Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende serplulimab i kombination med carboplatin og etoposid til behandling af småcellet lungekræft i udvidet sygdomsstadie (ES-SCLC)

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. serplulimab til ES-SCLC
2. Ansøgers endelige ansøgning vedr. serplulimab til ES-SCLC

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02.07.2025

DBS, LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	03.09.2025
Leverandør	Accord Healthcare AB
Lægemiddel	Hetronifly (serplulimab)
Ansøgt indikation	Hetronifly i kombination med carboplatin og etoposid som førstelinjebehandling af voksne patienter med småcellet lungekræft i udvidet sygdomsstadie (ES-SCLC).
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Hetronifly (serplulimab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Hetronifly	10mg/ml (10 ml)	9.610	[redacted]	[redacted]

Aftaleforhold

[redacted]

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 24 uger*(SAIP, DKK)
Hetronifly	10 mg/ml (10 ml)	4,5 mg/kg** IV hver 3. uge	[redacted]	[redacted]
Tecentriq	1.200 mg (1 stk.)	1.200 IV hver 3. uge	[redacted]	[redacted]
Imfinzi	50 mg/ml (10 ml)	1.500 mg IV hver 3. uge i 4 serier. Herefter 1.500 mg IV hver 4. uge	[redacted]	[redacted]

*Gennemsnitlig behandlingslængde

**Benyttet gennemsnitsvægt på 72 kg, baseret på Medicinrådets evidensgennemgang vedrørende lægemidler til uhelbredelig ikke-småcellet lungekræft - *Anbefaling og det kliniske sammenligningsgrundlag* – version 1.0

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link

England	Under vurdering	Link
Sverige	Under vurdering	Link

Opsummering

[redacted]

Application for the assessment of serplulimab (Hetronifly®) for the treatment of extensive-stage small cell lung cancer (ES-SCLC)

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

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Abbreviations

AE	Adverse Event
CCOD	Clinical cut-off date
ChT	Chemotherapy
CP/ET	Carboplatin plus etoposide

DFS	Disease-free survival
DLCR	Danish Lung cancer registry
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EORT QLQ	EORTC QLG Core Questionnaire
EpC	Etoposide plus carboplatin
EQ-5D	EuroQol Group 5 Dimension Quality of life measurement
EQ-5D-3L Dimensional	EuroQol Group 5 Dimension Quality of life measurement-3 levels
EQ-5D-5L	EuroQol Group 5 Dimension Quality of life measurement-5 levels
ES-SCLC	Extensive stage small cell lung cancer
FACT-L	Functional Assessment of Cancer Therapy-Lung
FDA	Food and Drug Administration
HRQoL	Health-related quality of life
HSUV	Health State Utility Values
ICI	Immune Checkpoint Inhibitor
IL-2	Interleukin-2
LC	Lung cancer
LS-SCLC	Limited-stage small cell lung cancer
MCMC	Markov Chain Monte Carlo
mOS	median overall survival
NICE DSU TSD	NICE Decision Support Unit Technical Support Document
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death 1 Ligand 1
PD-L2	Programmed cell death-ligand 2
PFS	Progression free survival

PT	Preferred Term
PtE:	Platinum + Etoposide
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy
SCLC	Small cell lung cancer
SD	Standard deviation
SLR	Systematic literature review
TMB	Tumour mutation burden

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Hetronifly
Generic name	Serplulimab
Therapeutic indication as defined by EMA	Hetronifly (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).
Marketing authorization holder in Denmark	Accord Healthcare S.L.U
ATC code	L01FF12
Combination therapy and/or co-medication	Indicated for use in combination with etoposide and carboplatin (EpC)
(Expected) Date of EC approval	03rd of February 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes (9 December 2022)
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	*Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)?* Yes *Is the product suitable for a joint Nordic assessment? [yes/no]* No *If no, why not?*

Overview of the medicine	
	In Norway and possibly Sweden: fast-track access for PD-(L)1 inhibitors. In those countries the application process is simplified and does not require HTA submission.
Dispensing group	Medicines only to be distributed to hospitals (BEGR)
Packaging – types, sizes/number of units and concentrations	Hetronifly (serplulimab) will be available as 10 mg/ml concentrate for solution for infusion.

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Indication relevant for the assessment	Hetronifly (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).
Dosage regiment and administration	Serplulimab is administered intravenously. The initial infusion rate should be set up to 100 mL per hour. If the first infusion is well tolerated, all subsequent infusions may be shortened to 30 minutes (± 10 minutes). Serplulimab must not be administered as an IV push or bolus injection. The total serplulimab dose required should be diluted with a sodium chloride 9 mg/mL (0.9%) solution for injection. When administered in combination with chemotherapy (ChT), serplulimab should be given first, followed by ChT on the same day. Use separate infusion bags for each infusion. The recommended dose 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. Dose withholding for up to 12 weeks for tolerability is acceptable.
Choice of comparator	Atezolizumab (Tecentriq) in combination with (Carbo)platinum + etoposide after prior communication with DMC (telephone conversation with assessor at DMC)
Prognosis with current treatment (comparator)	Survival of ES-SCLC patients is poor, and many patients die before completing treatment, which highlights a big unmet need for effective therapies. Death within 60 days from diagnosis, without completing treatment, was reported for 31.1% of extensive stage small cell lung cancer (ES-SCLC) patients. Median survival was 6.2 months and the 5-year

Summary	
	survival was 2%. Compare with figures in 3.3.1. Thus, the disease is associated with a large decrease in life expectancy and quality of life [1]. The addition of immunotherapy has extended median OS and it was 12.3 and 10.3 months with atezolizumab plus CP/ET and placebo plus CP/ET, respectively (hazard ratio, 0.76; 95% CI, 0.60 to 0.95; descriptive P 5 .0154). Progression free survival (PFS) was 5.2 months in the treatment arm, whereas the comparator had 4.3 months, resulting in a gain of 0.9 months with treatment; Hazard Ratio (HR) 0.77 (0.63-0.95) [44].
Type of evidence for the clinical evaluation	EMA EPAR Report [2], Systematic Literature Review and Network Meta-Analysis of the Effectiveness and Safety of serplulimab in Extensive-Stage Small Cell Lung Cancer [3].
Most important efficacy endpoints (Difference/gain compared to comparator)	Note: both serplulimab (Astrum-005) and atezolizumab (Impower 133) have studies in combination with carboplatin+etopisode vs. carboplatin+etopisode alone. According to ESMO magnitude of clinical benefit scale, serplulimab was given the score 4 while the other PD-(L)-inhibitors, durvalumab and atezolizumab were given a score of 3 [4] OS, PFS and confirmed ORR for different data cut-offs are summarized below:

	Hetronifly (Astrum 005)	**Atezolizumab (Impower 133)**
OS (months)	15.4 vs. 10.9 HR: 0.63 (0.49-0.82) 22 Oct 2021 [2, 5]	12.3 vs 10.3 HR: 0.70 (0.54-0.91) 24 Apr 2018 [6, 7]
OS cut off 2	**15.8 vs. 11.1** **HR: 0.62 (0.496-0.763)** **13 June 2022 [2]**	12.3 vs 10.3 HR: 0.76 (0.60-0.95) 24 Jan 2019 [6, 7]
OS cut off 3	15.8 vs. 11.1 HR: 0.61 (0.50–0.74)	-

Summary			
		13 June 2023 [8]	
	PFS (months)	**by IRRC:** **5.8 vs. 5.0** **HR: 0.47 (0.38-0.58)** **13 June 2022 [2]** [redacted]	5.2 vs. 4.3 HR: 0.77 (0.62-0.96) 24 Apr 2018 [6]
	Confirmed ORR (%)	67.4 vs. 58.7 [2, 5] OR. 1.46 (1.02-2.09) 22 Oct 2021 [2, 5]	60.2 vs 64.4 [6, 7] OR: 0.84 (0.56-1.25) 24 Apr 2018 [6]

Note: Values in bold correspond to updated analysis for Hetronifly (serplulimab) from the pivotal study also presented in EPAR [2].

Most important serious adverse events for the intervention and comparator	**ASTRUM-005 (cut-off: 13 Jun 2023)** Serious adverse events were reported in 152 patients (39.1%) for serplulimab plus chemotherapy and in 77 patients (39.3%) in placebo + chemotherapy. Most frequent severe adverse events were neutropenia, leukopenia, anaemia, and thrombocytopenia [2]. Adverse event data as in the EPAR is presented if not otherwise stated. According to EPAR, there are no notable differences in frequencies of adverse events between the cut-off dates 13 June 2022 and 13 June 2023 [2]. **Impower133** Serious adverse events were reported in 45 patients (22.7%) for atezolizumab + CP/ET and 37 (18.9%) in placebo+CP/ET. Most frequent serious adverse events were neutropenia and thrombocytopenia and febrile neutropenia [9].

Summary	
Impact on health-related quality of life	Clinical documentation: The EQ-5D-5L utilities were collected in the ASTRUM clinical study in line with the clinical study protocol. Serplulimab combined with EpC does not compromise patients' HRQoL as a first-line treatment in ES-SCLC compared with EpC alone [8]. Health economic model: Not applicable for application (14 weeks process)
Type of economic analysis that is submitted	Not applicable in the 14-week process
Data sources used to model the clinical effects	Not applicable in the 14-week process
Data sources used to model the health-related quality of life	Not applicable in the 14-week process
Life years gained	Not applicable in the 14-week process
QALYs gained	Not applicable in the 14-week process
Incremental costs	Not applicable in the 14-week process
ICER (DKK/QALY)	Not applicable in the 14-week process
Uncertainty associated with the ICER estimate	Not applicable in the 14-week process
Number of eligible patients in Denmark	Incidence: 160 Prevalence: not relevant – see section 3.2
Budget impact (in year 5)	Not applicable in the 14-week process

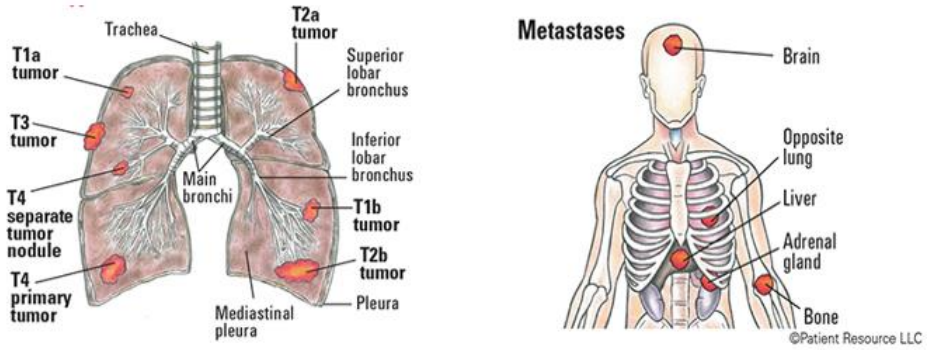
3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

cancer (SCLC) and non-small cell lung cancer (NSCLC) [10].

Limited-stage small cell lung cancer (LS-SCLC) is confined to one hemithorax and can be encompassed in a single radiation field, whereas extensive-stage small cell lung cancer (ES-SCLC) involves malignant pleural or pericardial effusions, contralateral lymph node involvement, or distant metastases [11]. Approximately 70% of ES-SCLC cases show presence of metastatic disease outside the hemi-thorax at first diagnosis [12, 13]. The most common sites of metastases are the brain, liver, adrenal gland and bone (Figure 1) [14, 15].

Figure 1. Anatomy of the lung and possible metastasis locations



Tumour suppressor genes are frequently involved in maintaining homeostasis. Loss of these genes causes cellular plasticity which drives numerous cancers, including SCLC [16]. Most patients have key tumour suppressor genes inactivated, such as the retinoblastoma 1 and tumour protein p53 but attempts to target these alterations remain unsuccessful. The high tumour mutation burden (TMB) is largely attributed to tobacco exposure [10, 13]. In addition, rapid tumour growth, increased vascularity, and a high metastatic potential are other characteristic factors linked to the disease [10].

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 [17]. A considerable portion of SCLC exhibits abnormal PD-L1 expression on tumour cells [18]. Therefore, the PD-1/PD-L1 signalling pathway is a major therapeutic

target for immunotherapies using immune checkpoint inhibitors [18, 19]. It has been observed that adding PD-L1 inhibitors to pre-existing cytotoxic regimens prolong survival in ES-SCLC patients [19].

3.1.1 Clinical presentation/symptoms of ES-SCLC

SCLC predominantly develops in patients aged 60 to 70 years old and is strongly associated with a history of smoking. SCLC is often asymptomatic early in the progression of the disease [20]. Symptoms present typically with a short duration, on average at 3 months, with the majority (≥70%) of patients with SCLC presenting with ES-SCLC at diagnosis [20], [21].

Symptoms vary depending on the tumour's location and size. In cases of localized disease, common symptoms include cough, wheezing, shortness of breath (dyspnoea), and coughing up blood (haemoptysis). Metastases, affecting organs such as the contralateral lung, brain, liver, adrenal glands, bones, or bone marrow, can lead to additional symptoms, including neurological issues, nerve pain, fatigue, loss of appetite (anorexia), and weight loss [22]. Endobronchial tumours may manifest persistent cough, wheezing, pain dyspnoea, or post-obstructive pneumonia [23]. Patients with ES-SCLC may 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 due to the central tumour nature [23].

3.1.2 Prognosis

SCLC is characterized by an aggressive undifferentiated neoplasia with a high proliferation rate and early metastasis [24]. It has a high propensity to spread to the brain, with approximately 10% to 20% of patients presenting with brain metastases at the initial diagnosis, and eventually up to 50% developing brain metastases during the course of their disease [25-27]. Although it is initially sensitive to chemotherapy (ChT) and radiotherapy (RT), it develops early resistance, showing early progression and lack of sensitivity to further pharmacological treatment [23, 24, 28]. Patients with ES-SCLC have, on average, a disease-free survival (DFS) of 5.5 months and a median survival of <10 months [24, 29]. ES-SCLC is deemed uncurable and treatment is palliative in nature with a poor mOS of between 8 and 13 months and a 5-year survival rate of less than 5% [20, 22, 25]. Poor survival in a chemo-sensitive population is attributed to rapid drug resistance development and failure of the second line of treatment and subsequent therapies [29]. Quitting smoking has been related to a reduction in the incidence of the disease and the risk of mortality [24].

3.1.3 Burden of ES-SCLC on the patients' functioning and health-related quality of life.

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 [22]. Symptoms in patients with ES-SCLC that have a high impact on physical, social and emotional aspects include shortness of breath, fatigue, coughing, chest pain, nausea and vomiting.

In addition to the physical burden affecting social wellbeing, mental health is impacted substantially. Lack of treatment options and the inherently progressive nature of the disease leave patients feeling afraid of dying, with their only hope being the postponement of death [22].

