculated; whether it was the total time alive or on treatment. Given that carboplatin + etoposide has a fixed period of treatment delivery, the greater number of AEs in the serplulimab arm suggests that some adverse events are related to serplulimab treatment rather than the carboplatin + etoposide, in which case there is a case

for modelling the risk of adverse events over time rather than as a cost that is incurred at the start of treatment. The risk of these adverse events over time was not reported, however.

4.2.5 Health-related quality of life

Table 4.4 summarises the EAG's critique on HRQoL within the economic model.

Table 4.4: Summary of EAG's critique on HRQoL

Aspect of model	Section in CS where methods are reported	EAG's assessment
Identification of HRQoL data within the SLR	B.3.4.3[6]	**Appropriate** The EAG found that the company included an appropriate range of databases and undertook methods of SLR to identify the HRQoL data.
Source of preference data for valuation of changes in health-related quality of life	B.2.6.3[6]	**Appropriate** The HRQoL measures were informed by the ASTRUM-005 trial, in which the ITT population included more Asians, predominantly Chinese, than non-Asians. According to Feng et al.[85], EQ-5D-5L exhibits excellent psychometric properties across a broad range of populations, conditions and settings. The EAG has also found evidence that China EQ-5D preference weights show equivalent psychometric properties with those of UK.[86] See the Section 4.2.5.1 for detailed explanation.
Health state utility values	B.3.4.5[6]	**Appropriate** The health state utility values were informed by EQ-5D-5L value set from ASTRUM-005 trial.[87] The values were mapped to the NICE recommended instrument - EQ-5D-3L. The CS base-case model[88] included health state utilities based on disease progression of patients. There were two scenarios included around utilities: • utility estimates based on disease progression and treatment status • utility estimate calculated by time to death (TTD) in the model, informed by data from the ASTRUM-005 trial. See Section 4.2.5.1 for more details. **Some Concerns** The utility values based on the disease progression seemed high when compared to the utility estimates used in the economic evaluations from literature search and previous NICE submissions. There was a marked difference between the utility value of the disease progression health state used in the company submission and the same obtained from other sources (e.g. Nafees et al. 2008[5], Paracha et al [89], Chouaid et

	B.3.4.5 Table 40[6]	al. 2013[90]). So, EAG has some concerns over the high utility values used in this submission. See the Section 4.2.5.1 for more information. 886
Disutilities	B.3.4.4[6]	**Appropriate** The utility decrement for AEs was applied to the company base case, while a scenario where no disutilities applied was explored to avoid any potential double counting of the disutilities in the patients. Another scenario where the effect of a utility decrement specifically related to non-Asians as opposed to all patients was explored by the company. See Section 4.2.5.2 for further details and disutility values. These values were informed by sources from literature search and the previous NICE submission – TA638.[8] The EAG is of the opinion that the utilities related to adverse events were appropriately informed and considered by the company.
Severity Modifier	CS PfC response, C13. Table 30[4]	**Some Concerns** A QALY weight of [redacted] was applied to the total QALYs as a severity modifier by the company. The EAG verified the absolute QALY shortfall, proportional QALY shortfall and severity weightage on QALYs using the QALY Shortfall Calculator by University of York[91], which uses R Shiny. The scenario selected to calculate the QALYs in the general population (without the disease) was based on the reference case, as specified by NICE TSD 23.[92] But since the instrument used in the ASTRUM-005 trial was EQ-5D-5L and the values obtained were mapped to EQ-5D-3L, the EAG notes the inconsistency in the methods used in evaluating the utility values for the general population. Carboplatin + etoposide was taken to be current practice. Were atezolizumab or durvalumab adopted as current practice then the severity modifier estimate would change. More information is given in Section 4.2.5.3.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ITT = Intention-to-treat; SLR = systematic literature review, HRQoL = health related quality of life		

4.2.5.1 Health state utility estimates

The health state utility values used in the CS base-case were informed by the ITT population in the ASTRUM-005 trial.[87] This population included more Asians than non-Asians (Chinese patient population). EQ-5D-5L, which was used in the trial, exhibits excellent psychometric properties across a broad range of populations, conditions and settings.[85]

The patient population in the trial used the EQ-5D-5L instrument to record their HRQoL. The responses were mapped to the NICE recommended EQ-5D-3L responses and values generated using the mapping function developed by Hernández-Alava and Pudney 2017 for

DSU, using the 'EEPRU dataset' Hernández-Alava et al. 2023.[83,84] The utility values were associated with disease progression (but not the treatment status) in the company base-case model. The utility estimates based on disease progression and treatment status were included to provide additional granularity in the estimation method. A scenario analysis was included using these estimates. The utility estimates used in the company model are reported in Table 4.5.

When compared to the utility values used in the economic evaluations and previous NICE submissions, the utility values mapped from ASTRUM-005 seemed higher. The EAG recognises that a good number of the economic evaluations from the literature search have used utility estimates of NSCLC. Given that fact that these utility values are used in economic evaluations for SCLC patients, the EAG assumes that the values could be used in all types of lung cancer patients (including for non-small cell and SCLCs). There is a marked difference between utility values of disease progression sourced from ASTRUM-005, those used in the economic evaluations identified in Appendix I[93] and other sources.[8,90,89] For example, Nafees et al. 2008 is a common source in many of the economic evaluations found in the literature search and, the reported utility values for progression free and disease progression health states were 0.673 and 0.473 respectively.[5]

The EAG thinks that, if for some reason the trial utility estimates are greater than those seen in England clinical practice, then this may affect the cost-effectiveness of serplulimab + carboplatin + etoposide. Alternative utility values have been used in EAG scenario analyses (see Section 6.1.2).

The alternative approach used for utility estimation was the TTD method, which used the patients' proximity to death. This was based on the utility estimation approach adopted in relevant previous appraisal – TA638.[94] But the consensus of committee appraisals in oncology with this method was that it should not be a standard approach in ES-SCLC. In the CS document, additional justification for excluding these estimates was that this method introduced time-dependent confounding bias because the proximity to death is influenced by the treatment itself.[6] Hence, the utility estimates using TTD was included as a scenario analysis in the company economic model.[88] However, the EAG has noticed that the utility estimates reported in CS document are significantly different from the estimates in the CS model. See Table 4.6 for the utility values. The EAG is concerned about the source and validity of the utility estimates by TTD method used in the Company's economic evaluation.[88]

4.2.5.2 Disutilities associated with adverse events

The company considered utility decrement for AEs in the base case. To address the possibility that the health state utility estimates may have taken the impact of AEs on the quality of life of patients into account, a scenario where no disutilities were applied, was explored to avoid any potential double counting of the impact of AEs. Another scenario where the effect of utility decrement, specifically related to non-Asians as opposed to all patients, on HRQoL of patients was explored by the Company. See Table 4.7 for the disutility estimates applied in the Company model. These values were informed by sources from literature search and the previous NICE submission – TA638.[94]

In the Company economic model,[88] the weekly probability of each AE was specific to each treatment. The disutilities associated with each AE were multiplied by the corresponding weekly probability and average duration reported in the ASTRUM-005 trial. The EAG is of

the opinion that the utilities related to adverse events were appropriately informed and considered by the Company.

4.2.5.3 Severity modifier

A QALY weight of [redacted] was applied to the total QALYs as a severity modifier by the Company. The absolute QALY shortfall, proportional QALY shortfall and severity weightage on QALY were verified by the EAG using the QALY Shortfall Calculator by University of York,[91] which uses R Shiny. The Company result could be replicated by using the reference case scenario to calculate the QALY in the general population (without the disease). This aligns with the method of calculating utility value for the general population, specified in the NICE TSD 23.[92] The Company used the same mapping algorithm and data set to produce the utility values for the general population. But since the instrument used in the ASTRUM-005 trial was EQ-5D-5L and the obtained values were then mapped to EQ-5D-3L. In the QALY shortfall calculator, the 'Alternative A' scenario uses the same mapping algorithm and health state utility data set as the Company (for mapping utility values of NSCLC patients from EQ-5D-5L to EQ-5D-3L). The Company approach follows NICE guidance, but the EAG notes inconsistency in the value sets used. Using the same approach for both the condition and the general population does not change the QALY weights applied in the model (but the utility estimate of general population).

The carboplatin + etoposide model predictions were used for the condition in calculating the severity modifier. The severity modifier did not change using the EAG base case model predictions for carboplatin + etoposide. Were current practice to become atezolizumab or durvalumab then the severity modifier would need to be recalculated.

Table 4.5: Health state utility values based on disease progression

Health state	Utility value	95% Confidence Interval
By disease progression state (CS base-case)		
PFS	0.838	0.826 - 0.849
Progressed disease	0.805	0.785 - 0.825
By disease progression and on/off-treatment status		
On-Treatment		
PFS	0.855	0.843 - 0.866
Progressed disease	0.836	0.813 - 0.859
Off-Treatment		
PFS	0.757	0.741 - 0.773
Progressed disease	0.786	0.760 - 0.812

Source: CS Document[6]
Abbreviations: PFS = progression free survival, CS = company submission

Table 4.6: Health state utility values based on proximity to death and on/off treatment

Health state	Model-based estimate in report	Actual model-based estimate in the economic model
On-treatment		
0-≤5 weeks	0.849 (0.785, 0.913)	[redacted]
>5-≤15 weeks	0.825 (0.799, 0.852)	[redacted]
>15-≤30 weeks	0.836 (0.819, 0.854)	[redacted]
>30 weeks	0.862 (0.851, 0.873)	[redacted]
Off-treatment		
0-≤5 weeks	0.464 (0.361, 0.567)	[redacted]
>5-≤15 weeks	0.697 (0.640, 0.753)	[redacted]
>15-≤30 weeks	0.765 (0.718, 0.812)	[redacted]
>30 weeks	0.817 (0.785, 0.850)	[redacted]
Source: CS document[6], CS economic model[88]		

Table 4.7: Disutility values applied in the model

Adverse event	Disutility	Original source
Anaemia	-0.07346	Assumed equal to fatigue in Nafees et al. 2008[5]
Diarrhoea	-0.0468	Nafees et al. 2008[5]
Fatigue	-0.07346	Nafees et al. 2008[5]
Febrile neutropenia	-0.09002	Nafees et al. 2008[5]
Hyperglycaemia	-0.03	Assumed the same as hypertension
Hypertension	-0.03	Nafees et al. 2008[5]
Hypertriglyceridaemia	-0.03	Assumed the same as hypertension
Hypocalcaemia	-0.03	Assumed the same as hypertension
Hypokalaemia	-0.03	Assumed the same as hypertension
Hyponatraemia	-0.085	NICE TA428 disutility: KEYNOTE-10
Infusion-related reaction	-0.05	Doyle et al. 2008
Leukopenia	-0.08973	Assumed equal to neutropenia
Lymphocyte count decreased	0	Assumption
Neutropenia	-0.08973	Nafees et al. 2008[5]
Neutrophil count decreased	0	Assumption
Pancytopenia	-0.08973	Assumed equal to neutropenia
Platelet count decreased	-0.05	Assumption based on nintedanib NICE appraisal (TA347)
Pneumonia	-0.008	Marti et al. 2013
Thrombocytopenia	-0.08973	Assumed equal to neutropenia
Vomiting	-0.04802	Nafees et al. 2008[5]
White blood cell count decreased	-0.05	Assumption based on nintedanib NICE appraisal (TA347)

Source: CS document[6]

4.2.6 Resources and costs

Resource use data on the comparator arms was sourced from TA638 ES-SCLC.[8] Please see Table 38 in the CS for additional detail.[6] For serplulimab, the Company stated that the resource use was assumed to be equivalent to atezolizumab and this assumption was validated by clinical experts.[6] In the PfC, more details were requested by the EAG on the validation of assumptions and cost estimates in TA638[8] by clinical experts. In the Company PfC response, it was stated that since there were no relevant published studies on resource use, therefore the expected average resource use of a patient in each stage of treatment and disease were obtained via nine UK clinicians and the Committee and EAG were satisfied by their approach.[95]

The unit costs were sourced from different NHS reference costs at 2022/23 and the literature. Regarding the discrepancy in the price years used by the Company, the Company stated in their PfC response that the costs were not directly sourced from the NHS reference costs such as cost of palliative care, were inflated to 2024 prices using PSSRU Hospital and

Community Health Services(HCHS) and NHS cost inflation index values (NHSCII).[96] It was stated that for these costs not obtained from NHS reference costs the average rate of inflation over the previous three years was used due to unavailability of the inflation index at the time of submission.[95] The medication price for atezolizumab and topotecan were obtained from the BNF January 2024[64] while for other drugs except serplulimab, obtained from eMIT 2024.[97]

The EAG has some concerns regarding evidence on resource use, please see EAG's critique on the resources and costs within the economic model in Table 4.8 below.

Table 4.8: Summary of EAG's critique on resources and costs

Aspect of model	Section in CS where methods are reported	EAG's assessment
Resource use and cost data identified in the SLR	Appendix J Section 3.3, pp: 38-46	**Appropriate** The company conducted an SLR to identify evidence on critical domains related to treatments of ES-SCLC including economic evaluations, utility, cost and resource use. In total, 39 individual reports from the SLR were included in the review, and from these, 7 studies were related the economic burden and healthcare use of ES-SCLC. Please see Appendix J for more details. See Section 4.1.
Time on treatment	Document B, Section 3.5.1page 120 Table 45 Response to Clarification letter, page 3	**Key Issue [4]** For the serplulimab, TTOT was modelled using parametric models fitted to the Kaplan-Meier curves from ASTRUM-005. The selected log-logistic model was not a close fit to the Kaplan-Meier curve. See Section 4.2.6.1. **Some concerns** For atezolizumab [8] and durvalumab [88], TTOT was derived by applying the reciprocal of the OS hazard ratio to the TTOT hazard rates for serplulimab. There is a lack of time on treatment evidence. See Section 4.2.6.1. **Some concerns** The Kaplan-Meier curve for TTOT for carboplatin + etoposide from ASTRUM-005 indicates that roughly [redacted]% of patients are still on treatment after 26 weeks when the last of the 4 cycles of treatment is given in week 9 in the model.
Treatment stopping rules/ discontinuation/(see	B.3.3.5 [6]	**Appropriate** Serplulimab was given in combination with carboplatin and etoposide. Carboplatin +

Section 4.2.7.1 for time on treatment)		etoposide treatment lasted for 4 cycles. Serplulimab was given continuously until treatment discontinuation. The EAG clinical advisor stated that this was plausible in England clinical practice. The same approach was taken for atezolizumab and durvalumab. In the serplulimab arm of the ASTRUM-005 trial, the main reason for treatment discontinuation was progressive disease ([redacted]), followed by withdrawal by subject ([redacted]), AEs ([redacted]), study terminated by sponsor ([redacted]). **Some concerns** The percentage of patients on treatment was assumed to be independent of disease progression status. While some patients continued to receive serplulimab after disease progression, the EAG thinks this assumption is unlikely to be correct. This has a small effect on costs through subsequent treatment after disease progression and cessation of serplulimab. This was not considered a Key Issue because of the limited impact on the ICER. See Section 4.2.6.2.
Dose		**Appropriate** The treatment dose on serplulimab, carboplatin and etoposide were informed by the ASTRUM-005[49] trial and validated by UK clinical experts. Atezolizumab dose was considered as a fixed dose and obtained from the dosing schedule of IMpower133, aligned with its marketing authorisation[98] and TA638. Durvalumab dose was considered as a fixed dose in line with the dosing schedule of the CASPIAN trial[19] and TA1041.[7] Carboplatin and etoposide in atezolizumab[6] and durvalumab were assumed as the same dose and frequency as the serplulimab arm.[88]
Dose intensity	Document B, Section 3.5.1 Page119 Clarification response, page 4	**Appropriate** RDI was applied to all treatment arms: using patient-level data for serplulimab, carboplatin, and etoposide; TA638[6] for atezolizumab; and TA1041[7] (95.4%) for durvalumab.[88] Please see Table 43 page 119 in the CS.
Vial sharing	Document B, Section 3.5.1 Page118	**Appropriate** In the CS, it is stated that vial sharing was not assumed for serplulimab in the base case, the assumption is validated by clinical opinion.[8] The EAG requested the details on clinical opinion used to validate the assumption of no vial sharing

		for serplulimab in the clarification letter. However, the company stated that they did not elicit the clinician opinion on vial sharing and wish to correct their submission by removing this statement.[95] The CS considered vial sharing for the administration of chemotherapy drugs based on TA638[6] in the base-case analysis. However, NICE has released guidelines about not including vial sharing in the base case.[99]
Acquisition costs	Section 3.5.1 page 118	**Key Issue [5]** To calculate treatment cost per each cycle, the company calculated the average number of packs required per treatment cycle and multiplied it by the pack prices.[8] For serplulimab and chemotherapy drugs which are based on the weight and BSA, the company used a mean body weight of 68.4 kg and height of 167 cm in the model informed by ASTRUM-005. The EAG has some concerns regarding generalizability of drug acquisition costs due to discrepancy between body weight and BSA assumptions used in the model with England general public. [3] To counteract that, it is possible that patients lose weight when they have this stage of cancer. In addition, the average height of older patients be lower than the average in the population. The EAG used different body weight and BSA based on the information from NHS Health Survey on England Adults' mean weight and height by age and sex in 2022.[3] Please see section 4.2.6.3 for more details.
Administration costs	3.5.3 Page 121	**Appropriate** To calculate drugs administration costs for each treatment cycle, the company obtained unit costs of administration from NHS reference costs 2022-2023 and applied it in the model. Please see Table 47 in the CS as they are different values based on the timing (day 1, or day 2 and 3) and treatment type (mono or combination therapy).
Monitoring and disease management costs	Document B, section 3.5.4 Page 121	**Appropriate** Weekly surveillance costs (£85.13) were applied to patients receiving surveillance or subsequent second line therapy until death. The resource use obtained from TA638.[6] Please see Tables 48 and 49 in the CS on resource uses and unit costs, respectively.
Subsequent treatment costs	Document B, section 3.5.2 Page 121	**Some concerns**

	Response to PfC	Subsequent treatment costs were applied to all patients who had disease progression or who were still progression-free but off-treatment. The proportion of patients on other treatment was informed by clinical expert opinion obtained in TA638 and were assumed to be the same in the different treatment arms in the model (TA638: 10-20% on second-line treatment once their disease relapse).[6] According to a clarification request by the EAG, 53.0% and 48.0% patients in the serplulimab group and placebo went to the subsequent treatment after first disease progression, with a similar proportion of Asian and non-Asian subjects.[95] Please see Section 4.2.6.4 for more details.
Adverse event costs	Section 3.3.9, Table 36, Page 108 Section 3.5.6 Table 50, Page 125	**Some Concern** A weekly probability of associated with AEs were obtained from the ASTRUM-005 and atezolizumab appraisal from TA638[6] respectively. No information was provided on the distribution of the occurrence of adverse events over time. In the durvalumab arm, the weekly probabilities of AEs and hence the associated costs, are assumed to be the same as the serplulimab arm.[88] Then AEs probabilities were multiplied by the cost of each AE considering the duration of time in which a patient is on treatment.[8]
Terminal care costs	Document B, section 3.5.5, Page 125	**Appropriate** Terminal care costs related to the ES-SCLC was obtained from Oliver et al. 2001,[100] and inflated to 2024 prices using the PSSRU inflation index for Hospital and Community Health Services.
Health state costs	Document B, section 3.5.4, pages 122-125 Tables 48 and 49.	**Appropriate** The company reported resources use, unit costs and the average cost for a patient in each treatment and disease stage.
Abbreviations: AE = adverse event; BSA = body surface area; CS = company submission; EAG = Evidence Assessment Group; SLR = systematic literature review; TTOT = time-to-off treatment; ES-SCLC = extensive-stage small cell lung cancer; OS = overall survival; RDI = Relative dose intensity; SCLC = small cell lung cancer		

4.2.6.1 Time on treatment

4.2.6.1.1 Serplulimab and carboplatin + etoposide

For serplulimab and carboplatin + etoposide, time-to-off treatment (TTOT) was modelled using parametric models fitted to the Kaplan-Meier curves from ASTRUM-005. The Kaplan-Meier curves are presented in Figure 4.5. It is not clear what the Kaplan-Meier curve represents for carboplatin + etoposide when the last of the 4 cycles of treatment is administered in week 9.