3.2 Patient population

Pathology data in the Danish Lung Cancer Registry (DLCR) originate from the National Pathology Registry. The distribution between NSCLC and SCLC has over the years been constant; 80% is NSCLC, 14% is SCLC, and 6% is without a pathologic diagnosis [30].

A study by Green *et al.* [1] identified SCLC patients diagnosed in Denmark during 2006-2015 from the DLCR and found that during the study period, 6,353 patients were diagnosed with SCLC, with a mean age of 68.5 years and approximately 1:1 split of male and female. Overall, 68.2% of these 6,353 patients had ES-SCLC. Median survival was 6.2 months, and the 5-year survival was 2%.

Table 1 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark*	12.4%	12.2%	12.0%	11.6%	N/A
Prevalence in Denmark	615	618	616	595	N/A

* Of all lung cancer patients in Denmark; Source: [31]

The patient population relevant for this application covers the Hetronifly indication on SCLC: Hetronifly, in combination with carboplatin and etoposide, is indicated for the first line (1L) treatment of adult patients with ES-SCLC [32]. For the estimated number of patients eligible for treatment, see Table 2. ES-SCLC constitute around two thirds of all newly diagnosed SCLC patients.

Table 2 Estimated number of patients eligible for treatment

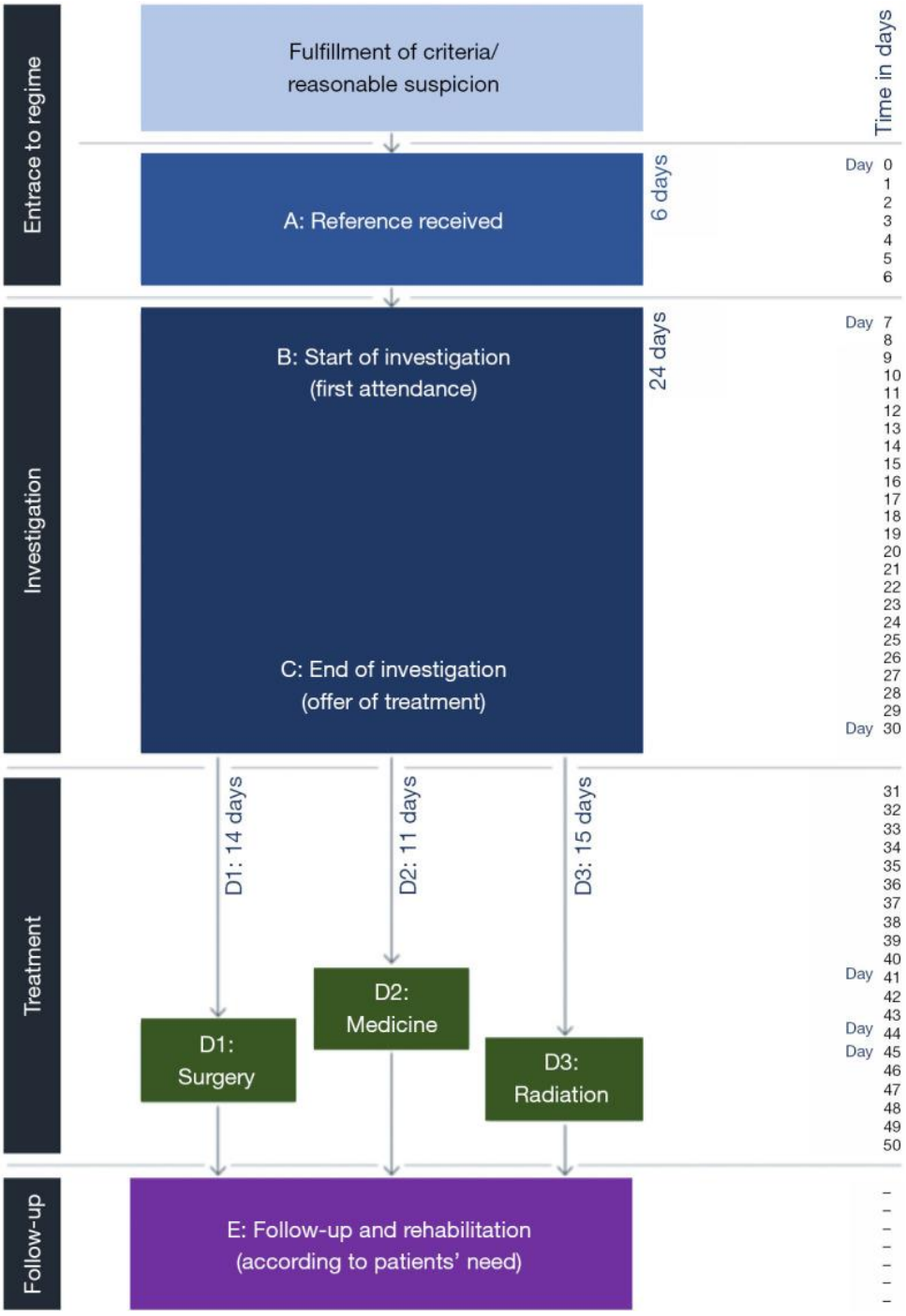
Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	160	160	160	160	160

3.3 Current treatment options

If a general practitioner suspects that a patient may have lung cancer, they should consider referral for a CT scan with contrast of the thorax and upper abdomen. If the patient meets certain criteria (malignancy suspect lung infiltrates or tumour in the mediastinum on diagnostic imaging, biopsy from a metastasis indicating primary lung cancer, clear symptoms of possible lung cancer, such as haemoptysis or shortness of breath for more than a week without any other explanation) then they must be referred

to the lung cancer algorithm, which covers investigation, treatment, and follow-up (Figure 2) [33, 34]

Figure 2. Specific regime for suspected lung cancer



Source: [32]

If ES-SCLC is suspected, referral is made to oncological (rather than surgical) treatment [35]. Investigation and treatment proceed in accordance with the Danish Lung Cancer Group's (DLCG) clinical guidelines. Before treatment is prescribed, there should be sufficient investigations to clarify final staging, which includes assessment of any spread to local and regional lymph nodes, as well as assessment for distant metastases. For patients with ES-SCLC, treatment is considered palliative (i.e., non-curative). The preferred first-line treatment for decades has been platinum ChT and is associated with significant side effects such as non-haematological toxicity (e.g., nausea, vomiting and renal toxicity) for cisplatin and myelosuppression for carboplatin [28]. Treatment with carboplatin is preferred over cisplatin due to shorter treatment duration and less non-haematological toxicity [36]. The two chemotherapy regimens are equally effective for the treatment of ES-SCLC, cf. a meta-analysis from 2012 [36, 37].

Since the most recent recommendations by DMC, new treatments have become available. The recommended palliative oncological treatment for ES-SCLC in Denmark is ChT with etoposide plus carboplatin (EpC) or etoposide monotherapy [38]. In the latest assessment of the PD-(L)1 inhibitors atezolizumab and durvalumab for 1L ES-SCLC, H2 2024, The Danish Medicines Council concluded that atezolizumab and durvalumab in combination with carboplatin and etoposide prolongs patients' survival rate and for some patients the survival after end of treatment compared with carboplatin and etoposide alone. As atezolizumab and durvalumab have obtained similar DMC assessment, this application solely compared serplulimab with the first approved product, i.e., atezolizumab [39]. In general, it is not expected that serplulimab will lead to changes in the treatment of patients.

3.3.1 Prognosis with current treatment

Survival of SCLC patients is poor, even with treatment, and many patients die before completing treatment. As described in Section 3.1.2, there is a high propensity for SCLC to spread to the brain, and it is not uncommon for disease to develop early resistance to ChT and RT [23, 24, 28].

Patients with ES-SCLC have, on average, a disease-free survival (DFS) of 5.5 months and a median survival of <10 months [24, 29]. ES-SCLC is deemed uncurable and treatment is palliative in nature with a poor mOS of between 8 and 13 months and a 5-year survival rate of less than 5% [22, 25, 40]. Death within 60 days from diagnosis, without completing treatment, has been reported for 31.1% of ES-SCLC patients [1].

Overall, the low screening program adoption rates, the lack of an early diagnosis, rapid development of resistance to ChT treatment, platinum ChT 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 those patients with ES-SCLC [40, 41].

Currently the PD-(L)1 inhibitors atezolizumab and durvalumab are available in combination with ChT (etopside and carboplatin or cisplatin) in Denmark for the treatment of ES-SCLC.

Treatment with atezolizumab and durvalumab showed to prolong survival of ES-SCLC patients compared to the use of ChT alone:

The clinical study of atezolizumab showed overall survival (OS) of 12.3 months, compared to 10.3 months with ChT alone, resulting in a gain of 2 months with treatment. HR 0.76 (0.60-0.95.) Progression free survival (PFS) was 5.2 months in the treatment arm, whereas the comparator had 4.3 months, resulting in a gain of 0.9 months with treatment. Hazard Ratio (HR) 0.77 (0.63-0.95) [42].

For durvalumab, the difference in median OS was small but statistically significant (12.9 vs. 10.5 months). The absolute difference in the 3-year survival rate was 11.8% points (17.6% vs. 5.8%). There was a small difference in median progression-free rate (PFS) in favor of the chemotherapy arm, but more patients were progression-free at 2 years in the durvalumab + ChT arm (11.0% vs. 2.9%), and the hazard ratio of 0.80 was statistically significant in favor of durvalumab + chemotherapy [36]

3.4 The intervention

Serplulimab is a humanized antibody (immunoglobulin G4 [IgG4]/kappa isotype with a stabilizing sequence alteration in the hinge region) produced in Chinese hamster ovary cells by recombinant deoxyribonucleic acid (DNA) technology. It is indicated in combination with EpC for the first-line treatment of adult patients with ES-SC.

In 2022, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) granted orphan drug designation for serplulimab (HLX10) for the treatment of patients with SCLC. Although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Hetronifly may be of potential significant benefit to those affected by the orphan condition still holds. Hetronifly showed a better overall survival outcome compared to atezolizumab and durvalumab. These results suggest that Hetronifly may offer a significant benefit in terms of efficacy, as demonstrated through indirect comparisons [43].

Table 3 Overview of Intervention

Overview of intervention	
Indication relevant for the assessment	Hetronifly (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).
ATMP	N/A
Method of administration	Serplulimab is administered intravenously.
Dosing	The recommended dose is 4.5 mg/kg body weight 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. Dose withholding for up to 12 weeks for tolerability is acceptable.
Dosing in the health economic model (including relative dose intensity)	Not applicable. 14 weeks process no need for Health Economics assessment
Should the medicine be administered with other medicines?	Yes, it is indicated for use in combination with carboplatin and etoposide [32].
Treatment duration / criteria for end of treatment	The treatment should continue until disease progression or unacceptable toxicity. Serplulimab should be withheld or discontinued to manage adverse reactions [32].
Necessary monitoring, both during administration and during the treatment period	Treatment must be initiated and supervised by a physician experienced in the treatment of cancer.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Not applicable. 14 weeks process no need for Health Economics assessment
Package size(s)	Hetronifly (serplulimab) will be available as 100 mg/10ml concentrate for solution for infusion.

3.4.1 Mechanism of action

Serplulimab (HLX10) is a humanized 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.

3.4.2 The intervention in relation to Danish clinical practice

Serplulimab significantly improves overall survival (OS) when combined with EpC compared with EpC alone among patients with previously untreated ES-SCLC [44] (see Section 6). Therefore, in Danish clinical practice, it is expected to be placed as first-line treatment for patients with ES-SCLC along with atezolizumab and durvalumab.

As described in Section 3.3. treatment for ES-SCLC is considered palliative, as this stage of disease is not eligible for curative treatment. The current palliative oncological treatment for ES-SCLC in Denmark is ChT with EpC or etoposide monotherapy according to the 2022 guidelines from Danske Multidisciplinære Cancer Gruppe [38]. The Danish

Medicines Council concluded in H2 2024 that atezolizumab and durvalumab in combination with carboplatin and etoposide will prolong patients' survival rate and for some patients the survival after end of treatment compared with carboplatin and etoposide alone [36, 42].

3.5 Choice of comparator(s)

As described in Section 3.3, the recommended palliative oncological treatment for ES-SCLC in Denmark is according to the recent evaluation of durvalumab and the re-evaluation of atezolizumab (for the first-line treatment of adults with ES-SCLC in combination with etoposide and either carboplatin or cisplatin), the comparators will be atezolizumab in combination with etoposide and either carboplatin or cisplatin. Atezolizumab has been chosen as the comparator as it was first and both products have received similar assessments.

Details on the pharmaceutical features of atezolizumab are shown below.

Table 4 Overview of comparator

Overview of comparator	Tecentriq (atezolizumab)
Generic name	atezolizumab
ATC code	L01FF05
Mechanism of action	PD-L1 inhibitor
Method of administration	Intravenous or subcutaneous
Dosing	Intravenous (1): Induction and maintenance phases: - 840 mg every 2 weeks or - 1 200 mg every 3 weeks or - 1 680 mg every 4 weeks. Atezolizumab should be administered first when given with other treatments on the same day.
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	In ES-SCLC, atezolizumab should be given in combination with carboplatin and etoposide.
Treatment duration/ criteria for end of treatment	Until disease progression or unmanageable toxicity. Treatment beyond disease progression may be considered at the discretion of the physician
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A

Overview of comparator	Tecentriq (atezolizumab)
Package size(s)	1 vial - 840 mg/14 mL for infusion 1 vial - 1200 mg/20 mL for infusion 1 vial - 1875 mg/15 mL for injection

3.6 Cost-effectiveness of the comparator(s)

Atezolizumab has been evaluated by the Danish Medicines Council. Treatment with atezolizumab in combination with chemotherapy is more expensive than platinum-based chemotherapy. However, the Medicines Council considers the costs to be reasonable in relation to the expected effect (the same was concluded by the Danish Medicines Council in their assessment of durvalumab with the same indication) [39, 45].

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Rationale for the efficacy outcomes

Long-term time-to-event outcomes were extrapolated based on individual patient data (IPD) from the ASTRUM-005 trial that compared serplulimab plus chemotherapy compared with placebo plus chemotherapy as first-line treatment in patients with extensive-stage SCLC [44].

Overall survival

OS is often considered the gold standard efficacy endpoint in oncology clinical trials. It measures the time from randomization or treatment initiation until death from any cause. For ES-SCLC, where the disease is advanced and often fatal, improving overall survival is a critical goal of therapy.

Progression-free survival

PFS measures the time from randomization or treatment initiation until disease progression or death from any cause. In ES-SCLC, where disease progression significantly impacts quality of life and treatment decisions, delaying disease progression is an important therapeutic goal.

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) [ASTRUM-005]	A period from randomization through death regardless of causality. At the time of the interim analysis (primary analysis) cut-off on 22 October 2021 when 66% OS events were observed (defined approximately 226, actual 246 OS events), patients had a median survival follow-up time of 12.3 months [44].	OS is defined as the time from randomization to death from any cause.	Kaplan–Meier methodology was used to estimate the probability of OS, as well as to calculate the median time from randomization to death (for OS) for each group, and the Brookmeyer and Crowley method was used to construct the 95% confidence interval (95% CI) for the medians. The hazard ratios (HR) and 95% CI for OS were estimated with the use of a stratified Cox regression model, with the same stratification factors that were used in the stratified logrank test
Progression-free survival (PFS) [ASTRUM-005]	At DCO (22 October 2021) for the primary analysis, the median follow-up time was 12.3 months [2]	PFS is defined as the time from randomisation to first disease progression or death from any cause.	Assessed both by an independent radiology review committee and by the investigators using version 1.1 of RECIST.

* Time point for data collection used in analysis (follow up time for time-to-event measures); DCO: Data cut-off

Validity of outcomes

OS is universally recognised as being unambiguous, unbiased, with a defined endpoint of paramount clinical relevance, and positive results that provide confirmatory evidence that a given treatment extends the life of a patient [46]. PFS is well-established and widely used as a clinical endpoint in randomised controlled trials for cancer therapies [38, 47].

4. Health economic analysis

Not applicable. 14 weeks process, no need for Health Economics assessment

4.1 Model structure

Not applicable. 14 weeks process, no need for Health Economics assessment

4.2 Model features

Table 6 Features of the economic model

Model features	Description	Justification
Not applicable. 14 weeks process no need for Health Economics assessment		

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was carried and aimed at identifying and synthesizing evidence on the clinical safety and efficacy of relevant treatments for untreated extensive-stage small-cell lung cancer (ES-SCLC) from randomised controlled trials and open-label extension studies. A complete description of the SLR can be found in Appendix H.

A summary of the studies identified in the SLR is outlined in Table 7. A total of 16 unique studies were identified. Four studies had multiple publications (JCOG1201 [48, 49], and the ASTRUM-005 [5, 8, 44, 49-51], CASPIAN [52-59] and IMpower133 [7, 9, 60, 61] studies). Regarding study design, all trials were RCTs, of which most trials (n=13) were phase 3, two were phase 2, and only one phase 2/3 ((Shimokawa et al., 2021 [48] and Shimokawa et al., 2023 [49]). Seven were open-label, and one was single-blinded (Quoix et al., 2005 [62]). Fifteen studies were two-arm, and one study was a three-arm trial (CASPIAN [52-59], Of note, Schmittel et al., 2006 [63] was the phase 2 trial preceding the Schmittel et al., 2011 ([49]) phase 3 trial.

All studies focused on untreated or chemo-naïve ES-SCLC patients only. The median sample size of the included studies was 347 patients, ranging from 70 (Schmittel et al., 2006 [63]) to 805 patients (CASPIAN [52-59]). The median age of patients ranged between 37 (Hanna et al., 2006 [64] and 80 years (Eckardt et al., 2007 [65], Schmittel et al., 2011 [66] and Kim et al., 2019 [67]. Two studies focused specifically on elderly patients with an average age of around 75 years old (Okamoto et al., 2007 [68], Shimokawa et al., 2023 [49].

Table 7 Relevant literature included in the assessment of efficacy and safety of serplulimab + EpC

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Cheng et al. 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. JAMA. 2022;328(12):1223-1232 [44]. Cheng et al. 8505: Serplulimab, a novel anti-PD-1 antibody, plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small cell lung cancer: An international randomized phase 3 study. American Society of Clinical Oncology. 2022 [44]. Cheng et al., 2022 (ESMO Asia) [50]. Cheng et al., 2024 (ASCO 2024) [8].	ASTRUM-005	NCT04063163	Start: 12/09/2019 Primary completion: 22/10/2022 Study completion: 12/2022 Data cut-off (interim analysis reported in (4)): 22/10/2021 Data cut-off updated analysis: 13/06/2022 Data cut-off: 13/06/2023	Serplulimab + EpC vs. EpC for patients with ES-SCLC
Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab plus	IMpower133	NCT02763579	Start: 07/06/2016	Atezolizumab combined with carboplatin and etoposide vs.

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018 Dec;379(23):2220–9 [9]. Nishio M, Sugawara S, Atagi S, Akamatsu H, Sakai H, Okamoto I, et al. Subgroup Analysis of Japanese Patients in a Phase III Study of Atezolizumab in Extensive-stage Small-cell Lung Cancer (IMpower133). Clin Lung Cancer. 2019;20(6):469-476.e1 [60]. Mansfield AS, Każarnowicz A, Karaseva N, Sánchez A, De Boer R, Andric Z, et al. Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial. Ann Oncol Off J Eur Soc Med Oncol. 2020;31(2):310–7 [61].			Primary completion date: 24/04/2018 Study completion date: 07/07/2022 Clinical cut-off date PFS: 04/04/2018 [7] Clinical cut-off date OS: 24/01/2019 [7]	carboplatin and etoposide for 1L ESSCLC

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Liu SV, Reck M, Mansfield AS, Mok T, Scherpereel A, Reinmuth N, et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients with Extensive-Stage Small-Cell Lung Cancer Treated with Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol. 2021;39(6):619–30 [7].				

Abbreviations NR: Not Reported

5.2 Literature used for the assessment of health-related quality of life

The addition of immunotherapy (durvalumab, atezolizumab, or serplulimab) to standard chemotherapy (ChT) in the treatment of ES-SCLC generally maintains or improves patient-reported outcomes without increasing the overall treatment burden. Amelioration in specific symptoms and prolonged time to deterioration in various HRQoL domains suggest that these combination therapies not only extend survival but also enhance the HRQoL for patients.

The main tools used for HRQoL assessment were EQ-5D, the Lung Cancer Symptom Scale, the FACT-L, the Symptom Scale and the European Organization for Research and the EORT QLQ.

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Chen et al; 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. American Society of Clinical Oncology; 2024 [8, 69]	First line ES-SCLC in real world setting	Section 10
Mansfield et al; Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial. Ann Oncol Off J Eur Soc Med Oncol. 2020 [61]	First line ES-SCLC in real world setting	Data not available

5.3 Literature used for inputs for the health economic model

Not applicable. 14 weeks process: no need for Health Economics assessment

Table 9 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Not applicable. 14 weeks process no need for Health Economics assessment			

6. Efficacy

Here the clinical efficacy of Hetronifly (serpliulimab) and the comparator Tecentriq (atezolilzumab) are presented

6.1 Relevant studies - Hetronifly (serplulimab) in combination with carboplatin and etoposide compared to placebo in combination with carboplatin and etoposide in 1L Extensive Stage Small Cell Lung Cancer

ASTRUM-005 an international double-blind, Phase 3 randomized clinical trial enrolled patients from 114 hospital sites in six countries (China, Georgia, Poland, Russia, Turkey, and Ukraine) from September 12, 2019, to April 27, 2021. The clinical value of serplulimab for the first-line treatment of ES-SCLC has been evaluated in this randomised, double-blind, placebo control, global Phase 3 trial.

The objective of the ASTRUM-005 clinical trial was to evaluate the efficacy and AE profile of the PD-1 inhibitor, serplulimab (formerly HLX10) and etoposide plus carboplatin (EpC), compared with placebo plus EpC in untreated ES-SCLC patients [70].

See Table 10 below for more details

Table 10 Overview of study design for ASTRUM-005

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
ASTRUM-005, NCT04063163 *Cheng et al. 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. JAMA. 2022;328(12):1223-1232. [5]*	International, double-blind, Phase 3 randomised clinical trial.	A period from randomization through death regardless of causality (approximately up to 24 months).	Patients were aged 18 years or older, had histologically or cytologically confirmed ES-SCLC, and had not previously received systemic therapy for ES-SCLC. Patients must have had 1 or more measurable lesions assessed using version 1.1 of the RECISST, an ECOG PS score of 0 or 1, adequate organ function, and a life expectancy of 12 weeks or longer.	Patients received 4.5 mg/kg of serplulimab via intravenous infusion every 3 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent, or other reasons specified in the trial protocol. 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 4 cycles via intravenous infusions. N=389	Patients received placebo via intravenous infusions every 3 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent, or other reasons specified in the trial protocol. 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 4 cycles via intravenous infusions. N=196	Primary endpoint: The primary endpoint was overall survival (OS) [Time Frame: A period from randomization through death regardless of causality (approximately up to 24 months).] Secondary endpoints: There were 13 secondary outcomes, including progression-free survival (PFS), objective response rate (ORR), and duration of response (all 3 were assessed both by an independent radiology review committee and by the investigators using version 1.1 of RECIST), adverse events, and the relationship between PD-L1 expression and efficacy.

6.2 Relevant studies - Tecentriq (atezolizumab) in combination with carboplatin and etoposide compared to placebo in combination with carboplatin and etoposide in 1L Extensive Stage Small Cell Lung Cancer

The IMpower133 study was a Phase III clinical trial that tested the combination of Tecentriq® (atezolizumab) with carboplatin and etoposide in patients with extensive-stage small cell lung cancer (ES-SCLC) who had not previously received chemotherapy. This randomized, double-blind, placebo-controlled trial was conducted at multiple sites across North America, Europe, and Asia. The study began in June 2016 and concluded in March 2018.

The objective of the IMpower133 study was to evaluate the efficacy and safety of Tecentriq (atezolizumab) in combination with carboplatin and etoposide as a first-line treatment for patients with extensive-stage small cell lung cancer (ES-SCLC). The study aimed to determine whether this combination could improve overall survival (OS) and progression-free survival (PFS) compared to the standard chemotherapy regimen alone [70].

See Table 11 below for more details

Table 11 Overview of study design for Impower133

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
IMpower133, NCT02763579 Liu et al. 2021 [7] Mansfield et al. 2020 [61] Nishio et al. 2019 [60] Horn et al. 2018 [9]	Randomized phase I/III, double-blind, placebo-control in combination with CP/ET 1:1	Four 21-days cycles followed by a maintenance phase until disease progression or unacceptable toxicity. Median follow up by Data cut of: Start: 07/06/2016 Primary completion date: 24/04/2018 Study completion date: 07/07/2022 Clinical cut-off date PFS: 04/04/2018 Clinical cut-off date OS: 24/01/2019	Eligible patients had histologically or cytologically confirmed chemotherapy naive ES-SCLC. Patients with treated asymptomatic brain metastases were eligible, and those with active or untreated CNS metastases were excluded from the study. Patients were stratified by sex, Eastern Cooperative Oncology Group performance status (0 v 1), and presence of brain metastases (yes / no) at enrollment.	Four 21-day cycles of CP/ET (CP: area under the curve of 5 mg/mL/min, intravenous [IV] on day 1 of each cycle; ET: 100 mg/m2 of body surface area, IV on days 1-3 of each cycle) plus IV atezolizumab 1,200 mg (atezolizumab plus CP/ET) on day 1 of each cycle (induction phase), followed by the same dose of IV atezolizumab during a maintenance phase until unacceptable toxicity or disease progression. Treatment beyond disease progression was allowed if patients experienced clinical benefit N=201	Four 21-day cycles of CP/ET (CP: area under the curve of 5 mg/mL/min, intravenous [IV] on day 1 of each cycle; ET: 100 mg/m2 of body surface area, IV on days 1-3 of each cycle) plus placebo (placebo plus CP/ET) on day 1 of each cycle (induction phase), followed by the same dose of placebo during a maintenance phase until unacceptable toxicity or disease progression. N=202	The two primary endpoints were overall survival (OS) and investigator assessed PFS per RECIST 1.1 in ITT population. Key secondary endpoints were investigator-assessed ORR per RECIST 1.1; DOR; and safety. Median follow up was 22.9 months for OS. Exploratory endpoints included assessment of efficacy based on PDL1 expression levels and bTMB as previously described [9].

6.3 Comparability of studies

Not relevant for comparisons based on head-to-head studies

6.4 Comparability of patients across studies

Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	ASTRUM-005 [5]		IMpower133 [9] [6]	
	serplulimab + EpC (n=389)	placebo + EpC (n=196)	atezolizumab + EpC (n=201)	Placebo+ EpC (n=202)
Age, median (range), years	63 (28-76)	62 (31-83)	64 (28-90)	64 (26-87)
Aged <65 years, N (%)	235 (60.4)	119 (60.7)	111 (55.2)	106 (52.5)
Male, N (%)	317 (81.5)	164 (83.7)	129 (64.2)	132 (65.3)
Race, N (%) [a]				
Asian	262 (67.4)	139 (70.9)	33 (16.4)	36 (17.8)
Non-Asian [b]	127 (32.6)	57 (29.1)	168 (83.6)	166 (82.3)
Baseline ECOG (eCRF)				
0 (fully active)	71 (18.3)	32 (16.3)	73 (36.3)	67 (33.2)
1 (restricted in physical activity but ambulatory)	318 (81.7)	164 (83.7)	128 (63.7)	135 (66.8)
Smoking history, N (%)				
Never	81 (20.8)	35 (17.9)	9(4.5)	3 (1.5)
Current	102 (26.2)	48 (24.5)	74 (36.8)	75 (37.1)
Former	206 (53.0)	113 (57.7)	118 (58.7)	124 (61.4)

	ASTRUM-005 [5]		IMpower133 [9] [6]	
	serplulimab + EpC (n=389)	placebo + EpC (n=196)	atezolizumab + EpC (n=201)	Placebo+ EpC (n=202)
Size of target lesions, median (range), mm in diameter [d]	117.7 (13.8-323.7)	120.5 (14.5-269.6)	113.0 (12.0-325.0)	105.5 (15.0-353.0)
Type of metastases, N (%)				
Brain	50 (12.9)	28 (14.3)	17 (8.5)	18 (8.9)
Liver	99 (25.4)	51 (26)	77 (38.3)	72 (35.6)
Programmed cell death ligand 1 expression level, No./total (%)				
Tumour proportion score <1% [e]	317/379 (83.6)	152/186 (81.7)	29/33 (87.9)	38/42 (90.5)
Tumour proportion score ≥1% [e]	62/379 (16.4)	34/186 (18.3)	28/42 (66.7)	41/51 (80.4)
Previous cancer treatment, N (%)				
Chemotherapy [f]	9 (2.3)	3 (1.5)	8 (4.0)	12 (5.9)
Other [g]	1 (0.3)	2 (1)	N/A	N/A

[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] Measured using computed tomography or magnetic resonance imaging.

[e] Not evaluable or no data for 20 patients (3.4%). This was mostly due to inappropriate sectioning or poor sample quality (insufficient evaluable cells).

[f] 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).

[8] Herbal or traditional Chinese medicine (2 in the placebo group) and the immunostimulant lentinan (1 in the serplulimab group).