The same survival analysis methods as those used for fitting and selecting parametric models for OS and PFS were also applied for TTOT. Independent log-logistic parametric models were fit to the Kaplan-Meier data for serplulimab and carboplatin + etoposide. These are presented in Figure 4.6.

The EAG considers that Kaplan-Meier curves could have been used for serplulimab and carboplatin + etoposide to more accurately reflect the time on treatment. However, a parametric model that closely fits the Kaplan-Meier curve would be adequate and make it easier to derive the TTOT curves for atezolizumab and durvalumab. Uncertainty in the use of serplulimab after disease progression makes predictions difficult.

The EAG asked the company to fit models more flexible than the standard 6 parametric models, and the company provided the results from 1, 2, and 3 knot spline models in the clarification response.

The company made similar observations about the spline model predictions for TTOT as they made for OS and PFS. Consequently, the EAG has taken the same approach in the EAG analyses for TTOT as for OS. The 3 knot spline model was used until an appropriate time point. Since no at risk data were provided for the TTOT Kaplan-Meier curves, the cut-off time point was based on the PFS at-risk numbers for serplulimab (42 months). Further, after 42 months the percentage on treatment was limited to the percentage on treatment in each of the PFS and PD states in the previous cycle and the PFS and PD numbers in the current cycle. Plots of the EAG TTOT curves are presented in Figure 4.6.

See Section 4.2.6.2for a discussion on the implementation of the TTOT curves in the model.

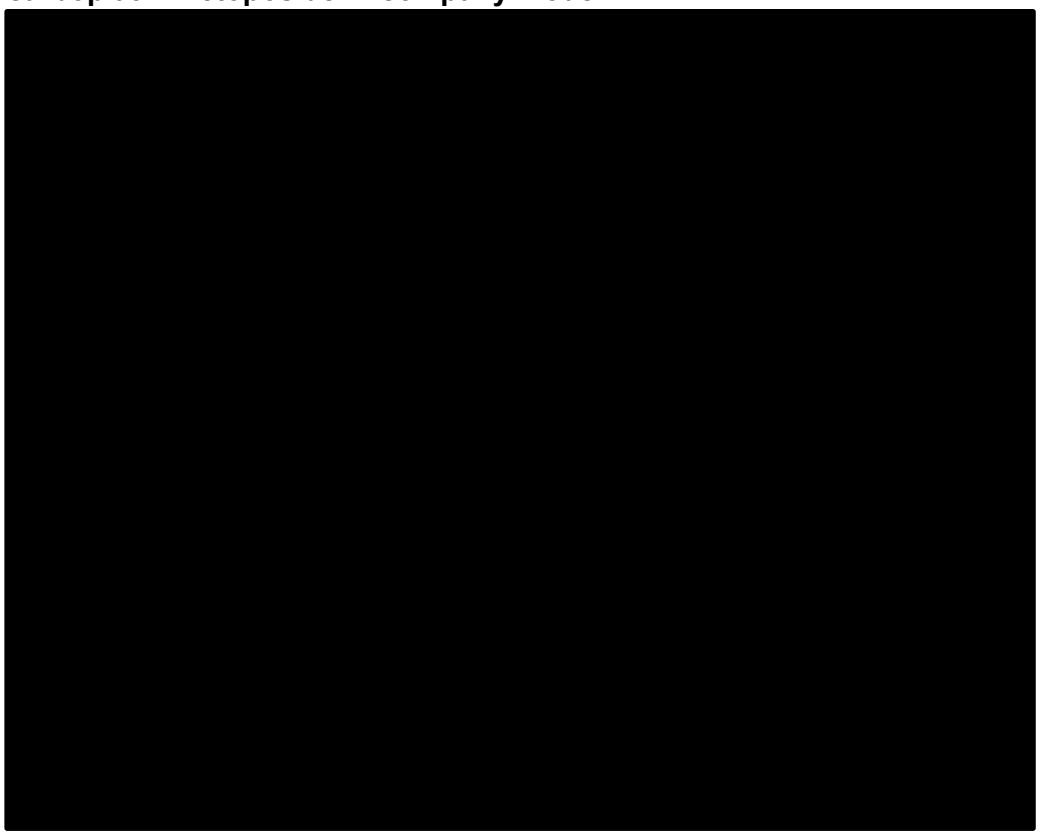
4.2.6.1.2 Atezolizumab and durvalumab

For atezolizumab[8] and durvalumab[88], TTOT was derived by multiplying the reciprocal of the OS HR estimates from the MAIC analyses with the hazard rates for stopping treatment for serplulimab. There is a lack of time on treatment evidence for atezolizumab and durvalumab. The EAG retained the approach of applying the OS HR estimates to derive the TTOT curves for atezolizumab and durvalumab until 42 months, and thereafter the percentage on treatment was limited to the percentage on treatment in each of the PFS and PD states in the previous cycle.

Figure 4.5: Kaplan Meier curves for OS, PFS and TTOT for serplulimab + carboplatin + etoposide and carboplatin + etoposide from ASTRUM-005

Source: Produced by EAG from the company economic model
Abbreviations: PFS: progression-free survival; OS: overall survival; S+C/E: serplulimab + carboplatin + etoposide; C/E: carboplatin + etoposide; TTOT: time to off treatment

Figure 4.6: TTOT curves in EAG model and TTOT and KM curves for serplulimab + carboplatin + etoposide in company model



Source: Produced by EAG from the company economic model
Abbreviations: Serplulimab: serplulimab + carboplatin + etoposide; KM: Kaplan-Meier

4.2.6.2 Treatment discontinuation

For all comparators, the company multiplied the percentage of patients in the PFS state by the percentage of patients on treatment from the TTOT curve to derive the percentage of patients in PFS and on treatment. The same was done for the PD state. This assumes that the percentage of patients on treatment is the same in the PFS and PD states. The clinical expert that the EAG consulted confirmed that some patients may continue on serplulimab, atezolizumab and durvalumab after disease progression. While the TTOT curve for serplulimab closely matches the PFS curve in Figure 4.5, this could be coincidental later in the curve when more patients in the disease progression state.

The distribution of patients on treatment across PFS and PD states affects the cost of subsequent treatment acquisition and administration costs. However, these costs are small and so this issue will have a minor impact on the ICER. Nevertheless, the EAG has investigated this to demonstrate the small effect.

The EAG does not have any information on the difference in percentages of patients on treatment between PFS and PD states. Regarding discontinuation, in the serplulimab arm of the ASTRUM-005 trial, the main reason for treatment discontinuation was progressive disease ([redacted]), followed by withdrawal by subject ([redacted]), AEs ([redacted]), study terminated by sponsor ([redacted]). However, the EAG believes this assumption of equal percentages across states on treatment as unlikely given that disease has progressed. Consequently, the EAG have taken a simple approach to exploring lower percentages of PD patients on treatment.

The percentage of PD patient receiving serplulimab is capped at 20% in the base case, and increased to 30% and reduced to 10% in scenario analyses. In each of these scenarios, the percentage of patients in the PD state on treatment decreases if the percentage of patients on treatment from the TTOT curve falls below the cap. The percentage of patients on treatment is either the cap or the percentage from the TTOT curve, whichever is smaller.

The percentage of patients on treatment for PFS patients and PD patients in the company model and the EAG model are presented in Figure 4.7 and Figure 4.8. The EAG base case has a cap of 20% of PD patients on treatment. The percentage of patients on treatment in the PFS state does not increase greatly in the short term, but increases in the later years, when compared to the TTOT curve.

For the carboplatin + etoposide arm of the ASTRUM-005 trial, the KM curve for TTOT represents the discontinuation of placebo. However, the TTOT KM curve is similar to the PFS curve, so it was not considered to be a problem.

See Section 4.2.6.1 for a discussion on the TTOT curve.

Figure 4.7: Proportion of PFS patients on treatment in the company model and in EAG scenarios

Source: Produced by EAG from the company economic model

Abbreviations: 20% PD: the percentage of patients on treatment in the PD state is capped at 20%

Figure 4.8: Proportion of PD patients on treatment in the company model and in EAG scenarios

Source: Produced by EAG from the company economic model
Abbreviations: 20% PD: the percentage of patients on treatment in the PD state is capped at 20%

4.2.6.3 Acquisition costs

The Company considered atezolizumab[8] and durvalumab[88] as fixed dose treatment regimens in the model, 1200 mg and 1500 mg, respectively. For serplulimab and chemotherapy drugs which are based on the weight and BSA, to calculate the average number of packs required per treatment cycle the company used a mean body weight of 68.4 kg and height of 167 cm in the model informed by ASTRUM-005. Then, cost per each treatment regimen per cycle was calculated by multiplying the pack price by the average number of packs required. For serplulimab, a weight-based dosing (4.5 mg/kg) was applied to calculate the cost per cycle. The mean BSA of 1.77 m² was cost per cycle of all chemotherapy drugs in the model. Please see Section 3.5.1 (Tables 44, 45 and 46) in the CS on the average number of packs per treatment cycle for serplulimab, dosing schedules and drug cost per treatment cycle for treatment regimens.[8] The EAG has some concerns regarding generalizability of drug acquisition costs due to discrepancy between body weight and BSA assumptions used in the model with England general public.

Initially, the EAG incorrectly identified the average weight and height for all adults in England, using the NHS Health Survey for England, 2022[3]. The mean weight for men and women was 85.8 kg (SE: 0.47). 72.8 kg (SE: 0.43), respectively. The average weight in England in 2022 for all adults was equal 79.3 kg (SE: 0.34) which means, on average, the England population is 11 kg heavier than the population in the ASTRUM-005 trial. (It should

be mentioned that although the majority of patients in ASTRUM-005 trial were male (more than 80%), since the gender distribution in ES-SCLC disease in the England was approximately equal[2] and ASTRUM-005 trial was considered imbalance regarding gender distribution, the EAG used the England average weight, 50% women.

According to this survey, the mean height of men was 176.2 cm (SE: 0.22), and of women was 162.3 cm (SE: 0.17). The EAG considered the average height of 168.4 cm for calculating BSA using the Dubois formula provided by the company (BSA = 0.007184 x (W0.425) x (H0.725), which resulted in 1.90 m².
The use of all adults was identified as an error from the FAC.Further review of the National Lung cancer audit [2] highlighted that the median age at diagnosis for SCLC was 70 years. Hence, the EAG decided to consider the 65–74 age group as a reference and update use the height and weight values in the base case to reflect this 65–74 age group. According to the Health Survey for England, individuals aged 65–74 years have the average weight and height of 79.3 kg (SE: 0.63) and 166.8 cm (SE: 0.32), respectively. [3] A 1.6 cm reduction in the average height affects the BSA for chemotherapy treatment, which only changes the ICER by £3 compared to atezolizumab and by £4 compared to carboplatin + etoposide.

The EAG has run a scenario with the ASTRUM-005 trial weight and height, and a scenario with the ASTRUM-005 trial non-Asian subgroup weight and height. The average weight for non-Asians from ASTRUM-005 listed in the company model was 78.84 kg and the average height for non-Asians was 171.29 cm.

4.2.6.4 Subsequent treatment

In the CS, it was stated that subsequent treatment costs were applied to all patients who were progressed or off-treatment and the proportion of patients were informed by clinical expert advice elicited to support the atezolizumab appraisal, TA638 and were assumed the same in the different treatment arms in the model.

Regarding the proportion, it was mentioned that according to TA638, 10-20% on second-line treatment, 80-90% receiving palliative care or surveillance only. They also, stated in the CS, the proportion of patients receiving each subsequent therapy in the base-case economic model were as follows: 85% second-line therapy, 5% re-challenge with their first-line chemotherapy (carboplatin-etoposide), 5% oral topotecan, and 5% cyclophosphamide, doxorubicin and vincristine, which was a typographical error.

In the Excel economic model file, only 15% of patients received subsequent treatment. However, the EAG was concerned about if the distribution of subsequent treatments accurately reflects current clinical practice in England. The EAG have elicited the opinions of a clinical experts and requested clarification regarding clinical expert's engagement details on the subsequent therapy distribution in ES-SCLC patients and explain the difference in subsequent therapy distributions between the trials included in this evidence submission for serplulimab and its comparators. The EAG also is interested on the proportion of patient that they stay on serplulimab after disease progression.

In response to clarification on subsequent treatment, it was stated that 53.0% and 48.0% patients in the serplulimab group and placebo group received ≥1 treatment after first disease

progression, with a similar proportion of Asian and non-Asian subjects, which is different from the value used by the company in the modelling. They assumed 15% which was informed by TA638 (10-20% on second-line treatment once their disease relapse). In the model, the company considered equal share for Re-challenge with 1st line chemotherapy, topotecan and CVA.

5 COST EFFECTIVENESS RESULTS

5.1.1 Company's cost effectiveness results

The cost-effectiveness results in Sections 3.8, 3.9 and 3.10 of the CS document were based on the list price of serplulimab while the results using patient access scheme (PAS) price of serplulimab were provide as Appendix N in the CS document. The full set of analyses reported using the list price for serplulimab were not reported using the PAS price for serplulimab. The analyses with durvalumab + carboplatin + etoposide as a comparator was provided as an addendum to the clarification response from the Company.[95] The results presented here are the results including the PAS price for serplulimab. See the CS for the serplulimab list price results.

The Company conducted pair-wise cost-effectiveness analysis between serplulimab + carboplatin + etoposide and its comparators in all patients (Asians and non-Asians). The Company's base-case deterministic cost-effectiveness results are shown in Table 5.1,Table 5.2 and Table 5.3. Results were presented using a x1.2 QALY severity modifier used (see Section 4.2.5).

The base-case pair-wise results between serplulimab + carboplatin + etoposide and durvalumab + carboplatin + etoposide showed that the cost decreased by [redacted] and improved QALY by 0.46. The net monetary benefit was [redacted], at a willingness to pay threshold of £30,000.

The base-case pair-wise results between serplulimab + carboplatin + etoposide and atezolizumab + carboplatin + etoposide showed that the cost decreased by [redacted] and improved QALY by 0.60. The net monetary benefit was [redacted], at a willingness to pay threshold of £30,000.

The base-case pair-wise results between serplulimab + carboplatin + etoposide and carboplatin + etoposide showed that the cost increased by [redacted] and improved QALY by 0.60. The net monetary benefit was [redacted], at a willingness to pay threshold of £30,000.

In the company pair-wise base-case deterministic full incremental cost-effectiveness analysis serplulimab + carboplatin + etoposide was [redacted] when compared to durvalumab + carboplatin + etoposide and atezolizumab + carboplatin + etoposide. When compared to carboplatin + etoposide, the incremental cost and QALY were [redacted] and 0.89 respectively, with the ICER being [redacted].

Table 5.1: Company base-case deterministic pairwise cost-effectiveness results with PAS price (x1.2 QALY severity modifier used)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER (£)
				costs (£)	LYG	QALYs (x1.2)	
serplulimab + carboplatin + etoposide	[redacted]	2.47	2.10				
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.64	[redacted]	0.60	0.46	[redacted]

atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.50	[redacted]	0.74	0.60	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.21	[redacted]	1.09	0.89	[redacted]

Source: CS PfC response[4], CS Clarification response addendum[95]
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Table 5.2: Company base-case deterministic full incremental cost-effectiveness results with PAS price (x1.2 QALY severity modifier used)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER (£)
				costs (£)	LYG	QALYs (x1.2)	
durvalumab + darboplatin + etoposide	[redacted]	1.87	1.64				
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.50	[redacted]	0.14	0.13	[redacted]
serplulimab + carboplatin + etoposide	[redacted]	2.47	2.10	[redacted]	-0.73	-0.60	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.21	[redacted]	1.09	0.89	[redacted]

Source: CS document[6], CS PfC Response[4], CS Clarification response addendum[95]
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Table 5.3: Company base-case deterministic pairwise results for net monetary benefit with PAS price (x1.2 QALY severity modifier used)

Technology	Incremental costs (£)	ICER (£)	NMB at £30,000	Incremental NMB at £30,000
serplulimab + carboplatin + etoposide			[redacted]	
durvalumab + carboplatin + etoposide	[redacted]	[redacted]	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Economic Model [88]
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit

5.2 Company's sensitivity analyses

To explore uncertainty within their cost-effectiveness analysis, the company conducted both deterministic sensitivity analyses and probabilistic sensitivity analyses.

5.2.1 Company's deterministic sensitivity analysis

The company did not provide the deterministic sensitivity analysis with results the PAS price for serplulimab. See the CS for the deterministic sensitivity analyses using the list price for serplulimab.