6.5 Comparability of the study population(s) with Danish patients eligible for treatment

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population [1])	ASTRUM-005 [5]	Impower133 [7]	Value used in health economic model
Age (mean, years)	68.5	63	NR	N/A
Gender (Male, %)	50.8	81.5	64.2	N/A
Patient weight (kg)	NR	NR	NR	N/A
ES-SCLC, %	68.2	100	100	N/A
≥1 co-morbidity, %	37.1	NR	NR	N/A
ECOG PS, %				
0	NR	18.3	36.3	N/A
1	NR	81.7	63.7	N/A

Abbreviations: NR - not reported; LS-SCLC - Limited-stage small cell lung carcinoma; ES-SCLC - Extended-stage small cell lung carcinoma; ECOG - Eastern Cooperative Oncology Group; PS - performance status

6.6 Efficacy – results for ASTRUM-005

The ASTRUM-005 trial is a randomized, double-blind, international, multicenter, phase 3 study. It enrolled 585 patients with extensive-stage small cell lung cancer (ES-SCLC) who had not previously received systemic therapy [5]. In the intention-to-treat population, patients treated with serplulimab plus chemotherapy showed a significant improvement in overall survival compared to those receiving placebo plus chemotherapy. The median overall survival was 15.4 months for the serplulimab group versus 10.9 months for the placebo group (hazard ratio, 0.63; 95% CI, 0.49-0.82; P < 0.001). The estimated overall survival rate at 1 year was 60.7% (95% CI, 54.9%-66.0%) in the serplulimab group compared with 47.8% (95% CI, 39.6%-55.6%) in the placebo group. The estimated overall survival rate at 2 years was 43.1% (95% CI, 34.1%-51.7%) in the serplulimab group compared with 7.9% (95% CI, 0.7%-27.2%) in the placebo group (Data cut-off date: 22.10.2021) [5].

A publication from 2024 confirmed the significant improvement in overall survival for patients treated with serplulimab plus chemotherapy: The median overall survival was

15.8 months for the serplulimab group versus 11.1 months for the placebo group (hazard ratio, 0.61; 95% CI, 0.50-0.74; P < 0.001) (Data cut-off date: 13.06.2023) [8].

In the interim analysis, the median PFS remained consistent with earlier results, showing 5.7 months for the serplulimab group compared with 4.3 months for the placebo group (hazard ratio, 0.48; 95% CI, 0.38-0.59) (Data cut-off date: 22.10.2021) [5].

The updated analysis based on the 13.06.2022 data cut-off presented in the EPAR, showed a independent radiology review committee (IRRC) median progression-free survival of 5.8 months (95% CI, 5.5-6.9 months) in the serplulimab group compared with 5.0 months (95% CI, 4.2-4.5 months) in the placebo group (HR, 0.47 [95% CI, 0.38-0.58]. Respective median OS was 15.8 months (95% CI, 14.1-17.6 months) compared with 11.1 months (95% CI, 10.0-12.4 months) (HR, 0.61 [95% CI, 0.50-0.74] [2].

6.7 Efficacy – results for IMpower133

IMpower133 is a randomized, double-blind, phase I/III study, that demonstrated that adding atezolizumab to carboplatin plus etoposide (CP/ET) for 1L treatment of ES-SCLC resulted in significant improvement in OS and PFS versus placebo plus CP/ET. The two primary endpoints, investigator-assessed PFS and OS, were statistically significant at the interim analysis. Updated OS and PFS were conducted in the updated analysis by Liu et al [7]. Clinical cut-off date (CCOD) for OS and PFS were 24.01.2019 and 24.04.2018, respectively.

The median OS was 12.3 months (95% CI, 10.8 to 15.8) in the atezolizumab plus CP/ET arm and 10.3 months (95% CI, 9.3 to 11.3) in the placebo plus CP/ET arm (HR, 0.76; 95% CI, 0.60 to 0.95). OS at 12 months demonstrated a survival increase of 12.9% in the atezolizumab plus CP/ET arm (51.9%) compared with the placebo plus CP/ET arm (39.0%). Similarly, at 18 months, 13.0% more patients were alive in the atezolizumab plus CP/ET arm (34.0%) than with placebo plus CP/ET (21.0%). Consistent with results observed at the primary analysis of IMpower133, the addition of atezolizumab was associated with consistent OS benefit across the majority of subgroups. At the updated analysis, confirmed ORRs in the intention to treat (ITT) population were 60.2% in the atezolizumab plus CP/ET arm (95% CI, 53.1 to 67.0) versus 64.4% (95% CI, 57.3 to 71.0; descriptive P 5 .3839) in the placebo plus CP/ET arm. The median DOR was 4.2 months (95% CI, 4.1 to 4.5) in the atezolizumab plus CP/ET arm versus 3.9 months (95% CI, 3.1 to 4.2) in the placebo plus CP/ET arm (HR, 0.67; 95% CI, 0.51 to 0.88; descriptive P 5 .0037).

At the updated analysis, 181 patients (90.0%) in the atezolizumab plus CP/ET arm and 194 patients (96.0%) in the placebo plus CP/ET arm had RECIST-defined disease progression. Median PFS in the ITT population at the updated analysis was 5.2 months (95% CI, 4.4 to 5.6) in the atezolizumab plus CP/ET arm and 4.3 months (95% CI, 4.2 to 4.5) in the placebo plus CP/ET arm (HR, 0.77; 95% CI, 0.62 to 0.96). Disease progression occurred with the following patterns in the atezolizumab plus CP/ET and placebo plus CP/ET arms, respectively: 57.7% and 64.9% at existing lesions, 42.8% and 49.0% at new lesions, and 20.9% and 28.2% at both new and existing lesions [7].

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

The relevant outcomes of interest were:

- PFS relative effect as Hazard Ratio (HR)
- OS relative effect as HR

The outcomes' definitions are described in Section 3.7. The endpoints well-defined and golden standard endpoints within oncologic research [46]. All outcomes are measured relatively objectively during clinical studies and hence the risk of bias is not expected to vary much within studies. No systematic differences in their definition are expected between studies, see Table 14.

Table 14 (added): Study outcome definitions and differences

Trial	PFS Definition [71]	OS Definition [71]
ASTRUM-005 (NCT04063163) (19–22)	Progression free survival (PFS) was assessed by the independent radiological review committee (IRRC) using RECIST v1.1 guidelines	Time from the date of randomization to the date of death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive
IMpower133 (NCT03043872) (23–26)		
Differences between studies [71]		
ASTRUM-005	Subjects with no reported PD and initiate non-protocol specified antitumor therapy were censored on the day of their last evaluable tumor assessment prior to initiation of non-protocol specified antitumor therapy. Tumor assessment every 6 weeks	No differences
IMpower133	No censoring for subjects who initiated non-protocol specified anticancer therapy. Tumor assessments every 6 weeks.	

7.1.2 Method of synthesis

[redacted]

7.1.3 Results from the comparative analysis

Table 15 Results from the comparative analysis of Hetronifly (serplulimab) in combination with carboplatin and etoposide vs. Tecentriq (atezolizumab) in combination with carboplatin and etoposide for 1L ES-SCLC

Outcome measure	Hetronifly (serplulimab) + EpC (N=389)	Tecentriq (atezolizumab) + EpC (N=201)	Result***
Median PFS, months (95% CI), **	5.8 vs. 5.0	5.2 vs 4.3	NR
HR (95% CI)	HR: 0.47 (0.38-0.58)	HR: 0.77 (0.62-0.96)	HR: 0.61 (0.46, 0.82)
[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI) *	15.8 vs. 11.1	12.3 vs 10.3	NR
HR (95% CI)	HR: 0.62 (0.496-0.763)	HR: 0.70 (0.54-0.91	HR: 0.88 (0.63, 1.23)
[redacted]	[redacted]	[redacted]	[redacted]

Source: Accord [71]; PFS & OS: [2]

Abbreviations: NR: Not Reported; PtE: Platinum + Etoposide EpC: Etoposide and Carboplatin; Notes: (1) HR<1 represents a risk reduction when treated with Serplulimab+PtE; (2) OR>1 represents higher odds of response when treated with Serplulimab+PtE

* DCO: 12.06.2022; ** DCO: 24. Apr 2018; *** Based on an anchored Bucher indirect treatment comparison. The reference is Atezolizumab + Chemotherapy

The NMA comparisons suggest that serplulimab+PtE provides benefits in terms of PFS, and OS compared to atezolizumab+ EpC [3].

ESMO has given serplulimab the score 4 out of 5 in the ESMO-Magnitude of Clinical benefits score in the non-curative setting. Atezolizumab and durvalumab did both get 3/5 on the same scale. For non-curative indications 5 is the highest possible grade with 4 also to be considered to trigger rapid consideration for reimbursement [72].

7.1.4 Efficacy – results per PFS

The PFS HRs indicate benefits of serplulimab+PtE, with the probabilities of being superior to atezolizumab+PtE being particularly notable. The HR against atezolizumab in the base model is 0.61 (95% CI 0.46, 0.82). These findings suggest that serplulimab+PtE effectively prolongs the time patients live without disease progression, making it a promising option in the therapeutic landscape [71].

7.1.5 Efficacy – results per OS

The OS data also favours serplulimab+PtE, although with less pronounced magnitude of the effect compared to PFS. The HRs against atezolizumab+PtE are lower, indicating a reduction in mortality risk. The base model shows an HR of 0.88 (95% CI 0.63-1.23) against atezolizumab+PtE. The result emphasizes the potential of serplulimab+PtE to improve overall survival outcomes, although the statistical certainty is somewhat lower compared to PFS [71].

7.1.6 Efficacy – Summary

In summary, serplulimab+PtE demonstrates substantial benefits in terms of PFS, with consistent reductions in disease progression risk and higher response rates compared to multiple standard treatments. The improvement in OS, while evident, is less certain but still suggests a positive impact on survival. These findings suggest that while serplulimab+PtE is a promising therapeutic option, particularly in enhancing PFS, its use must be carefully weighed against the potential for significant adverse events. Further studies and real-world data are needed to optimize patient selection and management strategies to maximize the clinical benefit of serplulimab+PtE [71].

8. Modelling of efficacy in the health economic analysis

Not applicable. 14 weeks process - no need for Health Economics assessment

8.1 Presentation of efficacy data from the clinical documentation used in the model

Not applicable. 14 weeks process - no need for Health Economics assessment

8.1.1 Extrapolation of efficacy data

Not applicable. 14 weeks process - no need for Health Economics assessment

Table 16 Summary of assumptions associated with extrapolation of effects

Method/approach	Description/assumption
Not applicable. 14 weeks process - no need for Health Economics assessment	

8.1.2 Calculation of transition probabilities

Table 17 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Not applicable. 14 weeks process no need for Health Economics assessment			

8.2 Presentation of efficacy data from additional documentation

Not applicable. 14 weeks process - no need for Health Economics assessment

8.3 Modelling effects of subsequent treatments

Not applicable. 14 weeks process - no need for Health Economics assessment

8.4 Other assumptions regarding efficacy in the model

Not applicable. 14 weeks process - no need for Health Economics assessment

8.5 Overview of modelled average treatment length and time in model health state

Not applicable. 14 weeks process - no need for Health Economics assessment

Table 18 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Not applicable. 14 weeks process no need for Health Economics assessment			

Table 19 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
Not applicable. 14 weeks process - no need for Health Economic assessment			

9. Safety

9.1 Safety data from the clinical documentation

9.1.1 ASTRUM-005

The safety population consists of data from ASTRUM-005 comparing Hetronifly (serplulimab) in combination with carboplatin and etoposide compared with carboplatin and etoposide, as presented in the Table 20 below. Additional safety data will be presented in text after the table. Safety data from the ASTRUM-005 originates from the initial pivotal study as shown in the EPAR [2] using data with cut-off date 13 Jun 2023 and Cheng et al., 2024 [8].

In ASTRUM-005, the median duration of treatment exposure was 22.00 weeks (Q1-Q3, 15.14 - 43.00 weeks) in the serplulimab arm compared with 16.43 weeks (Q1-Q3, 10.93-25.07 weeks) in the placebo arm [70].

Table 20 Overview of safety events. Summary of Treatment-Emergent Adverse Events (TEAEs) (DCO 13.06.2023)

	Serplulimab + EpC (N=389) EPAR [2]	Placebo + EpC (N=196) EPAR [2]	Difference, % (95 % CI)
Number of adverse events, n	NR	NR	NR
Number and proportion of patients with ≥1 adverse events, n (%)	375 (96.4)	192 (98.0)	1.6 (NA)
Number of serious adverse events*, n	NR	NR	NR

	Serplulimab + EpC (N=389) EPAR [2]	Placebo + EpC (N=196) EPAR [2]	Difference, % (95 % CI)
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	152 (39.1)	77 (39.3)	0.2 (NA)
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	329 (84.6)	163 (83.2)	1.4 (NA)
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	368 (94.6)	NR	NR
Number and proportion of patients who had a dose reduction, n (%)**	NR	NR	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	312 (80.2)	184 (93.9)	13.7 (NR)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	38 (9.8)	19 (9.7)	0.1 (NA)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). ** reported as treatment-related AEs

§ CTCAE v. 5.0 must be used if available.

Abbreviations: NR – Not Reported

As of the data cut-off date 13.06.2023, 89 (15.2%) subjects completed the study, 496 (84.8%) subjects 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%). The incidence of Grade ≥ 3 TEAEs was comparable between the groups. Grade ≥ 3 TEAEs with incidence ≥ 20% (in the HLX10 group) by preferred term (PT) were neutrophil count decreased (HLX10 group vs placebo group: 42.9% vs 40.3%), white blood cell counts decreased (24.4% vs 25.0%), and neutropenia (23.4% vs 20.9%).

In ASTRUM-020 the safety of serplulimab demonstrated a manageable profile with no safety signals noted by the investigators, and the number of grade ≥3 TRAEs were similar across both arms (35.2% vs. 32.4% in the serplulimab and placebo arms, respectively) [73].

Table 21 Serious adverse events (Data cut-off date May 7, 2024) from Astrum 005

Adverse events	Serplulimab + EpC (N=389)		Placebo + EpC (N=196)	
	Number of patients with serious adverse events	Number of adverse events	Number of patients with serious adverse events	Number of adverse events
Adverse event, n (%)	155 (39.1%)	N/A	77 (39.3%)	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Table 22 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Not applicable. 14 weeks process - no need for Health Economics assessment				

9.1.2 IMpower133

The safety population consists of patients with ES-SCLC from IMpower133. The safety data from IMpower133, is available in Table 23. In IMpower133, the median duration of treatment was 4.7 months with Tecentriq (atezolizumab) and 4.1 months with placebo.

Table 23 Overview of safety events in studies Impower133

	Atezolizumab + EpC (N=198) Horn et al. [9]	Placebo + EpC (N=196) Horn et al. [9]	Difference, % (95 % CI)
Number of adverse events, n	2291	1919	372 (N/A)
Number and proportion of patients with ≥1 adverse events, n (%)	198 (100)	189 (96.4)	3.6 (NA)
Number of serious adverse events*, n	74 (37.4)	68 (34.7)	2.7 (N/A)
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	45 (22.7)	37 (18.9)	3.8 (NA)
Number of CTCAE grade ≥ 3 events, n	137 (69.2)	136 (69.4)	0.2 (N/A)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	115 (58.1)	113 (57.6)	0.5 (NA)
Number of adverse reactions, n	188 (94.9)	181 (92.3)	2.6 (N/A)
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NR	NR	
Number and proportion of patients who had a dose reduction, n (%)**	NR	NR	
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NR	NR	
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	22 (11.1)	6 (3.1)	8 (NA)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). ** reported as treatment-related AEs ***Multiple occurrences of the same AE in one patient were counted once as the highest grade for the preferred term § CTCAE v. 5.0 must be used if available.
Abbreviations: NR – Not Reported

9.1.3 Descriptive comparison of safety

The selected AEs were among the most commonly reported throughout the studies, particularly focusing on the most frequently occurring Grade 3 and 4 hematologic AEs. The most common grade 3/4 adverse events reported across the studies is shown in Table 24. For a complete list see Appendix E.

The ASTRUM-005 [5, 8, 50, 51] and IMpower133 [7, 9, 60, 61] trials all reported compiled Grade 3 and 4 AEs, with frequently occurring AEs specifically being decreased neutrophil count, decreased platelet count, and decreased white blood cell count.

Mansfield et al., 2020 [61], as part of the IMpower133 trial [7, 9, 60, 61], reported Grade 3 and 4 AEs in both the induction and maintenance phases. In the atezolizumab arm, 124 [74] and 43 [9] AEs were reported in the induction and maintenance phases, respectively, while in the Placebo arm, 114 (58%) and 37 (23%) AEs were reported in the same phases, respectively.

Table 24 Adverse Events - Grade 3/4

Author, Year	Arm	Decreased neutrophil count, n (%)	decreased white blood cell count, n (%)	Decreased platelet count, n (%)	Anemia, n (%)	Neutropenia, n (%)	Leukopenia, n (%)	trombocytopenia, n (%)	Diarrhea n (%)
ASTRUM-005 [44] [1]	serpluli mab + EP	56 (14.4)	33 (8.5)	20 (6.2)	21 (5.4)	17 (4.4)	10 (2.6)	NR	NR
	EP	27 (13.8)	17 (8.7)	16 (8.2)	11 (5.6)	9 (4.6)	4 (2.0)	NR	NR
IMpower133 [9] [2]	atezoliz umab + EP	28 (14.1)	6 (3.0)	7 (3.5)	28 (14.1)	45 (22.7)	10 (5.1)	20 (10.1)	4 (2.0)

	EP	33 (16.8)	9 (4.6)	7 (3.6)	24 (12.2)	48 (24.5)	8 (4.1)	15 (7.7)	1 (0.5)

Notes: [1] ASTRUM-005 trial reported AEs Grade ≥ 3; any grade 5 AEs were not individually reported; [2]Results above for IMpower133 trial are based on Horn et al., 2018 [9]. Liu et al., 2021 [7] presents updated results on Grade 3/4 AEs: Arm 1: 134 (67.7); Arm 2: 124 (63.3).

Grade 3 and above Adverse events

As shown in Table 25, IMpower133 [9] and ASTRUM-005 [50] graded AEs according to National Cancer Institute Common Terminology Criteria (NCI CTCAE) version 4.0 IMpower133 [7, 9, 60, 61] or version 5.0 (ASTRUM-005 [5, 8, 50, 51].

Grade 3 is defined as severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living (ADL); Grade 4 is defined as life-threatening consequences or urgent intervention indication; Grade 5 is defined as AE related death.

Table 25 Grade 3 and above adverse events

Author, Year	Intervention / Comparator	Trial arm size	Exposed to treatment	Grade ≥3 AEs N of patients	Grade ≥3 AEs (%)
ASTRUM-005	serplulimab. + EpC	389	389	129	33.2
(NCT04063163) [50]	EP	196	196	54	27.6
IMpower133	atezolizumab + EpC	201	198	115	58.1
(NCT03043872) [9]	EP	202	196	113	57.7

Notes: Includes grade 3, grade 4 and grade 5 | Abbreviations: AE: Adverse Events; EpC: Etoposide + Carboplatin

Discontinuation due to AEs

Discontinuation of treatment due to adverse events was as illustrated in Table 26.

Table 26 Discontinuation rate due to AEs

Author, Year	Arm	Discontinuation rate (%)
ASTRUM-005 [44]	serplulimab. + etoposide + carboplatin	8.0%

	etoposide + carboplatin	7.7%
IMpower133 [7]	atezolizumab + etoposide + carboplatin	11.9%
	etoposide + carboplatin	3.0%

References for ICI studies: ASTRUM-005 1-year data (Cheng et al., 2022 [44]), IMpower133 1-year data (Liu et al., 2021 [7])

9.2 Safety data from external literature applied in the health economic model

Not applicable. 14 weeks process no need for Health Economics assessment

Table 27 Adverse events that appear in more than X % of patients

Adverse events	serplulimab. + EpC			atezolizumab + EpC			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	Not applicable. 14 weeks process no need for Health Economics assessment							

10. Documentation of health-related quality of life (HRQoL)

According to the DMC guidelines, HRQoL must be based on the generic measuring instruments EQ-5D-5L [75]. The ASTRUM 005 trial [8, 50] assessed QoL using this instrument for the intervention. Analogously this was the case for Tecentriq were the IMpower133 trial collected EQ-5D data[61]. Therefore, this section will focus on the EQ-5D-5L data derived from these trials

Table 28 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
ASTRUM 005 Trial		
EQ-5D-5L	ASTRUM-005 [8, 50]	The EQ-5D-5L data collected in the Astrum clinical study, Mapped to EQ-5D-3L.
IMpower 133 Trial		
EQ-5D-3L	Impower 133 [61]	Used to derive the HSUVs – **Data not available (not published)**

Abbreviations: EQ-5D-5L: EuroQol 5 Dimensions 5 Level

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The ASTRUM-005 trial included the EQ-5D-5L questionnaire, which was completed by patients at each scheduled study visit (Cheng et al. 2022). The EQ-5D is a standardised measure of self-reported health, developed by the EuroQol Group. There are 5 dimensions or domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. In the 5-level version of the questionnaire, there are 5 possible levels of response that a subject can give for each dimension: no, mild, moderate, severe and severe/unable to.

An EQ-5D profiles can be converted to health state utilities using country-specific value sets that are reflective of the country of interest. The maximum health states utility value is 1, with represent “full health”. A value of 0 corresponds to quality of life equivalent to being dead, and negative values are possible with represent a quality of life worse than death.

Utility values used for this analysis were derived according to NICE guidelines: NICE does not recommend using the EQ-5D-5L value set directly, instead, the EQ-5D-5L was mapped onto the EQ-5D-3L. The use of EQ-5D-3L data is based on concerns concerning

the reliability and quality of the 5L value set in the latest position statement on use of the EQ-5D-5L value set for England [76].

Management of missing data.

Missing scores were not imputed, but treated as random. Patients with no baseline assessment or post-baseline assessments were censored at the date of randomization.

Accounting for differences in baseline utility between treatment groups

The model was adjusted for baseline EQ-5D values and "proximity of death" with a random intercept for subject**.** The analyses take into consideration the health state each patient is in at each observation, not assigned treatment group.

10.1.2 Data collection

In total, 585 patients completed the EQ-5D-5L at baseline. In total, 3,378 measurements were collected within the ASTRUM-005 study.

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

Table 29 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
[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]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[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]
[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]
[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]

Source: [77, 78]

Notes: Completion: HRQoL analysis population as the denominator, defined as treated patients and with >=1 assessment completed at baseline or post-baseline. Data cut-off date: 13.06.2022

10.1.3 HRQoL results

The EQ-5D index increased after baseline in both arms. By week 18, ~40% of patients in the placebo arm had a measurement of EQ-5D, compared to ~60% in the serplulimab arm.

At baseline, 22% of patients in the ASTRUM-005 study reported perfect health, i.e. a '11111' EQ-5D profile. This is likely a reflection of the geographical distribution of patients in the ASTRUM-005 study, where 68% of patients were based in China, which is among the countries with the lowest proportion reporting of problems in the five EQ-5D dimensions [79].

Serplulimab combined with EpC does not compromise patients' HRQoL as a first-line treatment in ES-SCLC compared with EpC alone [8]. The analysis of Least square mean (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. Interestingly, 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 to -1.15), with a p-value of 0.0170 [8].

The mean (SD) change from baseline to end of treatment was -2.9 (18.47), n: 205 for the serplulimab arm and -1.2 (18.51), n:124 in the placebo arm [2].

Table 30 HRQoL [EQ-5D] Summary statistics

	Serplulimab + EpC, [77]		Placebo + EpC, [77]		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[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]

	Serplulimab + EpC, [77]		Placebo + EpC, [77]		Intervention vs. comparator
[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]
[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]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

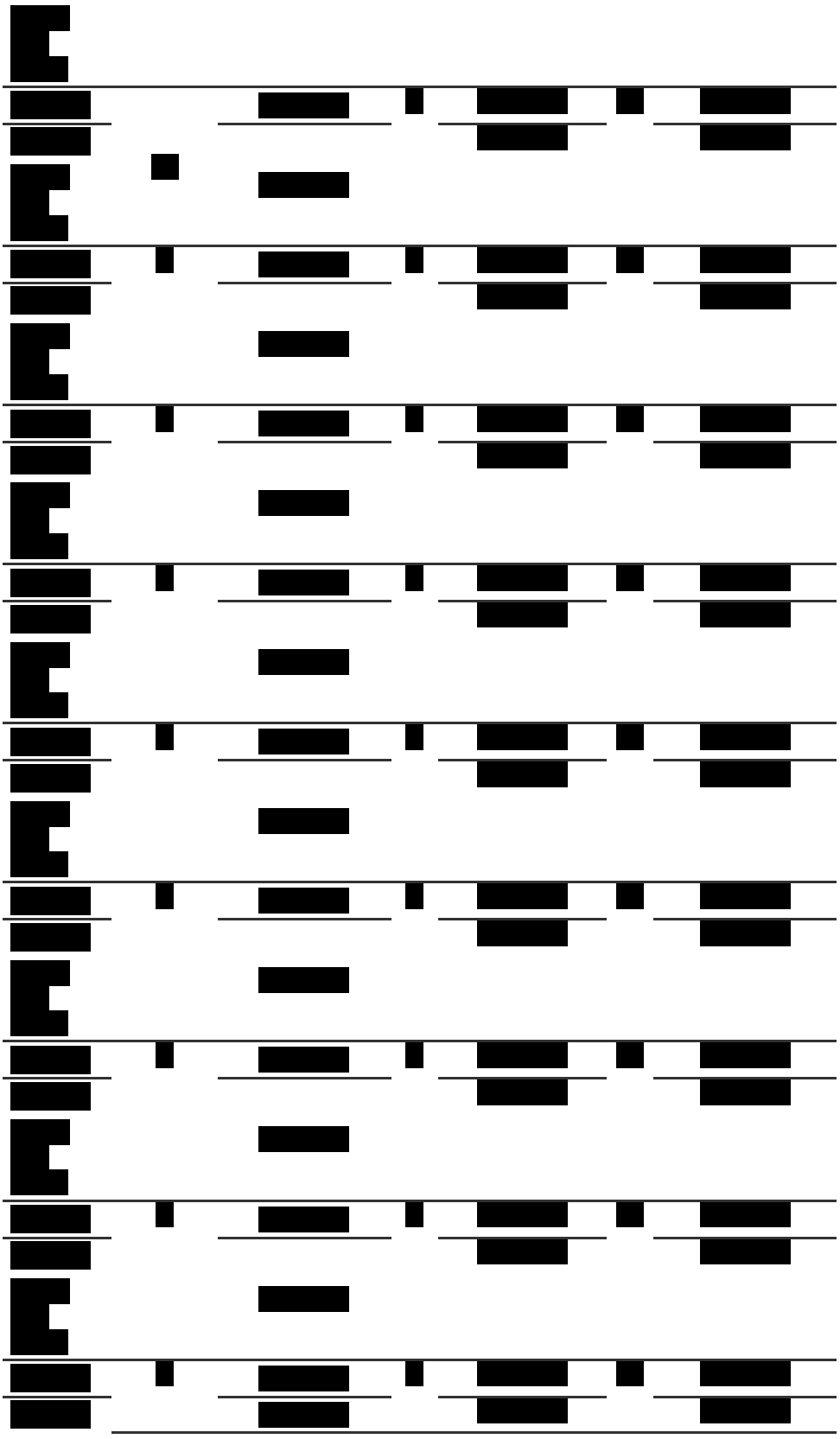
	Serplulimab + EpC, [77]		Placebo + EpC, [77]		Intervention vs. comparator
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Source: [77]; Data cut-off date: 13.06.2022

EQ5D-5L VAS scores were also collected [69] and reported in Table 31 below.

Table 31 EQ-5D-5L VAS Score and Index Value Change from Baseline by Visit – ITT set

Visit	Serplulimab + EpC, [71]		Placebo + EpC, [71]		Total	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
[redacted]						



Note: Baseline was defined as the last available pre-treatment assessment; Data cut-off date: 13.06.2022

10.2 Health state utility values (HSUVs) used in the health economic model

Not applicable. 14 weeks process no need for Health Economics assessment

10.2.1 HSUV calculation

Not applicable. 14 weeks process no need for Health Economics assessment

10.2.1.1 Mapping

Not applicable. 14 weeks process no need for Health Economics assessment

10.2.2 Disutility calculation

Not applicable. 14 weeks process no need for Health Economics assessment

10.2.3 HSUV results

Not applicable. 14 weeks process no need for Health Economics assessment

Table 32 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable. 14 weeks process no need for Health Economics assessment				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable. 14 weeks process no need for Health Economics assessment

10.3.1 Study design

Not applicable. 14 weeks process no need for Health Economics assessment

10.3.2 Data collection

Not applicable. 14 weeks process no need for Health Economics assessment

10.3.3 HRQoL Results

Not applicable. 14 weeks process no need for Health Economics assessment

10.3.4 HSUV and disutility results

Not applicable. 14 weeks process no need for Health Economics assessment

Table 33 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable. 14 weeks process no need for Health Economics assessment				

Table 34 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable. 14 weeks process no need for Health Economics assessment				

11. Resource use and associated costs

Not applicable. 14 weeks process no need for Health Economics assessment

11.1 Medicines - intervention and comparator

Not applicable. 14 weeks process no need for Health Economics assessment

Table 35 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Not applicable. 14 weeks process no need for Health Economics assessment				

11.2 Medicines– co-administration

- Not applicable. 14 weeks process no need for Health Economics assessment

11.3 Administration costs

Not applicable. 14 weeks process no need for Health Economics assessment

Table 36 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Not applicable. 14 weeks process no need for Health Economics assessment				

11.4 Disease management costs

Not applicable. 14 weeks process no need for Health Economics assessment

Table 37 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Not applicable. 14 weeks process no need for Health Economics assessment				

11.5 Costs associated with management of adverse events

Not applicable. 14 weeks process no need for Health Economics assessment

Table 38 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Not applicable. 14 weeks process no need for Health Economics assessment		

11.6 Subsequent treatment costs

Not applicable. 14 weeks process no need for Health Economics assessment

Table 39 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Not applicable. 14 weeks process no need for Health Economics assessment				

11.7 Patient costs

Not applicable. 14 weeks process no need for Health Economics assessment

Table 40 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Not applicable. 14 weeks process no need for Health Economics assessment	

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable. 14 weeks process no need for Health Economics assessment.