5.2.2 Company's probabilistic sensitivity analysis

To explore uncertainty within their cost-effectiveness analysis, the Company conducted pair-wise probabilistic sensitivity analysis (PSA) over 1,000 iterations using the list price and PAS price for serplulimab. **Error! Reference source not found.** and **Error! Reference source not found.** show the results of pair-wise probabilistic sensitivity analysis undertook by the Company using serplulimab PAS price. The Company reported the following probabilistic sensitivity analysis (PSA) results showing serplulimab + carboplatin + etoposide as the dominant intervention over durvalumab + carboplatin + etoposide and atezolizumab + carboplatin + etoposide. When compared to durvalumab + carboplatin + etoposide, the cost decreased by [redacted] and QALY increased by 0.42. There was a reduction of [redacted] in cost and an increase of 0.55 in QALY with respect to atezolizumab + carboplatin + etoposide as a comparator. While serplulimab + carboplatin + etoposide increased the cost by [redacted] and the QALY by 0.89, when compared to carboplatin + etoposide, thus resulting in an incremental cost-effectiveness of [redacted]. The EAG re-ran the PSA in the latest updated CS model[88] and obtained similar results.

Figure 5.1, Figure 5.2 and Figure 5.3 show the results of pair-wise PSA using PAS price, re-ran by EAG in a cost-effectiveness plane. The cost-effectiveness acceptability curves of serplulimab + carboplatin + etoposide against each of its comparators are given in

Figure 5.4, Figure 5.5, Figure 5.6.

The Company did not report the probability serplulimab was cost-effective compared to atezolizumab + carboplatin + etoposide or carboplatin + etoposide specifically at £20,000 and £30.000 per QALY thresholds, so the EAG calculated this using 5000 simulations. At a willingness to pay threshold of £20,000, serplulimab + carboplatin + etoposide was [redacted] cost-effective compared to atezolizumab + carboplatin + etoposide. At a willingness to pay threshold of £30,000, serplulimab + carboplatin + etoposide was [redacted] cost-effective compared to atezolizumab + carboplatin + etoposide.

At a willingness to pay threshold of £20,000, serplulimab + carboplatin + etoposide was [redacted] cost-effective compared to carboplatin + etoposide. At a willingness to pay threshold of £30,000, serplulimab + carboplatin + etoposide was [redacted] cost-effective compared to carboplatin + etoposide.

The Company did report the probability serplulimab was cost-effective compared to durvalumab + carboplatin + etoposide at a £30.000 per QALY threshold, At a willingness to pay threshold of £30,000, serplulimab + carboplatin + etoposide was [redacted] cost-effective compared to durvalumab + carboplatin + etoposide.

Table 5.4: Company base-case pair-wise probabilistic sensitivity analysis results with PAS price (1,000 iterations)

Technology	Total costs (£)	Total QALYs x1.2	Incremental		ICER (£) x1.2
			costs (£)	QALYs x1.2	
serplulimab + carboplatin + etoposide	[redacted]	2.10			
atezolizumab + carboplatin + etoposide	[redacted]	1.55	[redacted]	0.55	[redacted]
serplulimab + carboplatin + etoposide	[redacted]	2.10			
durvalumab + carboplatin + etoposide	[redacted]	1.68	[redacted]	0.42	[redacted]
serplulimab + carboplatin + etoposide	[redacted]	2.10			
carboplatin + etoposide	[redacted]	1.21	[redacted]	0.89	[redacted]

Source: CS and CS PofC Response[4]
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Figure 5.1: Cost-effectiveness plane from PSA – comparator atezolizumab (1,000 iterations)

Source: CS Economic Model[88]
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; MAIC: match-adjusted indirect comparison

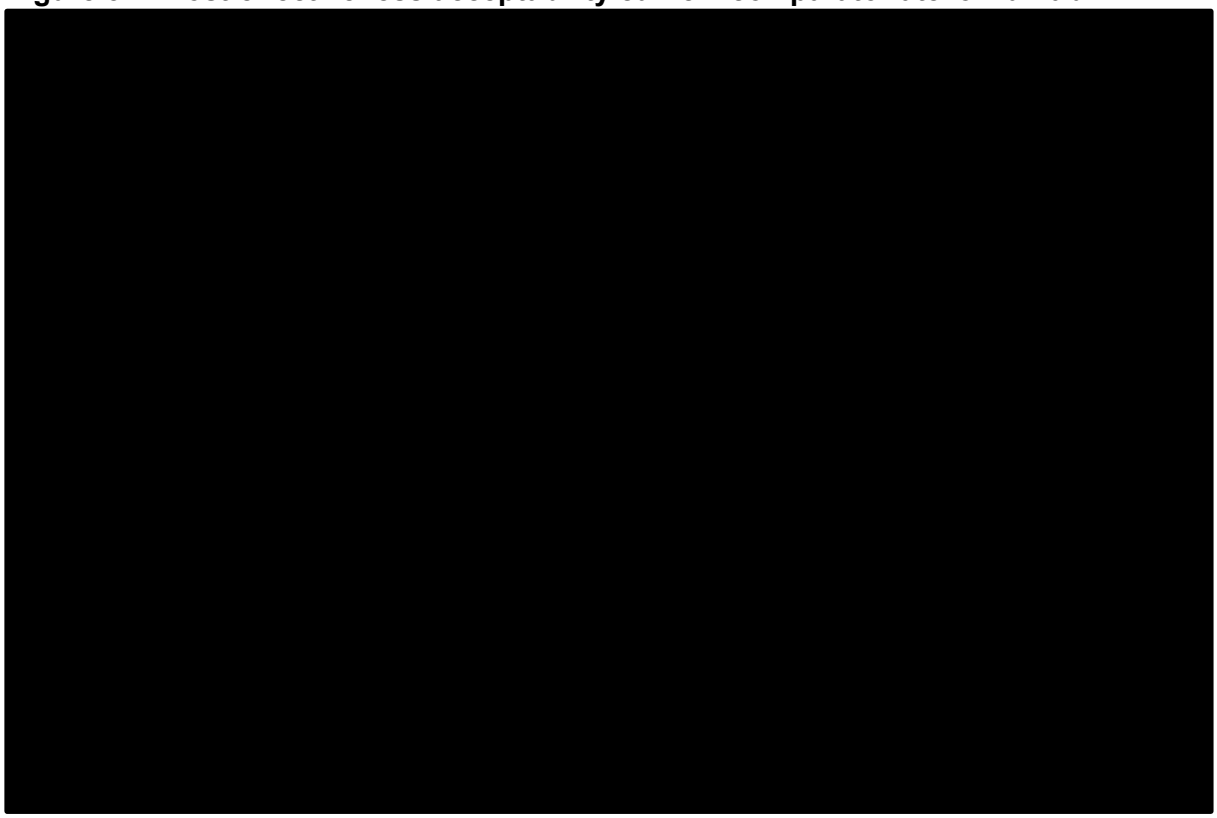
Figure 5.2: Cost-effectiveness plane from PSA – comparator carboplatin + etoposide

Source: CS[88]
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; MAIC: match-adjusted indirect comparison

Figure 5.3: Cost-effectiveness plane from PSA – comparator durvalumab (1,000 iterations)

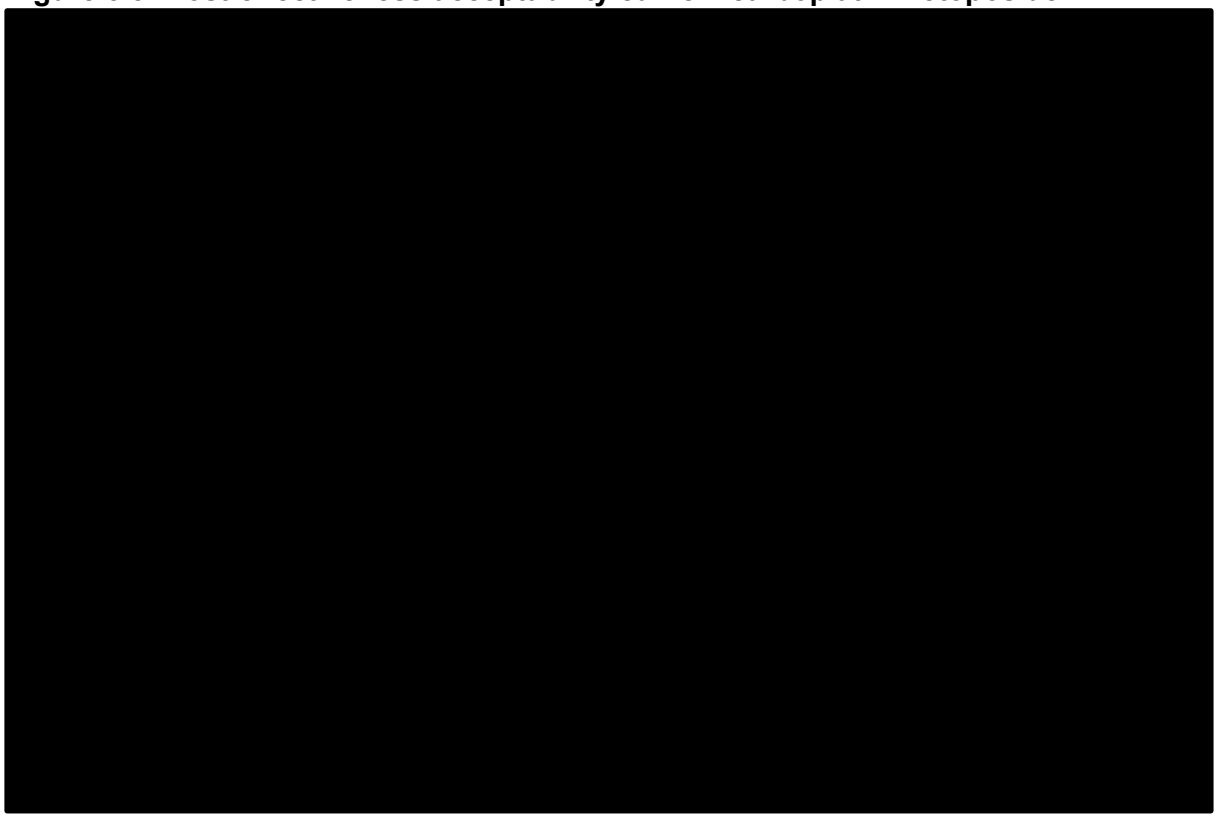
Source: Company clarification addendum[88]
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; MAIC: match-adjusted indirect comparison

Figure 5.4: Cost-effectiveness acceptability curve – comparator atezolizumab



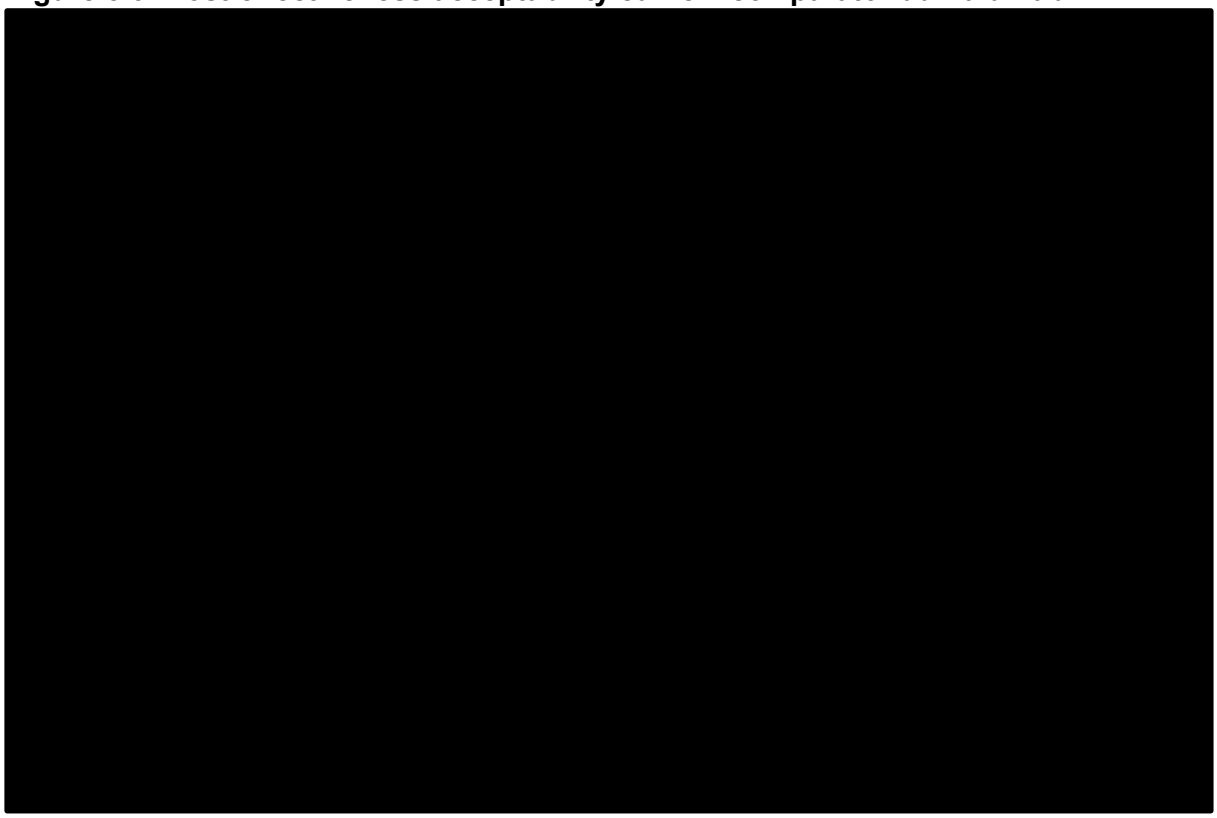
Source: CS[88]
Abbreviations: CEAC: cost-effectiveness acceptability curve; QALYs: quality-adjusted life years; MAIC: match-adjusted indirect comparison

Figure 5.5: Cost-effectiveness acceptability curve – carboplatin + etoposide



Source: CS[88]
Abbreviations: CEAC: cost-effectiveness acceptability curve; QALYs: quality-adjusted life years; MAIC: match-adjusted indirect comparison

Figure 5.6: Cost-effectiveness acceptability curve – comparator durvalumab



Source: Company clarification addendum[88]
Abbreviations: CEAC: cost-effectiveness acceptability curve; QALYs: quality-adjusted life years; MAIC: match-adjusted indirect comparison

5.2.3 Company's scenario analysis

Different scenarios were implemented by the Company to assess the effect of assumptions in the model. The scenario analysis was conducted deterministically using pair-wise incremental analysis in the model. Table 5.5, Table 5.6, Table 5.7 presents the scenario analyses of serplulimab + carboplatin + etoposide against atezolizumab + carboplatin + etoposide, carboplatin + etoposide, durvalumab + carboplatin + etoposide respectively. In the scenario analyses with atezolizumab + carboplatin + etoposide, there were no significantly large variations in the incremental results. When the HRs obtained from MAIC were replaced with pseudo-IPD from IMPower133 trial to obtain the survival curves, the incremental cost increased to [redacted] from [redacted] and QALY to 0.67. This had slightly more impact on the ICER when compared to other scenarios. The different scenarios did not have any significant effect on the ICER with carboplatin + etoposide and durvalumab + carboplatin + etoposide.

Table 5.5: Scenario analysis performed by the company on the company base-case with atezolizumab as a comparator (deterministic)

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
	Company base-case	**N/A**	**N/A**	[redacted]	**0.60**	[redacted]
1	OS parametric model: Scenarios using alternative parametric models are presented	Log-logistic	Exponential	[redacted]	0.49	[redacted]
			Weibull	[redacted]	0.43	[redacted]
			Gamma	[redacted]	0.42	[redacted]
			Log-normal	[redacted]	0.60	[redacted]
			Gompertz	[redacted]	0.66	[redacted]
			Gen. Gamma	[redacted]	0.59	[redacted]
2	PFS parametric model: Scenarios using alternative parametric models are presented.	Log-logistic	Exponential	[redacted]	0.60	[redacted]
			Weibull	[redacted]	0.60	[redacted]
			Gamma	[redacted]	0.59	[redacted]
			Log-normal	[redacted]	0.60	[redacted]
			Gompertz	[redacted]	0.61	[redacted]
			Gen. Gamma	[redacted]	0.60	[redacted]
3	TTOT parametric model: Scenarios using alternative parametric models are presented.	Log-logistic	Exponential	[redacted]	0.60	[redacted]
			Weibull	[redacted]	0.60	[redacted]
			Gamma	[redacted]	0.60	[redacted]
			Log-normal	[redacted]	0.60	[redacted]
			Gompertz	[redacted]	0.59	[redacted]
			Gen. Gamma	[redacted]	0.60	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
4	Data source for atezolizumab extrapolation: HR from the MAIC (after matching) applied to the selected serplulimab extrapolation in the base-case. Scenarios using the before-matching HR (more conservative) and using an independent model fitted to pseudo-IPD from IMpower133 (i.e., not HR-based) are presented.	HR from MAIC (after matching)	HR from MAIC (before matching)	[redacted]	**0.51**	[redacted]
			Independent model fitted to pseudo-IPD from IMpower133	[redacted]	0.67	[redacted]
5	Time horizon (years): Scenarios with shorter time horizons are presented.	20	5	[redacted]	0.36	[redacted]
			10	[redacted]	0.50	[redacted]
			15	[redacted]	0.57	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
6	Utility derivation method: Scenarios using the time to death approach and progression status by treatment status are presented. Scenarios using the time to death approach and progression status by treatment status are presented.	Progression status without on/off treatment	Time to death	[redacted]	0.44	[redacted]
			Progression status by on/off treatment	[redacted]	0.58	[redacted]
7	Adverse events: Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented.	AE disutilities for all patients included	Exclude AE disutilities	[redacted]	0.60	[redacted]
			Non-Asian AEs	[redacted]	0.56	[redacted]
8	Treatment waning: Scenarios	No treatment waning effect	Immediate loss of treatment effect at 5 years	[redacted]	0.51	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
	exploring different treatment waning assumptions beyond the end of the trial are presented.		Gradual loss of treatment effect from 5-10 years	[redacted]	0.55	[redacted]
9	Vial sharing assumed for serplulimab: A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	No Vial sharing assumed for serplulimab	Vial sharing assumed for serplulimab	[redacted]	0.60	[redacted]

Source: CS Document B [6], CS Economic Model[88]
Abbreviations: AE = adverse event; PFS = progression-free Survival, OS = Overall Survival; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life years; HR = hazard ratio; AE = adverse event

Table 5.6: Scenario analysis performed by the company on the company base-case with carboplatin + etoposide as a comparator (deterministic)

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
	Company base-case	**N/A**	**N/A**	[redacted]	0.89	[redacted]
1		Log-logistic	Exponential	[redacted]	0.79	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
	OS parametric model: Scenarios using alternative parametric models are presented		Weibull	[redacted]	0.75	[redacted]
			Gamma		0.75	
			Log-normal		0.95	
			Gompertz		1.10	
			Gen. Gamma		0.98	
2	PFS parametric model: Scenarios using alternative parametric models are presented.	Log-logistic	Exponential		0.89	
			Weibull		0.89	
			Gamma		0.89	
			Log-normal		0.90	
			Gompertz		0.91	
			Gen. Gamma		0.90	
3	TTOT parametric model: Scenarios using alternative parametric models are presented.	Log-logistic	Exponential		0.88	
			Weibull		0.89	
			Gamma		0.88	
			Log-normal		0.89	
			Gompertz		0.88	
			Gen. Gamma		0.89	
5	Time horizon (years): Scenarios with shorter time horizons are presented.	20	5	[redacted]	0.59	[redacted]
			10	[redacted]	0.78	[redacted]
			15	[redacted]	0.86	[redacted]
6	Utility derivation method: Scenarios using the time to death approach and progression status by treatment	Progression status without on/off treatment	Time to death	[redacted]	0.66	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
	status are presented. Scenarios using the time to death approach and progression status by treatment status are presented.					
			Progression status by on/off treatment	[redacted]	0.85	[redacted]
7	Adverse events: Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented.	AE disutilities for all patients included	Exclude AE disutilities	[redacted]	0.91	[redacted]
			Non-Asian AEs	[redacted]	0.84	[redacted]
8	Treatment waning: Scenarios exploring different treatment waning assumptions	No treatment waning effect	Immediate loss of treatment effect at 5 years	[redacted]	0.81	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
	beyond the end of the trial are presented.					
			Gradual loss of treatment effect from 5-10 years	[redacted]	0.85	[redacted]
9	Vial sharing assumed for serplulimab: A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	No Vial sharing assumed for serplulimab	Vial sharing assumed for serplulimab	[redacted]	0.89	Dominant.