12. Results

Not applicable. 14 weeks process no need for Health Economics assessment

12.1 Base case overview

Not applicable. 14 weeks process no need for Health Economics assessment

Table 41 Base case overview

Feature	Description
Not applicable. 14 weeks process no need for Health Economics assessment	

12.1.1 Base case results

Not applicable. 14 weeks process no need for Health Economics assessment

Table 42 Base case results, discounted estimates

	[Intervention]	[Comparator]	Difference
Not applicable. 14 weeks process no need for Health Economics assessment			

12.2 Sensitivity analyses

[Not applicable. 14 weeks process no need for Health Economics assessment

12.2.1 Deterministic sensitivity analyses

Not applicable. 14 weeks process no need for Health Economics assessment

Table 43 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Not applicable. 14 weeks process no need for Health Economics assessment					

12.2.2 Probabilistic sensitivity analyses

Not applicable. 14 weeks process no need for Health Economics assessment.

13. Budget impact analysis

Not applicable. 14 weeks process no need for Health Economics assessment

Number of patients (including assumptions of market share)

Table 44 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
Not applicable. 14 weeks process no need for Health Economics assessment					

Budget impact

Table 45 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Not applicable. 14 weeks process no need for Health Economics assessment					

14. List of experts

As no health economic analysis was performed, no experts were interviewed for this application

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Appendix A. Main characteristics of studies included

Table 46 Main characteristic of studies included – ASTRUM-005

Trial name: ASTRUM-005	NCT number: NCT04063163
Objective	To evaluate the efficacy and adverse event profile of the PD-1 inhibitor serplulimab plus chemotherapy compared with placebo plus chemotherapy as first-line treatment in patients with extensive-stage SCLC.
Publications – title, author, journal, year	Cheng et al. 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. JAMA. 2022;328(12):1223-1232. [5] Cheng et al. Abstract #8505: Serplulimab, a novel anti-PD-1 antibody, plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small cell lung cancer: An international randomized phase 3 study. American Society of Clinical Oncology. 2022 [51] Cheng et al. ASTRUM-005: Updated results of first-line serplulimab versus placebo combined with chemotherapy in extensive-stage small-cell lung cancer, an international, multicentre, phase 3 study. ESMO Asia 2022 [50] Cheng et al. Abstract #8100: 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 for the international phase 3 ASTRUM-005 study. ASCO Annual Meeting 2024 [8]
Study type and design	International, double-blind, Phase 3 randomised clinical trial.
Sample size (n)	585
Main inclusion criteria	Patients were aged 18 years or older, had histologically or cytologically confirmed ES-SCLC according to the Veterans Administration Lung Study Group staging system, and had not previously received systemic therapy for ES-SCLC. Patients must have had 1 or more measurable lesions assessed using version 1.1 of the RECISST, an ECOG PS score of 0 or 1, adequate organ function, and a life expectancy of 12 weeks or longer. Patients with asymptomatic and stable brain metastases were included (patients were considered to have stable brain metastases if there was

Trial name: ASTRUM-005	NCT number: NCT04063163
	no evidence of new or enlarging brain metastases for ≥2 months as confirmed by 2 radiological examinations at least 4 weeks apart after treatment and if patients had discontinued steroid use 3 days prior to study drug administration)
Main exclusion criteria	Key exclusion criteria included mixed-stage SCLC, active central nervous system metastases or carcinomatous meningitis, and autoimmune diseases.
Intervention	Patients received 4.5 mg/kg of serplulimab via intravenous infusion every 3 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent, or other reasons specified in the trial protocol. 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 4 cycles via intravenous infusions. N=389
Comparator(s)	Patients received placebo via intravenous infusions every 3 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent, or other reasons specified in the trial protocol. 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 4 cycles via intravenous infusions. N=196
Follow-up time	Median follow-up at first data-cut (October 22, 2021): 12.3 months Median follow-up at second data-cut (June 13, 2022): 19.8 months Median follow-up at final data-cut (June, 2023): 31.6 months
Is the study used in the health economic model?	Not applicable. 14 weeks process no need for Health Economics assessment
Primary, secondary and exploratory endpoints	**Primary endpoint:** The primary endpoint was overall survival [Time Frame: A period from randomization through death regardless of causality (approximately up to 24 months).] **Secondary endpoints:**

Trial name: ASTRUM-005	NCT number: NCT04063163
	There were 13 secondary outcomes, including progression-free survival, objective response rate, and duration of response (all 3 were assessed both by an independent radiology review committee and by the investigators using version 1.1 of RECIST), adverse events, and the relationship between PD-L1 expression and efficacy. PD-L1 expression was assessed centrally by Labcorp Drug Development using PD-L1 IHC 22C3 pharmDx assay kit on the Dako Autostainer link 48 platform (Agilent Technologies). **Additional endpoints:** Patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L) were presented in the most recent data-cut [8] .
Method of analysis	Efficacy was assessed in patients who underwent randomisation according to their randomised group. Adverse events were assessed in the adverse event set, which comprised randomised patients who received at least one dose of study treatment. Tumour responses were assessed at screening, every 6 weeks for the first 48 weeks, and every 9 weeks thereafter. The OS, PFS and duration of response were estimated using the Kaplan-Meier method. Data for patients who were alive were censored on the last known survival date. The Brookmeyer-Crowley method was used to calculate the 96% CIs for median OS, PFS and duration of response. The between-group comparisons were calculated using a stratified log-rank test. A stratified Cox proportional hazards model was used to estimate the HRs and 95% CIs. The proportionality assumption was tested using the Grambsch-Therneau test (2-sided *P* = 0.67) and visually checked on a Schoenfeld residual plot. The results indicated that the proportionality assumption was not violated. Missing data were imputed only under the following circumstances: (1) if the day of death was missing but the year and month were available, the date of death was imputed by the first day of the month or the latest known alive date, whichever was later or (2) if the day of tumour assessment was missing but the year and month were available and were earlier than the date when the patient was known to be alive, the date of tumour assessment or the first day in the month of disease progression or death, whichever was later. The *P*-value boundary for superiority of OS was 0.12 during the interim analysis. Treatment-emergent adverse events were recorded throughout the trial and for 90 days after the last dose was received and were graded

Trial name: ASTRUM-005	NCT number: NCT04063163
	according to version 5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events.
Subgroup analyses	Pre-planned subgroup analyses of OS were conducted according to demographics, prognostic factors, and PD-L1 expression level using descriptive statistics and HRs and 95% CIs. Post hoc tests for interaction were conducted by adding treatment, subgroup factors, and a subgroup factor x treatment interaction term into a Cox proportional hazards model.
Other relevant information	NA

Table 47 Main characteristic of studies included – IMpowe133r Trial

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
Objective	To demonstrate that adding atezolizumab (anti-programmed death ligand 1 [PD-L1]) to carboplatin plus etoposide (CP/ET) for first-line (1L) treatment of extensive-stage small-cell lung cancer (ES-SCLC) results in significant improvement in overall survival (OS) and progression-free survival (PFS) versus placebo plus CP/ET
Publications – title, author, journal, year	Horn et al. First-Line Atezolizumab plus Chemotherapy in Extensive Stage Small-Cell Lung Cancer, 2018. DOI: 10.1056/NEJMoa1809064 [9]. Liu et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133), 2021. DOI https://doi. org/10.1200/JCO.20. 01055 [7]. Liu et al. Five-year survival in patients with ES-SCLC treated with atezolizumab in IMpower133: IMbrella A extension study results, 2023, World conference on lung cancer [80]. Cheng et al. Abstract #8100: 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 for the international phase 3 ASTRUM-005 study. ASCO Annual Meeting 2024 [8]
Study type and design	IMpower133: Completed, randomized, double-blind, phase I/III study, where patients with untreated ES-SCLC were randomly assigned 1:1 to

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
	receive four 21-day cycles of CP/ET with atezolizumab or placebo and then maintenance phase. IMbrella A: open-label, non-randomized, multicenter extension and long-term observational study. Only patients in survival follow up and from atezolizumab treatment arm in IMpower133 could be enrolled.
Sample size (n)	IMpower133: intervention, n = 201, placebo, n = 202. IMbrella A: n = 18
Main inclusion criteria	IMpower133: Eligible patients were adults with histologically or cytologically confirmed extensive-stage small-cell lung cancer as defined according to the Veterans Administration Lung Study Group staging system, measurable extensive stage small-cell lung cancer according to RECIST v 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability) who had not received previous systemic treatment for extensive-stage small-cell lung cancer. Patients with treated asymptomatic central nervous system metastases were eligible IMbrella A: If they continued to receive atezolizumab at IMpower133 study closure or were in survival follow-up
Main exclusion criteria	IMpower133: Key exclusion criteria were a history of autoimmune disease and previous treatment with CD137 agonists or immunecheckpoint blockade therapies IMbrella A: if they were not in treatment with atezolizumab at IMpower133 study closure or were not in survival follow-up
Intervention	Patients received 4.5 mg/kg of serplulimab via intravenous infusion every 3 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent, or other reasons specified in the trial protocol. 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 4 cycles via intravenous infusions. N=389
Comparator(s)	IMpower133: receive four 21-day cycles of CP/ET with placebo and then maintenance CP/ET and placebo until unacceptable toxicity, disease progression, or loss of clinical benefit. 202 patients received intervention treatment

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
	IMbrella A: None. The study was a follow-up one-armed extension study of atezolizumab.
Follow-up time	Median follow up time was 22.9 months. Median follow up for OS was 23.1 months (range, 0-29.5 months) in atezolizumab arm and 22.6 months (range, 0-30.7 months) in placebo arm
Is the study used in the health economic model?	NA
Primary, secondary Eand exploratory endpoints	Endpoints included in this application: Primary efficacy endpoints: The co-primary endpoints of this study are the following: • To evaluate the efficacy of atezolizumab + carpoplatin+etoposide compared with placebo + carboplatin + etoposide in the intent-to-treat (ITT) population as measured by investigator assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors Carsion 1.1 (RECIST v1.1) • To evaluate the efficacy of atozelizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by overall survival (OS) Safety endpoints • To evaluate the safety and tolerability of atezolizumab in combination with CP/ET compared with CP/ET Other endpoints: The secondary efficacy endpoints for this study are • To evaluate the efficacy of atezolizumab + CP/ET compared with placebo + CP/ET in the ITT population as measured by investigator-assessed objective response rate (ORR) according to RECIST v1.1 • To evaluate the efficacy of atezolizumab + CP/ET compared with placebo + CP/ET in ITT population as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1

- To evaluate the efficacy of atezolizumab + CP/ET compared with placebo + CP/ET in ITT population as measured by investigator-assessed time in response (TIR) according to RECIST v1.1
- To evaluate the PFS rate at 6 months and t 1 year in each treatment arm for the ITT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm for the ITT population
- To evaluate the incidence and titers of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

The exploratory objectives for this study are:

- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the PD-L1−selected population as measured by PFS, OS, ORR, and DOR
- To evaluate investigator-assessed disease control rate (DCR) according to RECIST v1.1 in the ITT population
- To evaluate investigator-assessed PFS, ORR, DCR, and DOR according to modified RECIST for the atezolizumab-containing treatment arm in the ITT population
- To evaluate the relationship between tumor biomarkers (including but not limited to PD-L1, programmed death-1 (PD1), somatic mutations, and others), as defined by immunohistochemistry (IHC) or quantitative reverse transcriptase−polymerase chain reaction (qRT-PCR), next generation sequencing (NGS), and/or other methods and measures of efficacy
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue, blood, plasma and serum and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 5-Level (EQ-5D-5L) questionnaire to

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
	generate utility scores for use in economic models for reimbursement • To determine the impact of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide as measured by change from baseline in patient-reported outcomes (PRO) of health-related quality of life, lung cancer−related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and LC13 • To evaluate the impact of chemotherapy (both carboplatin and etoposide) on peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes
Method of analysis	IMpower133: The two primary endpoints were investigator-assessed progression-free survival and overall survival in the intention-to-treat population. Kaplan–Meier methodology was used to estimate the probability of overall survival and progression-free survival, as well as to calculate the median time from randomization to death (for overall survival) and the median time from randomization to disease progression or death (for progression-free survival) for each group, and the Brookmeyer and Crowley method was used to construct the 95% confidence interval for the medians. A similar approach was used for the analysis of the duration of response. The hazard ratios and 95% confidence intervals for overall survival and progression-free survival were estimated with the use of a stratified Cox regression model, with the same stratification factors that were used in the stratified log-rank test
Subgroup analyses	To assess the consistency of the study results in pre-specified subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases), and PD-L1 tumor expression status, the duration of PFS in these subgroups was examined. Summaries of PFS, OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS, was produced separately for each level of the categorical variables for the comparisons between treatment arms.
Other relevant information	NA

Appendix B. Efficacy results per study

Results per study

Table 48 Results per study

Results of ASTRUM-005 (NCT04063163)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS at data-cut 22/10/2021	Serplulimab	389	15.4 months (13.3-not evaluable)	4.5			HR: 0.63	0.49-0.82	<0.001	The OS was estimated using the Kaplan-Meier method. Data for patients who were alive were censored on the last known survival date. The Brookmeyer-Crowley method was used to calculate the 96% CIs. The between-group comparisons were calculated using a stratified log-rank test. A stratified Cox proportional hazards model was used to estimate the HRs and 95% CIs. The proportionality	Cheng et al., 2022 [44] , Cheng et al., 2022 [51] , Cheng et al., 2022 (ESMO Asia) [50] , Cheng et al., 2024 (ASCO 2024) [8]
	Placebo	196	10.9 months (10.0-14.3)								
Median OS at data-cut 13/06/2023	Serplulimab	389	15.8 months				HR: 0.61	0.50-0.74			
	Placebo	196	11.1 months								
	Serplulimab	389	60.7% (54.9%-66.0%)	12.9							