Source: CS Document B [6], CS Economic Model[88]
Abbreviations: AE = adverse event; PFS = progression-free Survival, OS = Overall Survival; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life years; HR = hazard ratio; AE = adverse event

Table 5.7: Scenario analysis performed by the company on the company base-case with durvalumab as a comparator (deterministic)

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
	Company base-case	**N/A**	**N/A**	[redacted]	**0.46**	[redacted]
1	OS parametric model: Scenarios using alternative	Log-logistic	Exponential	[redacted]	0.37	[redacted]
			Weibull	[redacted]	0.33	[redacted]
			Gamma	[redacted]	0.32	[redacted]
			Log-normal	[redacted]	0.47	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
	parametric models are presented		Gompertz	[redacted]	0.52	[redacted]
			Gen. Gamma	[redacted]	0.46	[redacted]
2	PFS parametric model: Scenarios using alternative parametric models are presented.	Log-logistic	Exponential	[redacted]	0.46	[redacted]
			Weibull	[redacted]	0.46	[redacted]
			Gamma	[redacted]	0.46	[redacted]
			Log-normal	[redacted]	0.46	[redacted]
			Gompertz	[redacted]	0.48	[redacted]
			Gen. Gamma	[redacted]	0.47	[redacted]
3	TTOT parametric model: Scenarios using alternative parametric models are presented.	Log-logistic	Exponential	[redacted]	0.47	[redacted]
			Weibull	[redacted]	0.46	[redacted]
			Gamma	[redacted]	0.47	[redacted]
			Log-normal	[redacted]	0.46	[redacted]
			Gompertz	[redacted]	0.46	[redacted]
			Gen. Gamma	[redacted]	0.46	[redacted]
4	Data source for durvalumab extrapolation: Scenarios with alternative approaches are presented.	HR from MAIC (after matching)	HR from MAIC (before matching)	[redacted]	0.35	[redacted]
			Independent model fitted to pseudo-IPD from CASPIAN	[redacted]	0.39	[redacted]
I 5	Time horizon (years): Scenarios with shorter time horizons are presented.	20	5	[redacted]	0.26	[redacted]
			10	[redacted]	0.38	[redacted]
			15	[redacted]	0.44	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
6	Utility derivation method: Scenarios using the time to death approach and progression status by treatment status are presented. Scenarios using the time to death approach and progression status by treatment status are presented.	Progression status without on/off treatment	Time to death	[redacted]	0.44	[redacted]
			Progression status by on/off treatment	[redacted]	0.47	[redacted]
7	Adverse events: Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented.	AE disutilities for all patients included	Exclude AE disutilities	[redacted]	0.48	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs (x1.2)	ICER
			Non-Asian AEs	[redacted]	0.47	[redacted]
8	Treatment waning: Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented.	No treatment waning effect	Immediate loss of treatment effect at 5 years	[redacted]	0.39	[redacted]
			Gradual loss of treatment effect from 5-10 years	[redacted]	0.43	[redacted]
9	Vial sharing assumed for serplulimab: A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	No Vial sharing assumed for serplulimab	Vial sharing assumed for serplulimab	[redacted]	0.46	[redacted]

Source: CS Document[6], CS Economic Model[88]
Abbreviations: AE = adverse event; PFS = progression-free Survival, OS = Overall Survival; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life years; HR = hazard ratio; AE = adverse event

5.3 Subgroup analysis

The Company implemented a subgroup analysis using the data specific to the non-Asian population, collected from the ASTRUM-00 trial, to reflect the UK clinical setting. But the exact results for all the comparators were not available in the company submission for the PAS price for serplulimab.[6]

The EAG ran the subgroup analysis for non-Asian patient population in the company model.[88] The results are presented in Table 5.8.

Table 5.8: Deterministic subgroup analysis results performed by EAG using the company model

Technology	Total costs (£)	Total LYG	Total QALYs (x1.2)	Incremental			ICER (£) (x1.2)
				costs (£)	LYG	QALYs (x1.2)	
serplulimab + carboplatin + etoposide	[redacted]	2.57	2.03	-	-	-	-
durvalumab + carboplatin + etoposide	[redacted]	1.92	1.65	[redacted]	0.61	0.48	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.76	1.43	[redacted]	0.81	0.60	[redacted]
carboplatin + etoposide	[redacted]	1.17	0.97	[redacted]	1.40	1.05	[redacted]

Source: CS Economic Model[88]
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

5.4 Model validation and face validity check

5.4.1 Face validity assessment and technical verification

The company model was updated by adding durvalumab as a relevant comparator, upon the request from EAG. The face validity and the technical verification of the model was found to be satisfactory by the EAG.

5.4.2 Comparison with external data

The survival estimates, subsequent treatment distributions and dosing of treatments were verified by the clinical expert opinion elicited by EAG. The utility estimates of patient population were found to be quite high when compared to the utility estimates from other sources. More information on this is provided in Section 4.2.5.1.

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on the considerations in the preceding sections of this EAG report, the EAG defined an EAG base-case. This EAG base-case included several adjustments to the company base-case presented in Section 5. These adjustments have been subdivided into three categories (derived from Kaltenthaler 2016).[101]

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

6.1.1.1 EAG base-case

Adjustments made by the EAG to derive the EAG base-case (using the CS base-case as starting point) are listed below.

6.1.1.2 Fixing errors

Some minor errors were identified by the EAG following the original submission of the cost-effectiveness model (CEM); however, these errors were corrected by the company prior to the PfC. The Company provided results of probabilistic sensitivity analysis, deterministic sensitivity analysis and scenario analysis, with durvalumab as the comparator after the PfC response submission.

6.1.1.3 Fixing violations

The economic model was not designed to efficiently produce a full incremental analysis results table. Consequently, pairwise analyses are presented in this section, and an asterisk used to identify the relevant ICER for serplulimab that would have been identified from a full incremental analysis.

6.1.1.4 Matters of judgement

See the Appendix for a basic description of the EAG models.

- Matter of Judgement 1 (Key Issue 2)

TSD14 recommends testing the fit of models more flexible than the 6 common parametric models if the lines in the log-cumulative hazard plots are not straight.[1] In the EAG base case, 3 knot spline model was fitted for the OS of serplulimab and OS of carboplatin + etoposide until the latest timepoint at which the number of patients still at risk was at least 10 (18 months and 42 months, respectively). See Section 4.2.3 for detailed information. For serplulimab, after 42 months, despite a fairly constant hazard ratio of [redacted] over the first 18 months, the EAG modelled an alternative survival curve to account for company clinical expert opinion of lower overall survival in the long-term. The hazard ratio was assumed to linearly increase from 0.6 to 1 from 3.5 years to 6.5 years, which is a significant time period given the median survival for this population with carboplatin + etoposide treatment. Alternatively, in EAG additional scenario, an exponential curve was fitted so that the

predicted OS at 10 years was the same as the predicted OS in the company base case. For carboplatin + etoposide, the 3 knot spline model is fitted until 18 months and then an exponential curve is fitted so that the OS at 10 years is similar to the logistic model prediction.

For PFS, the 3 knot spline model was selected for the EAG base case until 42 months and a 3 year waning assumption (until 6.5 years) was assumed, for serplulimab. For carboplatin + etoposide, the 3 knot spline model was selected for the EAG base case until 12 months and then an exponential curve was fitted to match the loglogistic model prediction at 5 years.

- Matter of judgement 2 (Key Issue 3)

For atezolizumab and durvalumab, the EAG base case the assumption was that the OS hazard ratios for atezolizumab vs serplulimab and for durvalumab vs serplulimab linearly tends towards 1 from 3.5 years to 6.5 years. For PFS, the atezolizumab vs serplulimab and for durvalumab vs serplulimab hazard ratios are assumed to remain constant for the duration of the model in the EAG base case. Refer Section 4.2.3.2.

- Matter of judgement 3 (Key Issue 4)

For TTOT in serplulimab arm, the company made similar observations about the spline model predictions as they made for OS and PFS. See Section 4.2.6.1. So, the EAG has taken the same approach in the EAG analyses for TTOT as for OS. Since no at risk data were provided for the TTOT Kaplan-Meier curves, the cut-off time point for the 3 knot spline model used was based on the PFS at-risk numbers for serplulimab (42 months). Further, after 42 months the percentage on treatment was limited to the percentage on treatment in each of the PFS and PD states in the previous cycle.

- Matter of Judgement 4

The EAG does not have any information on the difference in percentages of patients on treatment distributed between PFS and PD states. But equal percentages of patients across states on treatment is unlikely given that disease has progressed. Consequently, the EAG have taken a simple approach to exploring lower percentages of PD patients on treatment. In the EAG base-case, the percentage of PD patient receiving serplulimab was capped at 20%, and scenarios were explored using a 30% cap and 10% cap in the EAG additional analysis. In each of these scenarios, the percentage of patients in the PD state on treatment decreases if the percentage of patients on treatment from the TTOT curve falls below the cap. So, the percentage of patients on treatment is either the cap or the percentage from the TOT curve, whichever is smaller. Refer to Section 4.2.6.2 for details.

- Matter of Judgement 5 (Key Issue 5)

To reflect the UK patient population in the EAG base-case, an average weight of 79.3 kg was used in the model.[3] Although the majority of patients in ASTRUM-005 trial were male (more than 80%), since the gender distribution in SCLC disease in the England the disease distribution were approximately equal[2] and ASTRUM-005 trial was considered imbalance regarding gender distribution, the EAG used England average weight instead of calculating weighted average using the gender distribution in ASTRUM-005 trial. The average height in England in 2019 for all adults was 168.4 cm (SE: 0.14). The company had used 167.27 cm as mean height in the company base-case, informed by the population in the ASTRUM trial. Hence, EAG considered an average height of 168.4 cm for calculating BSA using the Dubois

formula provided by the company (BSA = 0.007184 x (W0.425) x (H0.725), which resulted in [redacted] in the EAG base-case.

By accident the EAG used the average height in England for all adults in 2019, which was 168.4 cm. The average height for 70 year olds was 166.8 cm in 2022. While this is an error, height only affects the cost of chemotherapy which is part of treatment in both arms of the model. Changing the height only changes the ICER by £3 compared to atezolizumab and by £4 compared to carboplatin + etoposide. The average weight and BSA of the patients were used to calculate the dose of serplulimab, its comparators and other chemotherapy drugs in the model. Consequently, the changes made in the mean weight and height of patients in the model would affect the acquisition costs of treatments calculated in the EAG base-case.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

- EAG exploratory scenario – 1

In the EAG exploratory scenario analysis, an exponential curve was fitted for serplulimab, so that the predicted OS at 10 years was the same as the predicted OS in the company base case.

For carboplatin + etoposide, the 3 knot spline model is fitted until 18 months and then an exponential curve is fitted so that the OS at 10 years is similar to the logistic model prediction.

See Section 4.2.3.1.

- EAG exploratory scenario – 2

The percentage of PD patient receiving serplulimab was capped at 20% in the base case. Since this was an arbitrary assumption made by the EAG, additional scenario exploring the effect of a decrease to 10% cap was explored in this scenario. and increased to 30% and reduced to 10% in scenario analyses. See Section 4.2.6.2 for more information.

- EAG exploratory scenario – 3

Similar to scenario 2, an exploratory scenario with the increase in the percentage of patients receiving the treatment in the PD state to a 30% cap was conducted. See Section 4.2.6.2 for more information.

- EAG exploratory scenario – 4

This utility estimates used in the economic model, informed by the ASTRUM-005 trial were significantly higher than the utility data available through literature search in Appendix I. [93] See Section 4.2.5.1 for detailed information on this. Hence, the EAG explored the impact of the use of alternative utility estimates sourced from Nafees et al. 2008[5] in the EAG base-case, on the incremental cost-effectiveness analysis. The utility value for PFS = 0.673 and PD = 0.473. See Section 4.2.5.1.

- EAG exploratory scenario – 5

Like EAG exploratory scenario – 4, utility estimates from Chouaid et al 2013[90] were used in the EAG scenario analysis. The utility estimates used in this scenario were PFS = 0.71 and PD = 0.67. See Section 4.2.5.1.

- EAG exploratory scenario – 6

The EAG base case was adjusted so that the average weight and height was that in the ASTRUM-005 trial (weight = 68.395 kg, height = 167.27 m^2). See Section 4.2.6.3.

6.1.3 EAG subgroup analyses

The Company base-case included a sub-group analysis with non-Asian population, to reflect the UK clinical settings. A short discussion of the subgroup analysis was provided in the Company submission.[6] The EAG went forward with replicating this subgroup analysis in the Company base-case and a detailed results table (Table 5.8) with the costs, QALY and ICER was included in Section 5.3 of the EAG report. The same sub-group analysis was conducted by the EAG, in the EAG base-case, to analyse the effect of changes in the EAG base-case on the subgroup analysis.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 The EAG base case

The Company presented results in the Excel model as pairwise results. The comparator had to be changed in the control tab is get the atezolizumab or durvalumab results. Consequently, pairwise results are presented in the tables below and the ICER for serplulimab calculated from completing full incremental analysis is identified using an asterisk.

QALY results are presented without a x1.2 modifier. Incremental QALYs are presented with a x1 modifier and a x1.2 modifier. ICER results are presented with a x1 modifier and a x1.2 modifier.

Life years were not discounted in the model. QALYs and costs were discounted.

The EAG base-case was presented in Section 6.1.1.1. A QALY weight of 1.2 was included, after checking whether the total QALYs in the EAG base-case qualified for a severity modifier, for calculating the ICER in the EAG base-case. Table 6.1 and Table 6.2 shows the EAG base-case results. The deterministic EAG base-case analysis showed that serplulimab + carboplatin + etoposide was dominant against durvalumab + carboplatin + etoposide, cost-effective at £20,000/QALY against atezolizumab + carboplatin + etoposide, and not cost-effective against carboplatin + etoposide. Serplulimab was dominant against durvalumab + carboplatin + etoposide, had an ICER of [redacted] against atezolizumab + carboplatin + etoposide, and was not cost-effective against carboplatin + etoposide.

Table 6.1: Deterministic EAG base-case

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
Company base-case									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.75						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.46	[redacted]	0.60	0.39	0.46	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.25	[redacted]	0.74	0.50	0.60	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.01	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]
Matter of Judgement 1 – Survival Curve assumption: serplulimab: Knot 3 survival curve + 3-year treatment waning (OS, PFS), carboplatin + eptoposide: Knot 3 survival curve + exponential (OS, PFS)									
serplulimab + carboplatin + etoposide	[redacted]	2.40	1.74						
durvalumab + carboplatin + etoposide	[redacted]	1.88	1.38	[redacted]	0.52	0.35	0.43	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.75	1.28	[redacted]	0.65	0.46	0.55	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.40	1.02	[redacted]	1.00	0.72	0.86	[redacted]	[redacted]
Matter of Judgement 2 – Atezolizumab and durvalumab HR waning to 1 from 3.5 years to 6.5 years									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.75						
durvalumab + carboplatin + etoposide	[redacted]	2.01	1.47	[redacted]	0.46	0.28	0.34	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
atezolizumab + carboplatin + etoposide	[redacted]	1.89	1.36	[redacted]	0.59	0.39	0.47	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.01	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]
Matter of Judgement 3 –TTOT: Knot 3 curve + weighted by PFS and PD									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.77						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.33	[redacted]	0.60	0.43	0.52	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.26	[redacted]	0.74	0.50	0.60	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.01	[redacted]	1.09	0.76	0.91	[redacted]	[redacted]
Matter of Judgement 4 – TTOT in PFS and PD states assumption: assume maximum of 20% in PD state									
serplulimab + carboplatin + etoposide	[redacted]	2.47	2.10						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.63	[redacted]	0.60	0.39	0.46	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.50	[redacted]	0.74	0.50	0.60	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
carboplatin + etoposide	[redacted]	1.38	1.21	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]
Matter of Judgement 5 – Drug Acquisition Costs: Weight = 79.3 kg, Height = 168.4 cm									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.75						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.46	[redacted]	0.60	0.39	0.46	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.25	[redacted]	0.74	0.50	0.60	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.01	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]
EAG base-case (Matter of Judgement 1-5): Deterministic									
serplulimab + carboplatin + etoposide	[redacted]	2.40	1.73						
durvalumab + carboplatin + etoposide	[redacted]	1.94	1.42	[redacted]	0.45	0.31	0.37	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.82	1.31	[redacted]	0.57	0.41	0.50	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.40	1.02	[redacted]	1.00	0.70	0.85	[redacted]	[redacted]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
Footnotes: *indicates that this result is the full incremental ICER result for serplulimab									

Table 6.2: EAG base-case deterministic pairwise results for net monetary benefit with PAS price

Technology	NMB at £30,000	NMB at £30,000 x1.2	Incremental NMB at £30,000	Incremental NMB at £30,000 x1.2
serplulimab + carboplatin + etoposide	[redacted]	[redacted]		
durvalumab + carboplatin + etoposide	[redacted]	[redacted]	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Economic Model [88]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; PAS = patient access scheme

6.2.2 EAG sensitivity analysis

6.2.2.1 EAG Probabilistic sensitivity analysis

The EAG ran 5000 simulations for each PSA. Table 6.3 shows the probabilistic results. Figure 6.1, Figure 6.2, and Figure 6.3 shows the cost-effectiveness plane of serplulimab + carboplatin + etoposide against its comparators. **Error! Reference source not found.**, **Error! Reference source not found.**, and **Error! Reference source not found.** shows the cost-effectiveness acceptability curve from the results of the PSA run. Compared to atezolizumab + carboplatin + etoposide, serplulimab + carboplatin + etoposide was [redacted] and [redacted] cost-effective at willingness to pay thresholds of £20,000 and £30,000. Serplulimab + carboplatin + etoposide was [redacted] and [redacted] cost-effective at willingness to pay thresholds (WTPs) of £20,000 and £30,000 against durvalumab + carboplatin + etoposide. When carboplatin + etoposide was the comparator, the probabilities of cost-effectiveness were [redacted] and [redacted] at £20,000 and £30,000 WTPs.