Results of ASTRUM-005 (NCT04063163)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
1-year survival rate	Placebo	196	47.8% (39.6%-55.6%)							assumption was tested using the Grambsch-Therneau test (2-sided *P* = 0.67) and visually checked on a Schoenfeld residual plot. The results indicated that the proportionality assumption was not violated. Missing data were imputed only under the following circumstances: (1) if the day of death was missing but the year and month were available, the date of death was imputed by the first day of the month or the latest known alive date, whichever was later or (2) if the day of tumour assessment was missing but the year and month were available and were earlier than the date when the patient was	
2-year survival rate	Serplulimab	389	43.1% (34.1%-51.7%)	35.2							
	Placebo	196	7.9% (0.7%-27.2%)								
3-year survival rate	Serplulimab	389	24.6% (19.5-30.1)	14.8							
	Placebo	196	9.8% (5.6-15.4)								

Results of ASTRUM-005 (NCT04063163)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										known to be alive, the date of tumour assessment or the first day in the month of disease progression or death, whichever was later. The *P*-value boundary for superiority of OS was 0.12 during the interim analysis.	
Median PFS at first data-cut	Serplulimab	389	IRC: 5.7 months (5.5-6.9) Investigators: 5.5 months	1.4			IRC HR: 0.48 Investigators HR: 0.58	0.38-0.59 0.48-0.71		The IRC and investigators assessed PFS using version 1.1 of RECIST. The PFS was estimated using the Kaplan-Meier method. The Brookmeyer-Crowley method was used to calculate the 96% CIs. The between-group comparisons were calculated using a stratified log-rank test. A stratified Cox proportional hazards model was used to	
	Placebo	196	IRC: 4.3 months (4.2-4.5) Investigators: 4.3 months								

Results of ASTRUM-005 (NCT04063163)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										estimate the HRs and 95% CIs. The proportionality assumption was tested using the Grambsch-Therneau test (2-sided *P* = 0.67) and visually checked on a Schoenfeld residual plot. The results indicated that the proportionality assumption was not violated. Missing data were imputed only under the following circumstances: (1) if the day of death was missing but the year and month were available, the date of death was imputed by the first day of the month or the latest known alive date, whichever was later or (2) if the day of tumour assessment was missing but the year and month were	

Results of ASTRUM-005 (NCT04063163)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										available and were earlier than the date when the patient was known to be alive, the date of tumour assessment or the first day in the month of disease progression or death, whichever was later.	
ORR at first data-cut	Serplulimab	389	80.2% (75.9-84.1)	10.2						The IRC and investigators assessed ORR using version 1.1 of RECIST. The ORR was analysed using the stratified Cochran-Mantel-Haenszel method.	
	Placebo	196	70.4% 63.5-76.7)								
Median duration of response	Serplulimab	389	5.6 months (4.2-6.8)	2.4						The IRC and investigators assessed duration of response using version 1.1 of RECIST.	
	Placebo	196	3.2 months (2.9-4.2)								

Abbreviations: CI, confidence interval; HR, hazard ratio; IRC, independent radiology review committee; PFS, progression-free survival; ORR, objective response rate; OS, overall survival

Results of IMpower133 (NCT02763579)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Updated OS - Median	Tecentriq(atezolizumab)	201	12.3 (10.8 – 15.8) months 2.0		N/A	N/A	HR: 0.70	0.54-0.91	0.007	The median survival is based on the Kaplan-Meier estimator at the updated analysis of the intention-to-treat population. The HR is based on a Cox proportional hazards model	Horn et al., 2018 [9]
	Placebo	202	10.3 months (9.3-11.3)								
Investigator assessed PFS per RECIST version 1.1 (RECIST 1.1) in the intentiont o-treat (ITT)	Tecentriq (atezolizumab)	201	5.2 months	0.9	N/A	N/A	HR: 0.77	0.62-0.96	0.02	Kaplan-Meier estimator was used to calculate the median time from randomization to disease progression or death in the intention-to-treat population. The HR is based on a Cox proportional hazards model	Horn et al., 2018 [9]
	Placebo	202	4.3 months								

Results of IMpower133 (NCT02763579)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
EORTC QLQ-C30 - Global Health Status	Tecentriq (atezolizumab) - Baseline	179	51.63 (48.3 to 54.9)	2.1	−2.72 to 6.88	0.39	NA	NA	NA	The absolute difference in effect is estimated using a twosided t-test.	Horn et al., 2018 and Mansfield 2020 [61]
	Placebo - Baseline	175	53.71 (50.2 to 57.2)								
	Tecentriq (atezolizumab) – Week 27	55	65.30 (59.6 to 70.1)	3.42	-12.55 to 5.70	0.46	NA	NA	NA		
	Placebo – Week 27	40	61.88 (54.80 to 68.97)								
	Tecentriq (atezolizumab) – Week 54	17	62.75 (53.66 to 71.84	0.63 -	17.02 to 15.76	0.94	NA	NA	NA		
	Placebo – Week 54	11	62.12 (48.66 to 75.58								

Results of IMpower133 (NCT02763579)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ORR	Tecentriq (atezolizumab)		60.2% (53.1-67.0)	-4.2%						Proportion of patients with an objective response, either CR or PR Clopper-Pearson method for 95% CI of response rates 95% CI for the difference in ORRs between the two treatment arms was estimated using the normal approximation to the binomial distribution method	Liu et al [7]
	Placebo		64.4% (57.3-71.0)								

Appendix C. Comparative analysis of efficacy

This appendix is based on the post-hoc statistical analysis plan performing an ITC between indirect treatment comparison (ITC) between serplulimab and atezolizumab [71] (I). Also, a discussion on subsequent treatments after the trial was included upon request by DMC (II)

I - Indirect Treatment comparison:

C.1 Study Overview

Table 49: Study overview

Study number (name)	Design	Primary Study Objective	Study Population
HLX10-005-SCLC301 (ASTRUM-005, EudraCT 2019-003063-21)	Double-blind, placebo-controlled, phase 3, randomized.	To evaluate the efficacy and adverse event profile of the PD-1 inhibitor Serplulimab plus chemotherapy compared with placebo plus chemotherapy as first-line treatment of extensive-stage SCLC.	Adults with histologically or cytologically confirmed extensive-stage SCLC who have not previously received systemic therapy for extensive-stage SCLC.
GO3008 (IMPOWER133, EudraCT 2015-004861-97)	Double-blind, placebo-controlled, phase 3, randomized.	To evaluate the efficacy and safety of adding Atezolizumab or placebo to first-line treatment with carboplatin and etoposide in patients with extensive-stage SCLC.	Adults with histologically or cytologically confirmed extensive-stage SCLC who have not previously received systemic treatment for extensive-stage SCLC.

C1.1 Study Objectives

The study objective of the ASTRUM-005 study was to evaluate the efficacy and adverse event profile of the PD-1 inhibitor Serplulimab plus Chemotherapy (Carboplatin and Etoposide) compared with Placebo plus Chemotherapy as first-line treatment in subjects

with extensive-stage SCLC. Similarly, the objective of the IMPOWER133 trial was to evaluate the efficacy and safety of adding Atezolizumab or Placebo to first-line treatment with Carboplatin and Etoposide in subjects with extensive-stage SCLC.

C1.2 Study Designs and Populations

Both trials, ASTRUM-005 and IMPOWER133, were double-blind, placebo-controlled, phase 3, randomized clinical trials. The population investigated was adults with histologically or cytologically confirmed extensive-stage SCLC who have not previously received systemic therapy for extensive-stage SCLC.

In ASTRUM-005, subjects were randomized 2:1, stratified by PD-L1 expression level (tumor proportion < 1%, >=1%, or not evaluable or available), brain metastasis (yes, no), and age (>=65, <65 years), to the Serplulimab group or the Placebo group. Subjects received either Serplulimab or Placebo via intravenous infusions in addition to concomitant Etoposide and Carboplatin. In IMPOWER133, subjects were randomized 1:1, stratified by sex (male, female), ECOG status (0, 1) and brain metastasis (yes, no) to receive either Atezolizumab or Placebo via intravenous infusions in addition to concomitant Etoposide and Carboplatin.

For further details on study designs and populations, see the respective study protocols.

C.2 Analysis sets

C 2.1. Intention-to-treat (ITT)

In ASTRUM-005, efficacy was assessed in subjects who were randomized according to their allocated treatment group, regardless of the treatment actually received.

In IMPOWER133, the ITT set was defined as all subjects who underwent randomization. Subjects were analyzed according to assigned treatment, regardless of the actual treatment received.

These analysis sets will both be referred to as the ITT set hereafter.

C 2.2 Safety Analysis Set (SAF)

In ASTRUM-005, safety outcomes were assessed in the Adverse Event set which consisted of all subjects who received at least one dose of study treatment. Subjects were analyzed according to the treatment actually received.

In IMPOWER133, safety outcomes were assessed in subjects who received at least one dose of Atezolizumab or Placebo. Subjects will be analyzed according to the treatment actually received.

These analysis sets will both be referred to as the SAF set hereafter

C.3 Analysis variables

Data considerations:

- Most of the variables necessary for the analyses described in this PHAP are defined in the study SAPs (see section 10) and are available in the study ADaMs. Where this is not the case, definitions are given. All definitions of study periods have been derived as part of the primary analysis and are available in the study ADaMs. For the definitions, please see the study SAP.

- Identical definitions and calculations of baseline and post-baseline values will be used as defined in study SAP, unless specified otherwise.

- Where both IWRS/IVRS and eCRF versions of baseline variables are available in datasets, the IWRS/IVRS will be used for stratification in accordance to original study SAP for ASTRUM-005. The eCRF version of the variables will be used for subgroup analysis which will not be stratified by the analogous IWRS/IVRS variable.

This section describes the definition of endpoints in ASTUM-005, for which there is access to IPD and summaries differences in endpoint definitions across studies. For further details on endpoints in ASTUM-005 and IMPOWER133, see the respective trial protocols and SAPs

C.3.1 Efficacy - Mortality and Morbidity

C.3 1.1 Overall survival

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Subjects with no post-baseline information will be censored at the date of randomization. The derivation of this endpoint has already been conducted as part of the CSR analyses

C.3.1.2 Progression-free survival

Progression free survival (PFS) was assessed by the independent radiological review committee (IRRC) using RECIST v1.1 guidelines. PFS is defined as the time between date of randomization and the date of first documented disease progression or death, whichever occurs first. Subjects who have not experienced disease progression or death (and have not received non-protocol specified anti-tumor therapy) at the time of analysis will be censored at the time of their last IRRC tumor assessment. Subjects with no post-baseline tumor assessment will be censored at the date of randomization.

The derivation of this endpoint already conducted as part of the CSR analyses censored subjects without documented PD and who initiated non-protocol specified antitumor therapy at the date of their last evaluable tumor assessment prior to the initiation of non-protocol specified antitumor therapy. This censoring rule will be removed to align the definitions of the PFS endpoint between the ASTRUM-005 and IMPOWER133 studies to remove a potential source of bias in the ITC. This will increase the number of PFS events compared to the original CSR analysis. Subjects who subsequently died on study (after initiation of non-protocol specified antitumor therapy) will be recorded as

experiencing a PFS event at the date of death, subjects who did not die on study will be censored at the date of their last tumor assessment.

Time-to event in days will be calculated as (Event date/censoring date – Randomization date + 1). The duration in days will be converted to duration months as (12×Number of days / 365.25).

C.4 Statistical methodology

C4.1 General considerations

All efficacy analyses will be based on the ITT and will be presented by planned treatment. Safety analysis will be based on the SAF and will be presented by treatment received.

For continuous variables, descriptive statistics will include the number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum. When needed, the use of other percentiles (e.g., 10th, 25th, 75th and 90th) will be specified.

For categorical and binary data, descriptive statistics will include number of subjects, frequencies, and percentages. Percentages by categories will be based on the number of subjects with no missing data, i.e., will add up to 100%. Therefore, the ITT determines the denominator for percentages for responder analyses.

All statistical comparisons will be made using two sided tests at the α=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided, unless specifically stated otherwise. All analyses described in this PHAP are post hoc in nature. Therefore, no adjustment will be made for multiple testing.

All data processing, summarization, and analyses will be performed using SAS® version 9.4 or R version 4.2.1 (or higher).

C.4.2 Direct comparison

This section details the statistical methods for the direct comparison of Serplulimab + Carboplatin – Etoposide vs Placebo + Carboplatin – Etoposide. Hereafter, Carboplation – Etoposide will be referred to as Chemotherapy.

The direct comparison will be performed for the following data cuts:

- 13th June 2022
- 7th May 2024

C.4.3 Analysis of Efficacy

C4.3.1 Overall Survival

For the overall survival endpoint defined in section 5.2.1, the number and percentage of subjects with an event and the number of censored will be presented.

The Kaplan-Meier method will be used to estimate the median survival time and the Brookmeyer-Crowley method will be used to construct its corresponding 95% CI.

A stratified Cox proportion hazard regression model, stratifying by PD-L1 expression level (tumor proportion score (TPS) <1%, ≥1%, or not evaluable or available), brain metastasis (yes, no), and age (≥65, <65 years) with treatment as the only covariate, will be used to estimate the hazard ratio (HR) comparing the hazard in the Serplulimab + Chemotherapy arm to the Placebo + Chemotherapy arm and its corresponding 95% CI. Tied events will be handled using Efron's method.

A stratified log-rank test, using the same stratification factors as the Cox proportional hazards regression model will be used to produce a two-sided p-value testing against the null hypothesis of no treatment difference. Tied events will be handled using the Kaplan Meier method which treats tied events as occurring simultaneously.

At months 3, 6, and 9, the number of subjects at risk, the survival rate and corresponding 95% CI will also be presented.

No figures will be produced for the overall survival endpoint.

C.4.3.2 Progression-free survival

Analysis will be conducted following methods described in **C4.3.1** for overall survival

C.5 Missing data, outliers, visit windows and other information

C5.1 Missing Data

As a general principle, no imputation of missing data for variables will be done other than that already described in the study SAPs and implemented in the study Analysis Data Models (ADaMs)

C.5.2 Outliers

No outlying values will be excluded from the analyses

C.6 Reported results based on ITC

C.6.1 Efficacy

The following efficacy values were yielded from the above described analysis and reported also in Section 7.1.3.