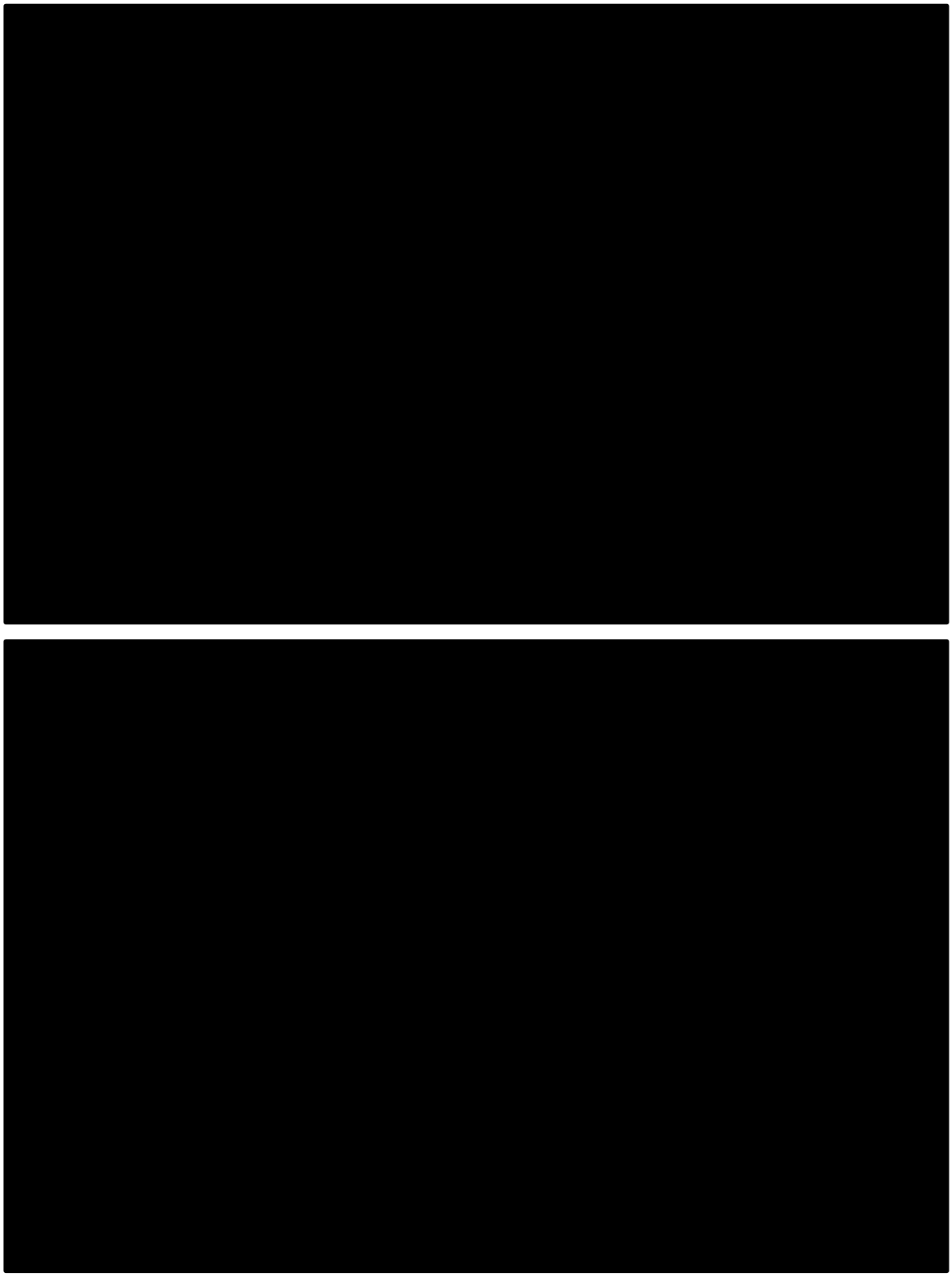
Table 6.3: EAG base-case probabilistic pair-wise incremental cost-effectiveness results with PAS price

Technology	Total costs (£)	Total QALYs x1.2	Incremental			ICER (£) x1	ICER (£) x1.2
			costs (£)	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.06					
durvalumab + carboplatin + etoposide	[redacted]	1.72	[redacted]	0.29	0.35	[redacted]	[redacted]
serplulimab + carboplatin + etoposide	[redacted]	2.07		0			
atezolizumab + carboplatin + etoposide	[redacted]	1.60	[redacted]	0.383	0.46	[redacted]	[redacted]
serplulimab + carboplatin + etoposide	[redacted]	2.06					
carboplatin + etoposide	[redacted]	1.23	[redacted]	0.7	0.84	[redacted]	[redacted]

Source: EAG model

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Figure 6.1: Cost-effectiveness plane from PSA in the EAG base-case– comparator atezolizumab



Abbreviations: EAG = Evidence Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MAIC = matching-adjusted indirect comparison; PSA = probabilistic sensitivity analysis; QALY = quality adjusted life year

Figure 6.2: Cost-effectiveness plane from PSA in the EAG base-case– comparator carboplatin + etoposide

Abbreviations: EAG = Evidence Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MAIC = matching-adjusted indirect comparison; PSA = probabilistic sensitivity analysis; QALY = quality adjusted life year

Figure 6.3: Cost-effectiveness plane from PSA in the EAG base-case– comparator durvalumab

Abbreviations: EAG = Evidence Assessment Group; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; PSA = probabilistic sensitivity analysis; QALY = quality adjusted life year

6.2.2.2 EAG Deterministic sensitivity analysis

The one-way sensitivity analysis could not be run using the joint spline model in the Company base-case; the joint spline models were added in response to the clarification letter. Errors were returned, and the EAG did not have time to investigate and correct any errors. Hence, after creating the EAG base-case with 3 knot spline models, the one-way sensitivity results could not be obtained.

6.2.3 EAG Scenario analysis

6.2.3.1 Company Scenario analysis on EAG base-case

The results of the Company scenario analysis on the EAG base-case are given in Table 6.4, Table 6.5 and Table 6.6. The Company scenario analysis 1, 2 and 3, where different parametric models were fitted to the survival curves of OS, PFS and TTOT were not tested in the EAG base-case because the EAG is of the opinion that a flexible model is visually a better fit for the survival curves. Hence, the other parametric models were not suitable for being used in the EAG base-case as scenarios. Also, a scenario with treatment waning (scenario 8) effect was not necessary to be implemented in the EAG base-case because the EAG has already considered this in its base-case. The incremental QALY was affected by implanting the utility values by on/off treatment, there were no major drivers of incremental costs among the scenarios.

Table 6.4: Company Scenario analysis on EAG base-case using PAS price, with atezolizumab as comparator

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	EAG base-case	**N/A**	**N/A**	[redacted]	0.41	0.50	[redacted]	[redacted]
1	OS parametric model: Scenarios using alternative parametric models are presented	3 knots + 3 years treatment waning	EAG is of the opinion that this scenario is not relevant to the EAG base-case.					
2	PFS parametric model: Scenarios using alternative	3 knots + 3 years treatment waning	EAG is of the opinion that this scenario is not relevant to the EAG base-case.					

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	parametric models are presented.							
3	TTOT parametric model: Scenarios using alternative parametric models are presented.	3 knots spline model	EAG is of the opinion that this scenario is not relevant to the EAG base-case.					
4	Data source for atezolizumab extrapolation: HR from the MAIC (after matching) applied to the selected serplulimab extrapolation in the base-case. Scenarios using the before-matching HR (more conservative)	HR from MAIC (after matching)	HR from MAIC (before matching)	[redacted]	0.35	0.42	[redacted]	[redacted]
			Independent model fitted to pseudo-IPD from IMpower133	[redacted]	0.54	0.65	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	and using an independent model fitted to pseudo-IPD from IMpower133 (i.e., not HR-based) are presented.							
5	Time horizon (years): Scenarios with shorter time horizons are presented.	20	5	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
			10	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
			15	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
6	Utility derivation method: Scenarios using the time to death approach and progression status by treatment status are presented. Scenarios using the	Progression status without on/off treatment	Time to death	[redacted]	0.42	0.51	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	time to death approach and progression status by treatment status are presented.							
			Progression status by on/off treatment	[redacted]	0.40	0.48	[redacted]	[redacted]
7	Adverse events: Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented.	AE disutilities for all patients included	Exclude AE disutilities	[redacted]	0.41	0.50	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
			Non-Asian AEs	[redacted]	0.41	0.49	[redacted]	[redacted]
8	Treatment waning: Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented.	No treatment waning effect	Immediate loss of treatment effect at 5 years	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
			Gradual loss of treatment effect from 5-10 years	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
9	Vial sharing assumed for serplulimab: A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	[redacted]	[redacted]	0.41	0.50	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
Source: EAG Economic Model Abbreviations: AE = adverse event; EAG = Evidence Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IPD = individual patient data; MAIC = matching-adjusted indirect comparison; OS = Overall Survival; PAS = patient access scheme; PFS = progression-free Survival, QALY = quality adjusted life years; TTOT = time-to-off treatment								

Table 6.5: Company Scenario analysis on EAG base-case using PAS price, with carboplatin + etoposide as comparator

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	EAG base-case	**N/A**	**N/A**	[redacted]	0.70	0.85	[redacted]	[redacted]
1	OS parametric model: Scenarios using alternative parametric models are presented	3 knots + 3 years treatment waning	EAG is of the opinion that this scenario is not relevant to the EAG base-case.					
2	PFS parametric model: Scenarios using alternative parametric models are presented.	3 knots + 3 years treatment waning	EAG is of the opinion that this scenario is not relevant to the EAG base-case.					

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
3	TTOT parametric model: Scenarios using alternative parametric models are presented.	3 knots spline model	EAG is of the opinion that this scenario is not relevant to the EAG base-case.					
5	Time horizon (years): Scenarios with shorter time horizons are presented.	20	5	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
			10	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
			15	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
6	Utility derivation method: Scenarios using the time to death approach and progression status by treatment status are presented. Scenarios using the	Progression status without on/off treatment	Time to death	[redacted]	0.71	0.86	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	time to death approach and progression status by treatment status are presented.							
			Progression status by on/off treatment	[redacted]	0.67	0.81	[redacted]*	[redacted]*
7	Adverse events: Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented.	AE disutilities for all patients included	Exclude AE disutilities	[redacted]	0.73	0.87	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
			Non-Asian AEs	[redacted]	0.71	0.85	[redacted]	[redacted]
8	Treatment waning: Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented.	No treatment waning effect	Immediate loss of treatment effect at 5 years	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
			Gradual loss of treatment effect from 5-10 years	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
9	Vial sharing assumed for serplulimab: A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab	[redacted]	[redacted]	0.70	0.85	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
Source: EAG Economic Model Abbreviations: AE = adverse event; EAG = Evidence Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IPD = individual patient data; MAIC = matching-adjusted indirect comparison; OS = Overall Survival; PAS = patient access scheme; PFS = progression-free Survival, QALY = quality adjusted life years; TTOT = time-to-off treatment								

Table 6.6: Company Scenario analysis on EAG base-case using PAS price, with durvalumab as comparator

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	EAG base-case	**N/A**	**N/A**	[redacted]	0.31	0.37	[redacted]	[redacted]
1	OS parametric model: Scenarios using alternative parametric models are presented	3 knots + 3 years treatment waning	EAG is of the opinion that this scenario is not relevant to the EAG base-case.					
2	PFS parametric model: Scenarios using alternative parametric models are presented.	3 knots + 3 years treatment waning	EAG is of the opinion that this scenario is not relevant to the EAG base-case.					
3	TTOT parametric model: Scenarios using alternative parametric models are presented.	3 knots spline model	EAG is of the opinion that this scenario is not relevant to the EAG base-case.					

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
4	Data source for durvalumab extrapolation: Scenarios with alternative approaches are presented.	HR from MAIC (after matching)	HR from MAIC (before matching)	[redacted]	0.23	0.27	[redacted]	[redacted]
			Independent model fitted to pseudo-IPD from CASPIAN	[redacted]	0.31	0.37	[redacted]	[redacted]
5	Time horizon (years): Scenarios with shorter time horizons are presented.	20	5	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
			10	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
			15	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
6	Utility derivation method: Scenarios using the time to death approach and progression status by treatment status are presented.	Progression status without on/off treatment	Time to death	[redacted]	0.31	0.38	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	Scenarios using the time to death approach and progression status by treatment status are presented.							
			Progression status by on/off treatment	[redacted]	0.29	0.35	[redacted]	[redacted]
7	Adverse events: Scenarios using AEs from the non-Asian population (more conservative) and excluding additional AE disutilities are presented.	AE disutilities for all patients included	Exclude AE disutilities	[redacted]	0.33	0.40	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
			Non-Asian AEs	[redacted]	0.32	0.38	[redacted]	[redacted]
8	Treatment waning: Scenarios exploring different treatment waning assumptions beyond the end of the trial are presented.	No treatment waning effect	Immediate loss of treatment effect at 5 years	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
			Gradual loss of treatment effect from 5-10 years	EAG is of the opinion that this scenario is not relevant to the EAG base-case.				
9	Vial sharing assumed for serplulimab: A scenario is presented assuming vial sharing (i.e., no wastage) for serplulimab.	Vial sharing assumed for serplulimab		[redacted]	0.31	0.37	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
Source: EAG Economic Model Abbreviations: AE = adverse event; EAG = Evidence Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IPD = individual patient data; MAIC = matching-adjusted indirect comparison; OS = Overall Survival; PFS = progression-free Survival, QALY = quality adjusted life years								

6.2.3.2 EAG Additional Scenario analysis on EAG base-case

Table 6.7, Table 6.8 and Table 6.9 shows the results of EAG additional scenarios on the EAG base-case. Scenario 2, where the patients under treatment in the PD state were capped at 10% of the total patients under treatment in the PD state, reduced the incremental cost significantly. But in scenario 3, in which the cap was at 30%, the results shows that it gets closer to the company base-case assumptions. Use of alternative utility values in scenarios 4 and 5 had the highest impact on the incremental QALYs.

Table 6.7: EAG Additional Scenario analysis on EAG base-case with PAS price of serplulimab and atezolizumab as Comparator 1 (deterministic)

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	EAG base-case	**N/A**	**N/A**	[redacted]	**0.41**	**0.50**	[redacted]	[redacted]
1	Survival Curve	Curve 2 in the Scenario tab: 3 knot + 3 years treatment waning effect	Curve 1 in the Scenario tab: 3 knot + exponential	[redacted]	0.45	0.53	[redacted]	[redacted]
2	TTOT in PFS and PD states	TTOT in PFS and PD states assumption: maximum of 20% in PD state are assumed to be on treatment	TTOT in PFS and PD states assumption: maximum of 10% in PD state are assumed to be on treatment	[redacted]	0.41	0.50	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
3	TTOT in PFS and PD states	TTOT in PFS and PD states assumption: maximum of 20% in PD state are assumed to be on treatment	TTOT in PFS and PD states assumption: maximum of 30% in PD state are assumed to be on treatment	[redacted]	0.41	0.50	[redacted]	[redacted]
4	Utility	Utility values from ASTRUM-005 trial were mapped to EQ-5D-3L	Utility values published in the study conducted by Nafees et al. (2008):[5] PFS = 0.673, PD = 0.473	[redacted]	0.32	0.38	[redacted]	[redacted]
5	Utility	Utility values from ASTRUM-005 trial were mapped to EQ-5D-3L	Utility values published in the study conducted by Chouaid et al. (2013): PFS = 0.71, PD = 0.67	[redacted]	0.35	0.42	[redacted]	[redacted]
6	Population characteristics	Weight = 79.3, Height = 168.4	Weight = 68.395, Height = 167.27 (average ASTRUM-005 values)	[redacted]	0.41	0.50	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
Source: CS Document B.3.8.3, EAG Analysis Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; OS = Overall Survival; PD = progressed disease; PAS = patient access scheme; PFS = progression-free survival; N/A = not applicable; NICE = National Institute of Health and Care Excellence; NMA = Network-Meta Analysis; PFS = progression-free Survival; QALY = quality adjusted life years; TTOT = Time-to-off treatment								

Table 6.8: EAG Additional Scenario analysis on EAG base-case with PAS price of serplulimab and carboplatin + Etoposide as Comparator (deterministic)

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	EAG base-case	**N/A**	**N/A**	[redacted]	0.70	[redacted]	[redacted]	[redacted]
1	Survival Curve	Curve 2 in the Scenario tab: 3 knot + 3 years treatment waning effect	Curve 1 in the Scenario tab: 3 knot + exponential	[redacted]	0.78	0.93	[redacted]	[redacted]
2	TTOT in PFS and PD states	TTOT in PFS and PD states assumption: maximum of 20% in PD state are assumed to be on treatment	TTOT in PFS and PD states assumption: maximum of 10% in PD state are assumed to be on treatment	[redacted]	0.70	0.85	[redacted]	[redacted]
3	TTOT in PFS and PD states	TTOT in PFS and PD states assumption: maximum of 20% in PD state are assumed to be on treatment	TTOT in PFS and PD states assumption: maximum of 30% in PD state are assumed to be on treatment	[redacted]	0.70	0.85	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
4	Utility	Utility values from ASTRUM-005 trial were mapped to EQ-5D-3L	Utility values published in the study conducted by Nafees et al (2008):[5] PFS = 0.673, PD = 0.473	[redacted]	0.54	0.65	[redacted]	[redacted]
5	Utility	Utility values from ASTRUM-005 trial were mapped to EQ-5D-3L	Utility values published in the study conducted by Chouaid et al (2013): PFS = 0.71, PD = 0.67	[redacted]	0.59	0.71	[redacted]	[redacted]
6	Population characteristics	Weight = 79.3, Height = 168.4	Weight = 68.395, Height = 167.27 (average ASTRUM-005 values)	[redacted]	0.70	0.85	[redacted]	[redacted]

Source: EAG base-case Economic model

Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; OS = Overall Survival; PD = progressed disease; PAS = patient access scheme; PFS = progression-free survival; N/A = not applicable; NICE = National Institute of Health and Care Excellence; NMA = Network-Meta Analysis; PFS = progression-free Survival; QALY = quality adjusted life years; TTOT = Time-to-off treatment

Footnote: *indicates that this result is the full incremental ICER result for serplulimab

Table 6.9: EAG Additional Scenario analysis on EAG base-case with PAS price of serplulimab and durvalumab as Comparator (deterministic)

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
	EAG base-case	**N/A**	**N/A**	[redacted]	**0.31**	**0.37**	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
1	Survival Curve	Curve 2 in the Scenario tab: 3 knot + 3 years treatment waning effect	Curve 1 in the Scenario tab: 3 knot + exponential	[redacted]	0.34	0.40	[redacted]	[redacted]
2	TTOT in PFS and PD states	TTOT in PFS and PD states assumption: maximum of 20% in PD state are assumed to be on treatment	TTOT in PFS and PD states assumption: maximum of 10% in PD state are assumed to be on treatment	[redacted]	0.31	0.37	[redacted]	[redacted]
3	TTOT in PFS and PD states	TTOT in PFS and PD states assumption: maximum of 20% in PD state are assumed to be on treatment	TTOT in PFS and PD states assumption: maximum of 30% in PD state are assumed to be on treatment	[redacted]	0.31	0.37	[redacted]	[redacted]
4	Utility	Utility values from ASTRUM-005 trial were mapped to EQ-5D-3L	Utility values published in the study conducted by Nafees et al (2008):[5] PFS = 0.673, PD = 0.473	[redacted]	0.26	0.31	[redacted]	[redacted]
5	Utility	Utility values from ASTRUM-005 trial were mapped to EQ-5D-3L	Utility values published in the study conducted by Chouaid et al. (2013): PFS = 0.71, PD = 0.67	[redacted]	0.26	0.31	[redacted]	[redacted]

#	Model aspect	Base-case	Scenario analysis	Incremental costs	Incremental QALYs x1	Incremental QALYs x1.2	ICER x1	ICER x1.2
6	Population characteristics	Weight = 79.3, Height = 168.4	Weight = 68.395, Height = 167.27 (average ASTRUM-005 values)	[redacted]	0.31	0.37	[redacted]	[redacted]

Source: EAG base-case Economic model

Abbreviations: ICER = incremental cost-effectiveness ratio; OS = Overall Survival; PD = progressed disease; PAS = patient access scheme; PFS = progression-free survival; N/A = not applicable; NICE = National Institute of Health and Care Excellence; NMA = Network-Meta Analysis; PFS = progression-free Survival; QALY = quality adjusted life years; TTOT = Time-to-off treatment

6.2.4 EAG Subgroup analysis

The deterministic EAG subgroup, with non-Asian population, analysis showed that serplulimab + carboplatin + etoposide was dominant against durvalumab + carboplatin + etoposide, cost-effective at £20,000/QALY against atezolizumab + carboplatin + etoposide, and not cost-effective against carboplatin + etoposide as shown in Table 6.10.

Table 6.10: Subgroup analysis on EAG base-case with pair-wise incremental analysis and PAS price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental				ICER (£) x1	ICER (£) x1.2
				costs (£)	LYG	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.30	1.56						
durvalumab + carboplatin + etoposide	[redacted]	1.82	1.50	[redacted]	0.43	0.35		[redacted]	
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.19	[redacted]	0.56	0.37	0.45	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.25	0.86	[redacted]	1.05	0.70	0.84	[redacted]	[redacted]

Source: EAG base-case Economic model

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

6.3 Overall conclusions of the EAG's cost-effectiveness analysis

The following results refer to using a x1.2 severity modifier to the QALYs.

Including the cPAS price for serplulimab, the estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted] per QALY gained vs carboplatin + etoposide, and was dominant (more effective and less costly) over atezolizumab and durvalumab. Compared to atezolizumab + carboplatin + etoposide, serplulimab + carboplatin + etoposide was [redacted] and [redacted] cost-effective at willingness to pay thresholds of £20,000 and £30,000. Serplulimab + carboplatin + etoposide was [redacted] and [redacted] cost-effective at willingness to pay thresholds (WTPs) of £20,000 and £30,000 against durvalumab + carboplatin + etoposide. When carboplatin + etoposide was the comparator, the probabilities of cost-effectiveness were [redacted] and [redacted] at £20,000 and £30,000 WTPs.

The most influential adjustments were the alternative OS, PFS and TTOT curves fit to all comparators, and the alternative weight and height values. The ICER increased most in the scenario analysis with alternative assumptions with lower utilities for PFS and PD states.

In the EAG base-case, the QALYs changed from 1.75 to 1.73 for serplulimab. Total costs for serplulimab increased from [redacted] to [redacted]

[redacted]

From the EAG additional scenario analyses, the scenarios 4 and 5 related to applying alternative utility estimates in the EAG base-case has a significant impact on the incremental QALYs. Using an exponential curve instead of the treatment waning effect in the flexible model approach undertaken by the EAG had a considerable effect on the incremental costs.

The EAG did not have the time to ensure that the OWSA Tornado diagram in the company model worked including the 3 knot spline values that were added in the company clarification response; errors were returned. In the company deterministic scenario analyses, the scenarios that impacted the incremental costs the most were scenarios 7, in which AE disutilities associated with non-Asian patients were applied. The scenario that impacted the incremental QALYs the most was scenario 7, where no AE disutilities were assumed.

The subgroup analysis showed that serplulimab + carboplatin + etoposide was dominant against durvalumab + carboplatin + etoposide, cost-effective at £20,000/QALY against atezolizumab + carboplatin + etoposide, and not cost-effective against carboplatin + etoposide in the non-Asian subgroup in the patient population.

Once more, it is worth emphasising these results are not appropriate for decision making as a PAS price is used for serplulimab only, with list prices for other immunotherapies and chemotherapies. Results using the confidential PAS prices for other immunotherapies and chemotherapies will be presented in the confidential PAS appendix.

6.4 Overall conclusions of the EAG's critique

The Company conducted SLRs focusing on clinical effectiveness, cost effectiveness and HRQoL. SLRs were conducted to identify evidence on the efficacy and safety of treatments

for untreated patients with ES-SCLC, evidence on economic evaluations, healthcare resource use and costs associated with ES-SCLC as well as impact on HRQoL in patients with ES-SCLC. The methodologies applied were overall considered to be appropriate by the EAG with some concerns regarding the search strategies and eligibility criteria.

In the absence of a head-to-head trial, the relative effectiveness of serplulimab compared to atezolizumab was estimated by the Company through conducting a MAIC using IPD from ASTRUM-005 and published aggregate data from IMpower133. The MAIC indicated [redacted], which were subsequently used to inform the cost-effectiveness analysis. At the request of the EAG and due to the recent recommendation by NICE of durvalumab with etoposide and either carboplatin or cisplatin for patients with untreated ES-SCLC, the company conducted a second MAIC. Using aggregate data from CASPIAN to generate efficacy estimates between serplulimab and durvalumab [redacted] The EAG have some concerns over the transitivity and transportability of the trials to the NHS population. The trial settings, and subsequent patient demographics and characteristics, as well as treatment offered after disease progression, may not align with that observed in UK clinical practice. While MAICs present a reputable method, a ML-NMR using individual patient level data from ASTRUM-005 with aggregate data from IMpower133 and CASPIAN, may have enabled the generation of population-adjusted ITC estimates from any number of treatments and studies to any specified target population, thus improving the reliability and precision of the relative effect estimates.

The company used a MAIC for estimating the relative efficacy of serplulimab + carboplatin + etoposide against the comparators – atezolizumab + carboplatin + etoposide, durvalumab + carboplatin + etoposide, carboplatin + etoposide. The OS, PFS and TTOT curves were informed by the ASTRUM-005 trial. The results from the MAIC [redacted]. The results were consistent across the patient population, including the non-Asian subgroup.

Key issues 2 and 4 relate to fitting parametric curves to ASTRUM-005 data. The loglogistic curve that the company selected in the base case analysis did not appear to be a good fit to all data in every case. Consequently, the EAG requested more flexible models to be fitted. The EAG used the 3 knot spline model for the KM period in each case for each treatment until there were at least 10 patients at risk according to the reported timepoints. For carboplatin + etoposide, the EAG then fitted an exponential curve to ensure that the predicted OS was similar to the company base case at 10 years and the PFS prediction was similar to the company base case at 5 years. For serplulimab, it was assumed the HR tended to 1 over a three-year period from 3.5 years to 6.5 years.

There is uncertainty in the long-term OS model predictions and the EAG included a scenario with an exponential curve matching the company 10-year OS predictions.

Key issue 3 relates to the company assumption that the HR for OS was assumed to be constant for the duration of the model. In line with the assumption for OS for serplulimab, the HRs for serplulimab versus atezolizumab and for serplulimab versus durvalumab were assumed to tend to 1 from 3.5 years to 6.5 years. A Markov model with PFS and PD specific mortality rates may have given greater confidence in the model OS predictions, but relevant data may not have been available for atezolizumab and durvalumab.

Key issue 5 relates to the average weight and height for patients with ES-SCLC in England. The average weight and height for in England are greater than the averages in ASTRUM-005, and are not dissimilar to the averages for the non-Asian ASTRUM-005 population quoted in the company model.

The EAG believes that there may be uncertainty in the generalisability of the EQ-5D utility estimates to clinical practice in England, and the ICER is sensitive to utility estimates. The uncertainty in generalisability of effectiveness evidence to England clinical practice could only be addressed through sensitivity analysis. Despite the effectiveness evidence being based on two MAICs and trial analysis given no strong evidence of transitivity issues, a full incremental cost-effectiveness analysis could be plausible. The Company model was not developed to efficiently conduct a full incremental cost-effectiveness analysis including 4 comparators, considering that durvalumab was only added in response to the clarification letter.

Based on probabilistic results including the cPAS price for serplulimab only, serplulimab dominated both atezolizumab and durvalumab. The EAG probabilistic ICER for serplulimab versus carboplatin + etoposide increased from the company probabiltistic ICER from [redacted] to [redacted], using the x1.2 severity modifier.

7 APPENDIX: EAG models

The EAG model was not designed to fit different parametric models to the OS, PFS and TTOT curves.

Go to the ‘Scenario setting’ tab to select the comparator and whether a 3 knot spline model with treatment waning or a 3 knot spline model with an exponential curve subsequently fitted.

For Comparator 1, leave the parametric curve as loglogistic for OS, PFS and TTOT. Although it should make no difference if this is changed. Select Atezolizumab HR for OS/PFS and for TTOT, and also select Atezolizumab in cell F23.

For the 3 knot spline model with treatment waning, select ‘2’ in cell E11. For the 3 knot spline model with an exponential curve subsequently fitted, select ‘1’ in cell E11.

OS: 3 knot spline with treatment waning

Sheet: ‘OS- in model’

For serplulimab, the 3 knot spline curve is adjusted in column EA. In column DZ, from row 280 the hazard ratio is increased from [redacted] to 1 over 3 years.

Atezolizumab OS is generated in column ET with the treatment waning calculation done in column EX.

Durvalumab OS is generated in column EZ with the treatment waning calculation done in column FD.

Carboplatin + etoposide OS is generated in column CX. An exponential curve is fitted from row 250, $\lambda = 0.4$.

OS: 3 knot spline with exponential curve

Sheet: ‘OS- in model’

For serplulimab, the 3 knot spline curve is adjusted in column FG. From row 280 the hazard rate becomes $\lambda = 0.28$ from an exponential model.

Atezolizumab OS is generated in column EU with the treatment waning calculation done in column EX.

Durvalumab OS is generated in column FA with the treatment waning calculation done in column FD.

Carboplatin + etoposide OS is generated in column CX. An exponential curve is fitted from row 250, $\lambda = 0.4$.

PFS: 3 knot spline with treatment waning

Sheet: ‘PFS- in model’

For serplulimab, the 3 knot spline curve is adjusted in column EA. In column DZ, from row 280 the hazard ratio is increased from [redacted] to 1 over 3 years.

Atezolizumab OS is generated in column ET with the treatment waning calculation done in column EX.

Durvalumab OS is generated in column EZ with the treatment waning calculation done in column FD.

Carboplatin + etoposide OS is generated in column CX. An exponential curve is fitted from row 250, $\lambda = 1$.

PFS: 3 knot spline with exponential curve

Sheet: 'PFS- in model'

For serplulimab, the 3 knot spline curve is adjusted in column FG. From row 280 the hazard rate becomes $\lambda = 0.4$ from an exponential model.

Atezolizumab OS is generated in column EU with the treatment waning calculation done in column EX.

Durvalumab OS is generated in column FA with the treatment waning calculation done in column FD.

Carboplatin + etoposide OS is generated in column CX. An exponential curve is fitted from row 250, $\lambda = 1$.

TTOT

Sheet: 'TTOT- in model'

Column AS was edited to switch the Comparator1 TTOT.

Sheet: 'Serplulimab'

Column Q introduced to find the cohort proportion on treatment. From Row 209, the proportion on treatment becomes a weighted average of patients in PFS and PD.

Sheet: 'Comparator arm 1'

Column P introduced to find the cohort proportion on treatment. From Row 209, the proportion on treatment becomes a weighted average of patients in PFS and PD.

On treatment in PD and PFS states

Sheet: 'Serplulimab'

Column S: proportion on treatment in PD capped to prorpotion in cell R20.

=IF(('TTOT - In model'!AR88)<=$R$20,N26*'TTOT - In model'!AR88,N26*$R$20)

Column R: proportion on treatment in PFS the difference between columns Q and S, but not negative.

=IF((Q26-S26)<=M26,(Q26-S26),M26)

Sheet: ‘Comparator arm 1’

Column R: proportion on treatment in PD capped to prorpotion in cell R20.

=IF(('TTOT - In model'!AS88*K26)<=$R$20,M26*'TTOT - In model'!AS88,M26*$R$20)

Column Q: proportion on treatment in PFS the difference between columns Q and S, but not negative.

=IF((P26-R26)<=L26,(P26-R26),L26)

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Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

Post PMB EAG Report Addendum

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Post PMB Meeting issues

NICE made a list of requests post-PMB meeting, which are discussed below for clarification.

1. ***Severity Modifier***

a) Severity Modifier applied to different comparators

Table 1 shows the total QALY thresholds for the comparator to meet the severity modifier criteria with a general population QALY of 11.91 (from the company submission) in Table 1. For example, if the total QALYs for one of the comparators is between 0.6 and 1.79 then the severity modifier of x1.2 can be selected.

The absolute QALY threshold is irrelevant in this case because the general population QALY (11.91) is less than the absolute QALY shortfall criteria; a severity modifier of x1 would always be selected using the absolute shortfall criteria. Hence, the proportional QALY shortfall criteria are used to determine the severity modifier in this case.

Table 1: Absolute and proportional shortfall criteria for severity modifier with the QALY threshold

Multiplier	Proportional shortfall	
	Criteria	Comparator total QALYs threshold
x1	<0.85	>1.79
x1.2	0.85–0.95	1.79-0.60
x1.7	≥0.95	≤0.60

All the comparators met the severity modifier of x1.2 criteria in the Company base case and in the EAG base case. For reference, see Table 2.

Table 2: Comparators with total QALYs and their QALY shortfall qualification

Comparator	Total QALY without Severity Modifier	Proportional QALY	Severity Modifier qualification		Severity Modifier applied in model
			Absolute QALY Shortfall	Proportional QALY Shortfall	
Company Base-case					
Serplulimab + Carboplatin + Etoposide	1.79	0.85	NA	Yes	Yes
Atezolizumab + Carboplatin + Etoposide	1.25	0.90	NA	Yes	Yes
Durvalumab + Carboplatin + Etoposide	1.36	0.89	NA	Yes	Yes
Carboplatin + Etoposide	1.01	0.92	NA	Yes	Yes
EAG Base-case					
Serplulimab + Carboplatin + Etoposide	1.73	0.85	NA	Yes	Yes
Atezolizumab + Carboplatin + Etoposide	1.31	0.89	NA	Yes	Yes
Durvalumab + Carboplatin + Etoposide	1.34	0.89	NA	Yes	Yes
Carboplatin + Etoposide	1.02	0.91	NA	Yes	Yes

b) Severity Modifier in mixed comparator scenarios

NICE requested an exploration of the relevant severity modifier for different combinations of current practice/comparators. In the Company base case and in the EAG base case, the proportional shortfall was between 0.85 and 0.95 when considering the total QALYs for every comparator. Consequently, the severity modifier remained x1.2 for every combination of comparators.

2. Population transitivity and ML-NMR for Effectiveness Analysis

The ASTRUM-005 trial, enrolling predominantly patients from China, poses a key issue regarding transitivity, and therefore generates uncertainty about the clinical effectiveness in the NHS patient population.

Previously application of a multilevel network meta-regression (ML-NMR) over a matching-adjusted indirect comparisons (MAIC) in a technology appraisal (due to concerns over generalisability of the key trial population to the NHS population) has been shown to

substantively influence the clinical effectiveness outcome, including changing an effect from favouring one treatment to no clear difference between treatments (TA1013).[1]

However, we acknowledge that a limited population overlap has already been demonstrated though application of a MAIC, and that the use of a ML-NMR would also be subject to the potential limitation of clinical heterogeneity given the two distinct populations and settings.

To make best use of the available evidence, the EAG continue to believe that a ML-NMR would provide better use of all existing data, including data that are more representative of the NHS patient population. Hence it would potentially support more informed decision making. Since these analyses were not presented in this submission, there is more uncertainty as to the magnitude and direction of effect, and the generalisabilty and usefulness of ASTRUM-005 for decision making within the UK.

3. Selection of Survival Assumptions

NICE requested clarification on the EAG preferred survival assumptions. The EAG considered that the 3 knot spline models were a slightly better fit for the duration of the trial than the log-logistic models, but that the long-term predictions were overestimates of survival given the clinical expert opinion elicited by the Company. Consequently, the EAG utilised the 3 knot spline models up to the time point in the Kaplan Meier curve at which at least 10 patients were still at risk, and then the hazard ratio (HR) for serplulimab combination therapy versus carboplatin + etoposide alone was assumed to increase towards 1 from 3.5 to 6.5 years. The rationale was that over time with patients off treatment the hazard ratio may be expected to get closer to 1. In a scenario analysis an exponential curve was modelled so that OS was the same at 10 years as predicted using the log-logistic model. These two approaches produced similar survival curves. Both approaches are similar to the Liverpool approach mentioned in Technical Support Document 21.[2]

The HR for atezolizumab versus serplulimab and for durvalumab versus serplulimab was assumed to get closer to 1 over the same timeframe as for the same survival assumption for serplulimab.

For TToT, the EAG adopted a similar approach to better match the Kaplan Meier curve for treatment and to be consistent with the approach for survival.

4. Data Source used for TToT Curve definition for carboplatin + etoposide

In ASTRUM-005 trial, the TToT curve for carboplatin + etoposide represents the discontinuation of placebo. The costs incurred for carboplatin + etoposide were for 4 cycles in the model. The TToT curve had a small effect on subsequent treatment. Based on the company's FAC report, the EAG made changes in the text in EAG FAC report in Section 4.2.6.2 for better clarity. However, a correction should have been made to Section 4.2.6.1 of the same document but was not implemented.

5. *Infusion Rates and administration*

The company source for unit cost of administration for infusion of all treatments was the National Schedule of NHS Costs 2022/23.

The company applied the same administration costs for serplulimab, atezolizumab and durvalumab. For instance, monotherapy administrations for atezolizumab, durvalumab, and serplulimab are all costed at £217.22 (NHS reference code: SB12Z, Outpatient procedure cost, £217.22).

The same unit cost also was used for the first administration of treatment cycle for all combination regimens (NHS reference code: SB13Z, Daycase, £518.82).

Subsequent elements of etoposide treatment on day 2 and 3 of each treatment cycle was considered equal to delivery of subsequent elements of a chemotherapy cycle – Daycase (NHS reference code: SB15Z, Daycase, £413.69).

Additional scenario analyses requested by NICE

In the company and EAG base case analyses, the IV administration cost for atezolizumab was used. NICE requested scenarios with the subcutaneous administration cost for atezolizumab and 75% of patients receiving atezolizumab subcutaneously and 25% of patients receiving atezolizumab as IV. The same drug cost for infusion vials was used in each scenario. The costs for IV and subcutaneous administration for atezolizumab are reported in Table 3. The subcutaneous administration was based on code N10AF that was used in TA1041, as requested by NICE. The results for the all-subcutaneous administration scenario for the company base case and the EAG base case are presented in Tables 4 and 6, respectively. The results for the 75% subcutaneous and 25% IV administration scenario for both the company base case and the EAG base case are presented in Tables 5 and 7, respectively.

Table 3: Atezolizumab monotherapy administration costs

Drug administration costs	Type of administration	NHS reference code	Cost per administration	Year	Source
Atezolizumab monotherapy administration (IV)	Deliver simple parenteral chemotherapy at first attendance as outpatient	SB12Z	£217.22	2023	National Schedule of NHS costs 2022/23
Atezolizumab monotherapy administration (SC)	Cancer Service: Specialist Nursing, Cancer Related, Adult, Face to face	N10AF	£110.64	2023	National Schedule of NHS costs 2022/23

Table 4: Company base-case: All patients receive atezolizumab SC

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs (not discounted)	QALYs x1 (discounted)	Costs	LYs	QALYs x1	QALYs x1.2		
Company base-case									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.75						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.36	[redacted]	0.60	0.39	0.46	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.50	[redacted]	0.74	0.50	0.60	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.21	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]

Source: CS, CEM clarification addendum 04042025

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Table 5: Company base-case: 75% patients receive SC, 25% patients receive IV for atezolizumab

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs (not discounted)	QALYs x1 (discounted)	Costs	LYs	QALYs x1	QALYs x1.2		
Company base-case									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.75						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.36	[redacted]	0.60	0.39	0.46	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.50	[redacted]	0.74	0.50	0.60	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.21	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]

Source: CS, CEM clarification addendum 04042025

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Table 6: EAG base-case: All patients receive atezolizumab SC

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs (not discounted)	QALYs x1 (discounted)	Costs	LYs	QALYs x1	QALYs x1.2		
EAG base-case									
serplulimab + carboplatin + etoposide	[redacted]	2.40	1.73						
durvalumab + carboplatin + etoposide	[redacted]	1.94	1.42	[redacted]	0.45	0.31	0.37	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.82	1.31	[redacted]	0.57	0.41	0.50	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.40	1.02	[redacted]	1.00	0.70	0.85	[redacted]	[redacted]

Source: EAG economic model
Abbreviations: EAG: Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Footnotes: *indicates that this result is the full incremental ICER result for serplulimab

Table 73: EAG base-case: 75% patients receive SC, 25% patients receive IV for atezolizumab

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs (not discounted)	QALYs x1 (discounted)	Costs	LYs	QALYs x1	QALYs x1.2		
EAG base-case									
serplulimab + carboplatin + etoposide	[redacted]	2.40	1.73						
durvalumab + carboplatin + etoposide	[redacted]	1.94	1.42	[redacted]	0.45	0.31	0.37	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.82	1.31	[redacted]	0.57	0.41	0.50	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.40	1.02	[redacted]	1.00	0.70	0.85	[redacted]	[redacted]

Source: EAG economic model
Abbreviations: EAG: Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Footnotes: *indicates that this result is the full incremental ICER result for serplulimab

6. Relative Dose Intensity source and discrepancy

NICE requested the EAG to clarify the source of RDI data for serplulimab and to check for consistency in RDI values for serplulimab. The Company submission references the CSR of ASTRUM-005 (CS Table 43) as the source of RDI data for serplulimab and the CS refers to individual patient data on page 92. The EAR mentions patient-level data were used (page 106). Where either the CS or the EAR mentioned individual patient-data in this context, both should have referenced ASTRUM-005 as the source. NICE requested the EAG to check for consistency in RDI values for serplulimab, and the EAG found that the reporting of the RDI was consistent where identified.

7. Weight and height in the model

For serplulimab, weight-based dosing (4.5mg/kg) was applied to a distribution of weights informed by the ASTRUM-005 trial (mean: 68.395kg; standard deviation: 15.1149kg) to calculate the number of packs required per treatment cycle. Using the SD, the distribution of weight in the target population was derived using a normal distribution. In the weight-based dosing approach, the average number of packs per treatment cycle was 3.578. In the scenario of no-wastage, the average needed dose per treatment cycle was calculated by multiplying average weight of 68.395 by 4.5 mg/kg resulted in 307.8 mg.

In the EAG base case analysis, we incorporated the weight and height of individuals aged 69–74 years from the Health Survey for England with the average weight and height of 79.3 kg (SE: 0.63) and 166.8 cm (SE: 0.32), respectively. But a standard deviation is required to derive the population weight distribution, so the EAG used the standard deviations provided by the company. For more detail please see Table 44 in the company submission.

We selected the age group based on the National Lung cancer audit report indicating the median age at diagnosis for SCLC was 70 years.

The changes made by the EAG in the mean weight and height of patients in the model would affect the acquisition costs of serplulimab, carboplatin, etoposide, topetecan, cyclophosphamide, doxorubicin and vincristine. Serplulimab drug acquisition costs were based on weight. The alternative EAG weight increased the number of dose and vials of serplulimab from 307.8 mg and 3.578 vial to the 356.9 mg and 4.068 vial, respectively. Please see Matter of Judgement 5 in Table 3 for the effect this has on the ICER. The acquisition costs of carboplatin, etoposide, topetecan, cyclophosphamide, doxorubicin and vincristine were all based on BSA using the Dubois formula.

8. Updated Results Table

Errors were identified in the cost and ICER results for in Matter of Judgement 2 and Matter of Judgement 5 from Table 6.1 in the EAG report after the Factual Accuracy Check (FAC). The correct results are reported in Table 8. Note that TToT may affect QALYs due to a small on-treatment disutility.

Table 8: Deterministic EAG base-case

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs (not discounted)	QALYs x1 (discounted)	Costs	LYs	QALYs x1	QALYs x1.2		
Company base-case									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.75						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.36	[redacted]	0.60	0.39	0.46	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.25	[redacted]	0.74	0.50	0.60	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.01	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]
Matter of Judgement 1 – Survival Curve assumption: serplulimab: Knot 3 survival curve + 3-year treatment waning (OS, PFS), carboplatin + eptoposide: Knot 3 survival curve + exponential (OS, PFS)									

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs (not discounted)	QALYs x1 (discounted)	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.40	1.74						
durvalumab + carboplatin + etoposide	[redacted]	1.88	1.38	[redacted]	0.52	0.35	0.43	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.75	1.27	[redacted]	0.65	0.46	0.56	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.40	1.02	[redacted]	1.00	0.72	0.86	[redacted]	[redacted]
Matter of Judgement 2 – Atezolizumab and durvalumab HR waning to 1 from 3.5 years to 6.5 years									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.75						
durvalumab + carboplatin + etoposide	[redacted]	1.97	1.42	[redacted]	0.50	0.33	0.40	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.84	1.31	[redacted]	0.63	0.44	0.53	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.01	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs (not discounted)	QALYs x1 (discounted)	Costs	LYs	QALYs x1	QALYs x1.2		
Matter of Judgement 3 –TTOT: Knot 3 curve + weighted by PFS and PD									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.74						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.36	[redacted]	0.60	0.38	0.46	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.25	[redacted]	0.74	0.49	0.59	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.01	[redacted]	1.09	0.73	0.88	[redacted]	[redacted]
Matter of Judgement 4 – TTOT in PFS and PD states assumption: assume maximum of 20% in PD state									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.75						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.36	[redacted]	0.60	0.39	0.46	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.25	[redacted]	0.74	0.50	0.60	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs (not discounted)	QALYs x1 (discounted)	Costs	LYs	QALYs x1	QALYs x1.2		
carboplatin + etoposide	[redacted]	1.38	1.01	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]
Matter of Judgement 5 – Drug Acquisition Costs: Weight = 79.3 kg, Height = 168.4 cm									
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.75						
durvalumab + carboplatin + etoposide	[redacted]	1.87	1.36	[redacted]	0.60	0.39	0.46	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.74	1.25	[redacted]	0.74	0.50	0.60	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.01	[redacted]	1.09	0.74	0.89	[redacted]	[redacted]
EAG base-case (Matter of Judgement 1-5): Deterministic									
serplulimab + carboplatin + etoposide	[redacted]	2.40	1.73						
durvalumab + carboplatin + etoposide	[redacted]	1.94	1.42	[redacted]	0.45	0.31	0.37	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	LYs (not discounted)	QALYs x1 (discounted)	Costs	LYs	QALYs x1	QALYs x1.2		
atezolizumab + carboplatin + etoposide	[redacted]	1.82	1.31	[redacted]	0.57	0.41	0.50	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.40	1.02	[redacted]	1.00	0.70	0.85	[redacted]	[redacted]

Amendment of Table 0.4: Deterministic EAG base-case in the EAG report corrected after the FAC
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year
Footnotes: *indicates that this result is the full incremental ICER result for serplulimab

References

1) Nevitt S, Phillippo D, Hodgson R, Welton N, Dias S. Application of multi-level network meta-regression in the NICE technology appraisal of quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia: an external assessment group perspective. *Pharmacoeconomics*. 2025;43:243 - 7. Available from: https://doi.org/https://doi.org/10.1007/s40273-024-01460-1.
2) Rutherford MJ, Lambert PC, Sweeting MJ, Pennington B, Crowther MJ, Abrams KR, Latimer NR. NICE DSU TECHNICAL SUPPORT DOCUMENT 21: Flexible Methods for Survival Analysis. January 202

Single Technology Appraisal

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

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

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 2 May 2025** using the below comments table.

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

Confidential information is redacted ([redacted]) throughout.

Issue 1 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 13, the EAG state that “The modelling assumptions that have the greatest effect on the ICER are:” without clarifying the quoted issues refer to the EAG’s assessment of the model sensitivities.	The Company request that the EAG amend the wording to “Based on the EAG’s assessment, the modelling assumptions that have the greatest effect on the ICER are:”.	This amendment helps differentiate the EAG’s assessment from the Company’s assessment of the model.	The EAG agrees with the suggested recommendation and made amendments on Section 1.2.

Issue 2 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 15, the EAG state that “the company presented spline models with 1, 2 and 3 knots was most closely fitted to the Kaplan-Meier curves.” This sentence lacks clarity.	The Company request that the EAG amend the wording to “the company presented spline models with 1, 2 and 3 knots. The 2/3 knot were most closely fitted to the Kaplan-Meier curves.”	The EAG’s sentence lacks clarity.	Thank you. The text has been amended accordingly.

Issue 3 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 15, the EAG state that “However, the company stated that according to clinical expert opinion, the long-term OS predictions appeared to be overestimated.” The Company didn’t present spline models to the clinician, which should be reflected in the EAG’s text.	The Company request that the EAG amend the wording to “However, the company stated that, according to the clinical experts, who had been consulted on standard parametric extrapolations, long-term OS predictions appeared to be overestimated.”	The EAG’s sentence lacks clarity.	Thank you. The text has been amended accordingly.

Issue 4 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 18, the EAG state that “In England, the average weight (79.3 kg) and height (168.4 cm) is significantly greater than the ASTRUM-005 trial population” without including a reference.	The Company request that the EAG include a reference to justify their use of higher height and weight data.	The EAG’s assumptions lack justification.	The EAG statements and assumptions on Adults' mean weight and height were based on the Health Survey for England. The reference was added by the EAG to the report. However, the company comment prompted the

			EAG to re-check values. We noticed that the average weight used in the report is the most recent data (2022), the average height was for 2019 (It should be 169.1 cm, not 168.4 cm). While the EAG intended to correct the average adult height, further review of National Lung cancer audit highlighted that the median age at diagnosis for SCLC was 70 years. Consequently, the EAG decided to use the 65–74 age group as a reference and update both height and weight values in the base case to reflect this 65–74 age group. According to the Health Survey for England, individuals aged 65–74 years have the same average weight of 79.3 kg as previously assumed. However, there is a small

			difference in height (166.8 cm) for this age group, which is 1.6 cm less that the value already assumed in the EAG model. The weight affects the cost of serplulimab (which is weight-based). Atezolizumab and durvalumab are fixed-dose therapies, they are not affected by changes in height or weight. The impact of height change is very small through influencing the BSA for chemotherapy treatment, resulting changes of the ICER by £3 compared to atezolizumab and by £4 compared to carboplatin + etoposide. Hence, the EAG decided to not re-run the analysis with the updated height. The EAG made associated amendments in Table 1.6: Key issue [5], Sections

			4.2.6.3, and 6.1.1.4 of the report.

Issue 5 Discrepancy in the quality appraisal

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 18, the EAG state that they "believe that about 48.7% of patients with ES-SCLC in England are women" referencing a National Lung Cancer Audit publication from 2024. However, the estimate reported by the EAG corresponds to Welsh patients with both SCLC and NSCLC. Furthermore, the EAG did not explicitly provide justification for why these estimates are more appropriate for use in their model.	The Company request that the EAG correct their proposed estimate to a combined estimate for England and Wales, which are both reported separately in the National Lung Cancer Audit. The Company also request the EAG explicitly state that this proposed estimate is not specific to ES-SCLC but reflects the proportion of women with both SCLC and NSCLC across England and Wales, and may therefore present as a plausible alternative to using ASTRUM-005.	The EAG's selected estimate is not reflective of England and Wales and is not specific to ES-SCLC. This could lead to misinterpretation.	The EAG agrees with the company's comment that the proportion of 48.7% is related to the Welsh data and the correct number for SCLC in England is 49.8% of 36,886 patients diagnosed with lung cancer in 2022. The EAG made the amendment in the report Table 1.6: Key issue [5] text. The EAG used the data on England population for the EAG model. In the average weight and height calculations mentioned in Issue 4.

Issue 6 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 62/63, the EAG state that “Specifically, the proportion of males in the durvalumab plus platinum-etoposide and platinum-etoposide arms combined is higher (69.6%), as is the percentage of patients who are ‘never smokers’ (6.9%).” This sentence does not clarify which population the proportions are higher than.	The Company request that wording be added to reflect that the proportion of males and ‘never smokers’ is higher in CASPIAN compared with the EAG’s selected source for lung cancer statistics, which include sources that are not specific to ES-SCLC, as well as including the relevant references.	The EAG’s statement lacks clarity and could lead to misinterpretation.	To provide clarity the text from Table 3.10, “Specifically, the proportion of males in the durvalumab plus platinum-etoposide and platinum-etoposide arms combined is higher (69.6%), as is the percentage of patients who are ‘never smokers’ (6.9%)”, which refers to a retrospective chart review of patients with SCLC (stratified by limited and extensive stage) has been removed. The patient characteristics in the latter study by Blackhall et al. 2023 have then been expanded on and referenced appropriately in Section 3.6.3.3.

Issue 7 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 67, the EAG state that “The treatment comparator durvalumab for patients with untreated ES-SCLC, included in the final scope and recently approved by NICE, was not included in the CS” without acknowledging that it was provided at a later stage during clarification questions.	The Company request that the EAG include wording to acknowledge that a MAIC for durvalumab was provided at a later stage.	The EAG’s wording is misleading.	The statement has been revised to state: “Subsequently, the company initially deemed durvalumab not to be a relevant comparator.” In the subsequent paragraph, the EAG have also expanded the following statement to ensure clarity that durvalumab was later included in this submission: “In response the Company included durvalumab in this submission by conducting a second MAIC using aggregate data from CASPIAN to generate efficacy estimates between serplulimab and durvalumab.”

Issue 8 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 79, the EAG state that “a relatively higher proportion of never smokers enrolled compared to that seen in UK clinical practice” without clarifying the proportion of non-smokers in England or providing a reference.	The Company request that the EAG include a numerical estimate and reference for the proportion of ‘never smokers’ in England for an accurate comparison with the clinical data.	The EAG’s sentence lack justification.	The numerical estimate and references have now been added for clarification.

Issue 9 Lack of justification in the generalisability of Canadian patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
One page 79 (and page 71), the EAG use a Canadian reference to justify the lack of generalisability of CASPIAN and IMpower133 to the NHS, without justifying why a Canadian population is an adequate proxy for England and Wales. There is no reference to suggest that the performance scores, organ function and metastases of	The Company request that the EAG include some justification for why the baseline characteristics of a Canadian population represent an adequate proxy for England and Wales.	The EAG’s text lack justification.	A UK retrospective study cohort reported on by Blackhall et al 2024 has been added to support the applicability of CASPIAN, IMpower133 and ASTRUM-005 trial settings to a real-world setting, and to provide context to the UK.

Canadian ES-SCLC patients are a reliable proxy for disease characteristics of ES-SCLC patients in England and Wales.			

Issue 10 Absence of durvalumab in the CS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the report, the EAG state that the Company omitted durvalumab as it was not a recommended treatment alternative at the time of submission. However, the Company were also informed by NICE at the decision problem meeting that durvalumab was not a relevant comparator.	The Company request that the EAG acknowledge throughout their report that the Company had consulted NICE before submission development and were informed that durvalumab was not a relevant comparator, although a positive recommendation for durvalumab was later published, and the Company provided an updated analysis.	The EAG's report does not fully reflect the CS.	In the existing report, we state the Company's viewpoint: "The Company indicated that "at the time of the decision problem meeting, Accord [the company] were informed that durvalumab was not a relevant comparator" (p.10).{Accord, 2025 #121} (Section 2.1) The EAG had email correspondence from NICE on 20th February 2025 which stated: [durvalumab] …'is a

			relevant comparator, and it would be very unusual for NICE to take the stance suggested in their submission (omitting durvalumab) and we don't recall this being said at the DPM'. Furthermore, the EAG clearly state that following the PfC, the Company supplied additional analyses with durvalumab. We consider this be factually accurate so no substantially changes to the report have been undertaken. Where we do state that durvalumab was not considered a relevant comparator initially, we have stated that this refers to the 'original' company submission and reference the relevant source (i.e., Document B).

			See also changes listed for Issue 7.

Issue 11 Discrepancy in description of EAG base-case assumptions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
There are discrepancies in the description of the EAG's preferred assumptions in the EAG base-case throughout the report. For example, in section 1.4 it is stated that "three changes were made in the company base case" before listing five changes. Furthermore, the EAG base-case listed in table 6.1 appears to specify that only matters of judgement 1-3 are included in the EAG base case, seemingly inconsistent with the EAG's additional scenario analysis presented in section 6.2.3.	The Company request that the EAG clearly specify which assumptions are used in the EAG base case, and that the descriptions are amended to be consistent throughout the report.	The EAG's report lacks clarity and consistency.	Thank you. This originates from a request by NICE to split one change into 3. These proposed amendments have been made.

Issue 12 Discrepancy in EAG base-case results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
There are discrepancies in the EAG base-case results throughout the report, including but not limited to: The EAG base case ICERs reported in section 1.4 do not match those reported in table 6.1. Table 6.1 lists the ICER vs atezolizumab as [redacted], compared to [redacted] in section 1.4 [redacted] is also listed in the text in section 6.2.1). Table 6.1 lists the ICER vs carboplatin + etoposide as [redacted], compared to [redacted] in section 1.4. Another example is that the expected impact on cost effectiveness estimates with key issue 5 was to increase the ICER to [redacted] (table 1.6) which does not match the corresponding ICER for matter of judgement 5 in table 6.1 ([redacted]).	EAG should thoroughly review all the reported results and cross-check with the Excel model.	The EAG's report contains errors, and lacks clarity and consistency.	Thank you. All the results in Section 1.4 have been checked and edited accordingly. The EAG model submitted was close to being the final model, but actually was not. The Final model is being submitted with this FAC response.

Furthermore, the results in the Excel model provided by the EAG are inconsistent with the report e.g., The ICER vs atezolizumab is [redacted] in the Excel model and [redacted] in the report. Note that this is not an exhaustive list of the errors identified.			

Issue 13 Errors in reporting of company base case results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 5.1.1, there are errors in the reporting of the results. For example, “The base-case pair-wise results between serplulimab + carboplatin + etoposide and atezolizumab + carboplatin + etoposide showed that the cost decreased by [redacted] and improved QALY by 0.60. The net monetary benefit was [redacted], at a willingness to pay threshold of £30,000. The base-case pair-wise results between serplulimab + carboplatin + etoposide and atezolizumab + carboplatin + etoposide showed that the cost increased by [redacted] and improved QALYs by 0.60. The net monetary benefit was [redacted], at a willingness to pay threshold of £30,000.” Note that this is not an exhaustive list of the errors identified.	The EAG should thoroughly review all the reported results.	The EAG’s report contains errors, and lacks clarity and consistency	Thank you. The results have been checked and edited.

Issue 14 Inconsistent reporting of results of different matters of judgement in the EAG base case (table 6.1)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Numerous issues were identified with the reported results in Table 6.1, including but not limited to: The table caption "deterministic/probabilistic EAG base case" is unclear as to whether the presented results are deterministic or probabilistic. The reporting of total QALYs and incremental QALYs is inconsistent for the different matters of judgement. The description of matter of judgement 2 doesn't appear to match the written text in 6.1.1.4. Matters of judgement 3 and 5 impact LYs and QALYs in a highly unexpected manner. Matter of judgement 5 incorrectly lists the weight as 79.8 kg.	Due to the numerous issues identified, the Company request that the EAG re-run their analysis.	The EAG's report contains errors, and lacks clarity and consistency.	Thank you. All of these points have been addressed and corrected accordingly.

Matter of judgement 1-3 is specified in the EAG base case, seemingly inconsistent with the rest of the report (see issue 13).			

Issue 15 Textual clarification – in text references to tables and figures

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Multiple errors with regards to in text references to table and figures were identified. For example, in section 5.2.2; “To explore uncertainty within their cost-effectiveness analysis, the Company conducted pair-wise probabilistic sensitivity analysis (PSA) over 1,000 iterations using the list price and PAS price for serplulimab. **Table 5.5** and **Table 5.6** show the results of pair-wise probabilistic sensitivity analysis undertook by the Company using serplulimab PAS price.”	The Company request that the EAG update all in text references to tables and figures.	The EAG’s report contains errors.	Table/figure cross-referencing have all been checked and amended where necessary.

Note this is not an exhaustive list of the errors identified.			

Issue 16 Textual clarification – explanatory table footnotes for asterisks

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Asterisks are present in tables with no explanation of what the asterisk represents in the table footnotes e.g., table 6.1.	The Company request that the EAG add explanatory footnotes to all tables where asterisks are present.	The EAG's report lacks clarity.	All footnotes have all been checked and amended where necessary.

Issue 17 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In table 4.2.2 it is stated that the "the EAG only found errors in the TTOT population proportion calculations". This is factually inaccurate.	The Company request that the text is amended to read "the EAG only found errors in the time to death (TTD) population proportion calculations"	The errors were identified in the time to death population proportion calculation, which were subsequently corrected in the Company's response to the clarification letter.	Thank you. The text has been amended as suggested.

Issue 18 **Textual clarification**

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 4.2.3, it is stated that “Consequently, in the EAG base case for OS, the 3 knot spline model is fitted for serplulimab and for carboplatin + etoposide until the latest timepoint at which the number of patients still at risk was at least 10 (**18 months** and **42 months, respectively**).” The timepoints at which the number of patients at risk was at least 10 appear to be the wrong way round.	The Company request that the text is amended to read “Consequently, in the EAG base case for OS, the 3 knot spline model is fitted for serplulimab and for carboplatin + etoposide until the latest timepoint at which the number of patients still at risk was at least 10 (42 months and 18 months, respectively).”	The original text is factually inaccurate.	Thank you. This has been edited as suggested.

Issue 19 **Figure legends**

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Some figures in the report are missing legends. For example, Figure 4.2 appears to be missing the legend for the serplulimab 3-	The Company request that the EAG update all the figure legends.	The EAG’s report lacks clarity	All figure legends have been checked and amended where necessary.

knot spline model. Figure 4.4 appears to be missing the legend for the durvalumab arm. Note this is not an exhaustive list.			

Issue 20 TTD utility estimates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 4.2.5, it is stated that “The utility values based on TTD in the CS model were significantly different from the values presented in the CS document.” The CS model uses TTD utility values based on descriptive statistics (rather than the model-based estimates which were also provided in the CS). The utility values based on descriptive statistics are provided in table 40 of the CS.	The Company requests that this statement is removed from the report.	This statement is factually inaccurate, as the TTD utility values implemented in the model are provided in the CS.	The EAG agrees and made amendments.

Issue 21 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 4.2.6 it is stated that “the Company stated in their PfC response that the costs were not directly sourced from the NHS reference costs such as cost of palliative care, but were inflated to 2024 prices using PSSRU Hospital and Community Health Services (HCHS) and NHS cost inflation index values (NHSCII). It was stated that for the costs obtained from NHS reference costs the average rate of inflation over the previous three years was used due to unavailability of the inflation index at the time of submission.” This text contains wording errors which may lead to an incorrect interpretation.	The Company requests that this text is amended to: “the Company stated in their PfC response that the costs that were not directly sourced from the NHS reference costs such as the cost of palliative care, were inflated to 2024 prices using PSSRU Hospital and Community Health Services (HCHS) and NHS cost inflation index values (NHSCII). It was stated that for these costs not obtained from NHS reference costs the average rate of inflation over the previous three years was used due to unavailability of the inflation index at the time of submission”	This amendment is necessary to clarify that costs sourced from the 2022/23 NHS reference costs were not inflated. Costs that were not sourced from the 2022/23 NHS reference costs were inflated to 2024 prices.	The EAG made the proposed amendment.

Issue 22 Time on treatment for carboplatin + etoposide

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6 contains multiple references to the TTOT KM curve for carboplatin + etoposide with the EAG stating: “It is not clear what the Kaplan-Meier curve represents for carboplatin + etoposide when the last of the 4 cycles of treatment is administered in week 9” and that it “is not clear how the KM curve for TTOT is consistent with the treatment protocol.” The TTOT KM curve for carboplatin + etoposide represents the discontinuation with placebo in the ASTRUM-005 trial. The costs for carboplatin + etoposide in the CS model are incurred for 4 cycles only, consistent with the trial protocol.	The Company request that the text stating that the modelling of TTOT in the carboplatin + etoposide is not consistent with the trial protocol be removed.	This amendment will add clarity to the EAG’s report.	Thank you. The text has been replaced with “For the carboplatin + etoposide arm of the ASTRUM-005 trial, the KM curve for TTOT represents the discontinuation of placebo.”

Issue 23 **Textual clarification**

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 5.2.1 it is stated that "When durvalumab + carboplatin + etoposide was used as comparator 1, the ICER was most sensitive to changes in the HR derived from the MAIC (atezolizumab vs serplulimab, HR = [redacted] used to inform the OS extrapolation in the atezolizumab arm, particularly when the HR was varied to the lower confidence interval value ([redacted])." This statement is factually inaccurate as it references the HR of atezolizumab vs serplulimab from the MAIC rather than durvalumab vs serplulimab.	The Company request that this text is amended to reference the correct values from the MAIC (durvalumab vs serplulimab).	This statement is factually inaccurate	Given that the company did not provide the full set of results using the PAS price for serplulimab, the EAG produced the results from the clarification model. However, the EAG thinks the whole set of results needs to be checked again, and so the content of the section has been removed. The content could potentially be provided in an Addendum on request.

Issue 24 **Textual clarification – company's deterministic sensitivity analysis**

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The captions for Table 5.4 and Table 5.5 describe two separate comparators. It is irrelevant to specify which comparators are selected as comparator 1 and comparator 2 in the model as the DSA is conducted in a pairwise manner. Furthermore, the captions for Table 5.4 and Table 5.5 incorrectly state that these are the results of the DSA provided by the company. The company provided only the results of the DSA at serplulimab list price, as the list price ICERs are more interpretable with fewer scenarios resulting in dominant ICERs.	The Company request the table captions include only the comparator against which the pairwise DSA is being conducted (i.e., the specification of comparator 2 is removed). The company also requests that it is made clear that these tables represent the EAG's analysis, rather than the company's analysis.	Specifying two different comparators when only one comparator is being compared to introduces unnecessary confusion and could lead to incorrect interpretations of the results.	All the sensitivity analysis tables (Table 5.4, 5.5 and 5.6) have now been deleted. See the response to Issue 23.

Issue 25 Company's deterministic sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The results of the DSA with carboplatin + etoposide as a comparator, presented in table 5.5 and figure 5.2, indicate that the HR from the MAIC (durvalumab vs serplulimab) is a driver of the ICER. This parameter should have no impact on the ICER against carboplatin + etoposide (should only impact the ICER against durvalumab). The Company have verified that changing this parameter doesn't have any impact on the ICER vs carboplatin + etoposide in the CS model, as expected.	The Company request that EAG re-run this analysis.	This result suggests there is an error in the EAG's reproduction of the company's DSA.	The EAG thinks that the entire deterministic section needs to be checked again. The company did not provide the DSA results with the PAS price for serplulimab. Consequently, the EAG has deleted the entire section. The content could potentially be provided in an Addendum on request.

Issue 26 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 5.2.2, it is stated that "The cost-effectiveness acceptability curves of	The Company request that the EAG remove the quoted statement and correct the captions in figure 5.8 and	This statement is factually inaccurate	EAG agrees with the company comment. The figures labelled correctly

serplulimab + carboplatin + etoposide against each of its comparators are given in Figure 5.7, Figure 5.8, Figure 5.9. Note that the company mislabelled the legends in the plots in the company model, and this was identified too late to correct. The correct comparator is stated in the Figure captions." This statement is factually inaccurate. The figure legends in figures 5.7, 5.8, and 5.9 are labelled correctly and appropriately align with the probabilities of cost-effectiveness reported in the text.	figure 5.9 to appropriately reflect the figure legends.		and appropriately. Therefore, the EAG made associated amendments in the report and figures 5.7, 5.8, and 5.9.

Issue 27 Textual clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 5.2.2 it is stated that "At a willingness to pay threshold of £20,000, serplulimab + carboplatin +	The Company request the EAG clarify if these results are using the company's or EAG's base case and re-run the analysis if necessary.	The EAG report lacks clarity	Thank you. The EAG has made sure that the results reported by the Company are in Section 5, and that

etoposide was [redacted]% cost-effective against atezolizumab + carboplatin + etoposide, [redacted]% cost-effective against carboplatin + etoposide and [redacted]% cost-effective against durvalumab + carboplatin + etoposide. At a willingness to pay threshold of £30,000, serplulimab + carboplatin + etoposide was [redacted]% cost-effective against atezolizumab + carboplatin + etoposide, [redacted]% cost-effective against carboplatin + etoposide and [redacted]% cost-effective against durvalumab + carboplatin + etoposide". The EAG should clarify if these results are using the company's or the EAG's base case. The context of the section implies that it should be the company's base case; however, there is a large discrepancy between the probabilities of cost-effectiveness provided by the			where there was missing information provided by the EAG that this was explicitly stated.

company and those reported in the quoted text, particularly with respect to the comparison against carboplatin + etoposide.			

Issue 28 Company's scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 5.2.3, the EAG state that they were unable to recreate some of the company's scenario analysis due to settings not being available in the scenario settings sheet. It is stated that "The scenario with changing the data source for survival estimate to HRs obtained from MAIC could not be replicated because the option was not available in the scenario settings in the model." This scenario can be explored by changing the inputs in the OS and PFS inputs sheets to	The Company request that the results of the scenario analyses that the EAG state could not be performed are presented. Also, the company request that the EAG re-run the treatment waning scenarios for all comparators.	To provide a complete set of scenarios to match the CS.	The EAG has checked that the scenario analysis results match the results presented in the Company clarification response and clarification response addendum. The text highlighted by the Company regarding non-Asian utilities and TTD has been deleted.

the before-matching HRs (reported in table 26 of the CS and in the company's response to clarification). It is also stated that "Similarly, the impact of vial sharing (with no wastage) on the unit price of serplulimab was calculated in the model. But the scenario settings to incorporate this into the total cost calculation was not available in the model". This scenario can be explored by using the "no wastage" costs for serplulimab in the cost inputs sheet. The EAG also state that "For atezolizumab + carboplatin + etoposide as comparator, the scenario analysis results around the utility estimation methods, application of non-Asians' disutilities instead of all patients and treatment wanning did not give the same incremental results as provided in the company submissions". Notably, the			

TTD scenario does not match the results provided in the CS as the TTD formulae were updated in the company's response to clarification. Furthermore, the results of "Immediate loss of treatment effect at 5 years scenario" re-run by the EAG match the results of the "Gradual loss of treatment effect from 5-10 years" provided by the company in the CS, indicating that the treatment waning scenarios have not been run correctly.			

Issue 29 Textual clarification – subgroup analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 5.3, it is stated that "The ICER results for atezolizumab as a comparator was not [redacted] as given in the company submission, but a	The Company request that the text be amended to state "The ICER results for atezolizumab as a comparator was not [redacted] as given in the company submission, but a ICER of [redacted] was incurred"	The EAG report lacks clarity	Thank you. The text in section 5.3 has been replaced with, "The Company implemented a subgroup analysis using the data specific to the non-Asian population, collected from the ASTRUM-00 trial, to

ICER of [redacted] was incurred" It is not clear whether the [redacted]ICER referred to in the quoted text refers to the ICER for the ITT or non-Asian populations. The CS reported an ICER of [redacted] against atezolizumab for the non-Asian population.			reflect the UK clinical setting. But the exact results for all the comparators were not available in the company submission for the PAS price for serplulimab.[6] The EAG ran the subgroup analysis for non-Asian patient population in the company model.[88] The results are presented in Table 5.8."

Issue 30 Subgroup analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The subgroup analysis presented in section 5.3 does not reproduce the results provided by the company in the CS. To conduct the analysis accurately, multiple settings in the CS model need to be change including:	The company request that the EAG re-run the analysis for the non-Asian population changing all the relevant dropdowns in the CS model.	The results presented in the EAG's report are inaccurate.	Thank you. This has been checked and corrected.

“PFS, OS, and TTOT selected” – change to non-Asian patients “Utilities selected” – change to non-Asian patients “AEs selected” – change to non-Asian patients			

Issue 31 **Textual clarification**

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
In section 6.4 it is stated that “The results from the MAIC suggested that there is comparable effectiveness between serplulimab and its comparators” This suggests that serplulimab has comparable effectiveness to	The Company request that the text be amended to clarify that MAIC demonstrates improved (rather than comparable) effectiveness for serplulimab compared to its comparators (atezolizumab and durvalumab).	This statement provides an inaccurate interpretation of the results of the MAIC	The text has now been amended: “The results from the MAIC [redacted].”

atezolizumab and durvalumab whereas the results of the MAIC demonstrate improved effectiveness for serplulimab.			