Figure 3: ITC serplulimab vs atezolizumab – Results for PFS

Figure 4: ITC serplulimab vs atezolizumab – Results for OS

II - Follow up treatments

For Hetronify (serplulimab) follow-up treatments are reported for the placebo group in the EPAR [2]:

Table 50 Follow-up treatment – Placebo group

		OS
No Subsequent Treatment (n=79, 40.3%)		9.95 (7.655, 10.710)
Chemo/Other (n=50, 25.5%)	Only Chemo (n=23, 11.7%)	8.15 (6.998, 13.832)
	Chemo+ Others (n=19, 9.7%)	12.65 (8.871, 21.290)

	Others (n=8, 4.1%)	8.23 (3.877, 12.945)
Placebo Continue (n=46, 23.5%)	Placebo Monotherapy (n=15, 7.7%)	15.21 (6.111, NA)
	Placebo+ Chemo/Others (n=27, 13.8%)	11.47 (6.439, 17.018)
	Placebo+ Other Anti-PD-1/PD-L1 (n=4, 2.0%)	NA (15.376, NA)
Continue with Other Anti-PD-1/PD-L1 Treatment (n=16, 8.2%)	Other Anti-PD-1/PD-L1+1L Chemo/1L Chemo+Others (n=4, 2.0%)	12.98 (6.899, NA)
	Other Anti-PD-1/PD-L1+2L Chemo/2L Chemo+Others (n=8, 4.1%)	15.80 (5.979, NA)
	Other Anti-PD-1/PD-L1+Targeted Therapy (n=4, 2.0%)	10.02 (5.257, NA)
Total (n=191, 97.4%)		10.91 (9.725, 12.320)

Source: EPAR Hetronifly (serplulimab) [2]

[redacted]

[redacted]

Table 51 lists subsequent cancer treatments after first disease progression [81].

Table 51 Subsequent anticancer treatment after the first disease progression

Characteristic	Serplulimab group (*n* = 389)	Placebo group (*n* = 196)
Patients with ≥ 1 treatment after first disease progression, *n* (%)	193 (49.6)	92 (46.9)
Line of therapy, *n* (%)		
2	187 (48.1)	88 (44.9)
3	35 (9.0)	20 (10.2)
4	9 (2.3)	7 (3.6)

5 and other[a]	15 (3.9)	15 (7.7)
Therapy type, *n* (%)		
Chemotherapy	146 (37.5)	82 (41.8)
Irinotecan	78 (20.1)	45 (23.0)
Carboplatin	45 (11.6)	24 (12.2)
Etoposide	44 (11.3)	21 (10.7)
Paclitaxel	34 (8.7)	17 (8.7)
Cisplatin	28 (7.2)	14 (7.1)
Docetaxel	11 (2.8)	9 (4.6)
Topotecan	10 (2.6)	4 (2.0)
Lobaplatin	10 (2.6)	1 (0.5)
Nedaplatin	3 (0.8)	5 (2.6)
Gemcitabine	1 (0.3)	5 (2.6)
Temozolomide	2 (0.5)	3 (1.5)
Cyclophosphamide	4 (1.0)	0 (0.0)
Doxorubicin	3 (0.8)	0 (0.0)
Vinorelbine	3 (0.8)	0 (0.0)
Mitoxantrone	2 (0.5)	1 (0.5)
Ifosfamide	2 (0.5)	0 (0.0)
Vincristine	2 (0.5)	0 (0.0)
Dianhydrogalactitol	1 (0.3)	0 (0.0)
Lomustine	1 (0.3)	0 (0.0)
Oxaliplatin	1 (0.3)	0 (0.0)
Thiotepa	0 (0.0)	1 (0.5)
Unknown	0 (0.0)	1 (0.5)
Immunotherapy	123 (31.6)	20 (10.2)
Serplulimab	107 (27.5)	0 (0.0)
Sintilimab	11 (2.8)	8 (4.1)
Atezolizumab	3 (0.8)	2 (1.0)
Toripalimab	2 (0.5)	3 (1.5)
Camrelizumab	2 (0.5)	2 (1.0)
Tislelizumab	2 (0.5)	2 (1.0)
Durvalumab	2 (0.5)	0 (0.0)
Envafolimab	1 (0.3)	0 (0.0)
Penpulimab	0 (0.0)	2 (1.0)
Nivolumab	0 (0.0)	1 (0.5)
Unknown	0 (0.0)	1 (0.5)
Targeted therapy	48 (12.3)	30 (15.3)
Catequentinib	47 (12.1)	26 (13.3)
Apatinib	2 (0.5)	2 (1.0)

Bevacizumab	0 (0.0)	3 (1.5)
SKB264	1 (0.3)	0 (0.0)
Other	36 (9.3)	30 (15.3)
Herbal or traditional Chinese medicine	22 (5.7)	26 (13.3)
Immunomodulator[b]	6 (1.5)	7 (3.6)
Antineoplastic agents (unknown)	4 (1.0)	2 (1.0)
Other clinical trial	7 (1.8)	0 (0.0)

Source: [81]

For Tecentriq (atezolizumab) follow-up treatments are reported in the EPAR [6]: Treatment continued until disease progression per RECIST v1.1, but patients could be considered for treatment beyond radiographic disease progression if they had evidence of clinical benefit. During the maintenance phase, prophylactic cranial irradiation and palliative thoracic radiation was permitted per local standard-of-care. Dose and scheduling of all drugs was based in previously approved indications.
The main challenges in relation to the design of the study include maintenance (treatment effect cannot be differentiated from induction); treatment beyond progressive disease (considering patients on the PBO+CE arm would continue on PBO+/-CE); not allowing consolidation thoracic radiotherapy; and not considering the choice between cisplatin and carboplatin for the backbone chemotherapy regimen.

Appendix D. Extrapolation

As no health economic analysis was performed for this application, the extrapolation appendix was not included.

Appendix E. Serious adverse events

[redacted]

Table 53 to Table 61 are sourced from the clinical Study Report [70].

Table 52

[redacted]

Source: [6]

Table 53

Table 54

Table 55

Table 56

Table 57

Table 58

Table 59

[redacted]

Table 60

[redacted]

Table 61

[redacted]

Appendix F. Health-related quality of life

No additional documentation available

Appendix G. Probabilistic sensitivity analyses

Not applicable. 14 weeks process no need for Health Economics assessment

Table 62. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Not applicable. 14 weeks process no need for Health Economics assessment				

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A SLR was carried out to ensure that the identification of studies is comprehensive, accurate, and unbiased, in order to synthesize the available comparative clinical evidence (efficacy and safety) of Serplulimab + EpC in the treatment of patients with untreated ES-SCLC.

SLR methods

SLR methodology followed guidance from the Centre for Reviews and Dissemination (CRD) guidance {Khan, 2001 #101}. Consistent with CRD guidance, the data selection process complied with the National Institute for Health and Care Excellence (NICE) guidance [82] and Cochrane methodology [83] for undertaking systematic reviews.

The methodical approach ensured that identification of studies was comprehensive, accurate, and unbiased; each study was evaluated for its relevance, scientific integrity, and validity by two independent reviewers. Any discrepancy was resolved through discussion. A third reviewer was consulted if an agreement was not reached between the two other reviewers.

Research objectives and research questions

- The primary research objective for this literature review was to identify randomised controlled trials (RCTs) and open-label extension (OLE) studies comparing the efficacy and safety of all relevant and available interventions recommended by European Guidelines (ESMO and NICE ({Dingemans, 2021 #34;NICE, 2019 #103})[1] (e.g., atezolizumab, durvalumab, carboplatin plus etoposide, etc.) to any comparators of interest for the treatment of ES-SCLC.
- This research also aimed to determine the feasibility of conducting an Indirect Treatment Comparison (ITC) to compare serplulimab with potential comparators in the absence of direct within-trial evidence, via a common comparator such as ChT.

This SLR aimed to answer the following narrow research question:

[1] At the time of writing the NICE ES-SCLC guidelines, some immunotherapy regimens had not yet received approval or reimbursement in UK. In this case, decisions regarding the recommendation for use of these therapies will be driven by reimbursement status as determined by the national HTA agency of the UK.

- How do the efficacy and safety of serplulimab compare against treatments recommended by European clinical guidelines (ESMO and NICE [28, 84] for treatment-naïve adult patients with ES-SCLC?

The electronic searches of this review covered the following databases:

Table 63 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	via EMBASE.com	E.g. 1970 until today	April 5th 2024
Medline	via EMBASE.com and via PubMed.gov		April 5th 2024
The Cochrane library (including the CENTRAL database)	via cochranelibrary.com		April 5th 2024

Abbreviations: : CENTRAL, Cochrane Central Register of Controlled Trials.

In addition to the searches through electronic databases, hand searches were conducted to capture data from recent studies not yet published or not captured by the electronic database registries. Searches for conference proceedings were limited to the last **three years** as it is assumed that studies are usually published within two to three years following presentation to a conference. Hand searches included:

Table 64 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Google Scholar	https://scholar.google.com/	Hand search	April 5th 2024
ClinicalTrials.gov	http://www.clinicaltrials.gov/	Hand search	April 5th 2024
EU Clinical Trials Register	www.clinicaltrialsregister.eu/	Hand search	April 5th 2024
WHO ICTRP	https://www.who.int/clinical-trials-registry-platform	Hand search	April 5th 2024
NICE	www.nice.org.uk	Hand search	April 5th 2024
SMC	https://scottishmedicines.org.uk/	Hand search	April 5th 2024

Source name	Location/source	Search strategy	Date of search
AWMSG	https://awttc.nhs.wales/about-us1/our-committees	Hand search	April 5th 2024
HAS	https://www.has-sante.fr/	Hand search	April 5th 2024
GBA	https://www.g-ba.de/english/	Hand search	April 5th 2024
IQWiG	https://www.iqwig.de/en/	Hand search	April 5th 2024
CADTH	https://www.cda-amc.ca/	Hand search	April 5th 2024
PBAC	https://www.pbs.gov.au/pbs/home	Hand search	April 5th 2024
ICER	https://icer.org/	Hand search	April 5th 2024

Abbreviations: AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; EU, European Union; G-BA, *Gemeinsamer Bundesausschuss* (Federal Joint Committee); HAS, *Haute Autorité de Santé* (National Authority for Health); ICER, Institute for Clinical and Economic Review; IQWiG, *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesenis* (Institute for Quality and Efficiency in Health Care); NICE, National Institute of Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium; WHO ICTRP, World Health Organisation International Clinical Trials Registry Platform.

Table 65 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	https://www.asco.org/meetings	Hand search		April 5th 2024
ECCO	https://www.europeancancer.org/	Hand search		April 5th 2024
ESMO	https://www.esmo.org/meetings/esmo-congresses	Hand search		April 5th 2024
ELCC	https://www.esmo.org/meetings/past-meetings/european-lung-cancer-congress-2020	Hand search		April 5th 2024
IASLC	https://www.iaslc.org/	Hand search		April 5th 2024

Abbreviations: ASCO, American Society of Clinical Oncology; ECCO, European Cancer Organisation Congress; ELCC, European Lung Cancer Congress; ESMO, European Society for Medical Oncology; IASLC, International Association for the Study of Lung Cancer World Conference on Lung Cancer.

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

H.1.1 Search strategies

The identification of studies utilized a search strategy composed of both free-text terms and controlled vocabulary terms, supplemented with the use of SIGN filters [85] to identify clinical studies.

With regards to interventions and comparators, searches conducted were broad, and for study selection, ESMO [28] and NICE [84] guidelines recommendations were followed to narrow down and focus on studies responding to the study question.

Inclusion and exclusion criteria for the search are presented in Table 67

The identification of studies utilized a search strategy composed of both free-text terms and controlled vocabulary terms, supplemented with the use of SIGN filters [85] to identify clinical studies.

With regards to interventions and comparators, searches conducted were broad, and for study selection, ESMO [28] and NICE [84] guidelines recommendations were followed to narrow down and focus on studies responding to the study question.

Inclusion and exclusion criteria for the search are presented in Table 67.

Table 66 Search terms for EMBASE (searched via www.embase.com)

No.	Query	Results
Population		
#1	'small cell lung cancer'/exp OR 'bronchial small cell cancer' OR 'bronchial small cell carcinoma' OR 'lung small cell cancer' OR 'lung small cell carcinoma' OR 'microcellular lung carcinoma' OR 'pulmonary small cell cancer' OR 'pulmonary small cell carcinoma' OR 'small cell bronchial cancer' OR 'small cell bronchial carcinoma' OR 'small cell lung cancer' OR 'small cell lung carcinoma' OR 'small cell pulmonary cancer' OR 'small cell pulmonary carcinoma' OR 'extensive stage small cell lung cancer'	217195
#2	'small cell lung cancer':ab,ti OR 'small cell lung carcinoma':ab,ti OR 'small cell lung neoplasm':ab,ti OR 'sclc':ab,ti OR 'es-sclc':ti,ab OR (('small cell lung' NEAR/3 cancer):ab,ti) OR (('small cell lung' NEAR/3 carcinoma):ab,ti) OR (('small cell lung' NEAR/3 neoplasm):ab,ti)	156161

No.	Query	Results
#3	#1 OR #2	218458
#4	'non small cell lung cancer'/exp OR 'lung nonâ€•small cell carcinoma cell line':ab,ti OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung neoplasm':ab,ti OR 'nsclc':ab,ti OR ((non NEAR/2 'small cell lung'):ab,ti)	242881
#5	#3 NOT #4	26768
Intervention and Comparators		
#6	'serplulimab'/exp OR 'hlx 10' OR 'hansizhuang'	118
#7	'carboplatin'/exp OR carboplatin OR (cyclobutanedicarboxylato NEAR/2 diammineplatinum) OR blastocarb OR boplatex OR carboplat OR carboplatino OR carbosin OR carbotec OR cycloplatin OR diamminecyclobutanedicarboxylatoplatinum OR kemocarb OR paraplatin OR paraplatine OR 'platinum'	176565
#8	'cisplatin'/exp OR cisplatin OR 'platinum diamminodichloride' OR 'cis-platinum' OR 'cis platinum' OR 'cisplatinum' OR 'dichlorodiammineplatinum' OR 'cis-diamminedichloroplatinum' OR 'cis diamminedichloroplatinum' OR 'cis-dichlorodiammineplatinum' OR 'platinol' OR 'platidiam' OR 'platino' OR biocisplatinum	237278
#9	'paclitaxel'/exp OR paclitaxel OR 'abi 007' OR abi007 OR abraxane OR 'albumin bound paclitaxel' OR 'albumin-bound paclitaxel' OR anzatax OR apealea OR asotax OR biotax OR 'bms 181339' OR bms181339 OR 'bmy 45622' OR bmy45622 OR bristaxol OR britaxol OR coroxane OR 'dts 301' OR dts301 OR 'endotag 1' OR formoxol OR genexol OR 'genexol pm' OR hunxol OR ifaxol OR infinnium OR intaxel OR 'mbt 0206' OR mbt0206 OR medixel OR mitotax OR 'nab paclitaxel' OR 'nanoparticle albumin bound paclitaxel' OR 'nsc 125973' OR 'nsc 673089' OR nsc125973 OR nsc673089 OR 'oas pac 100' OR oaspac100 OR oncogel OR onxol OR pacitaxel OR 'paclitaxel nab' OR pacxel OR padexol OR parexel OR paxceed OR paxene OR paxus OR pazenir OR praxel OR 'sb 05' OR sb05 OR taxocris OR taxol OR taxus OR taycovit OR yewtaxan	152117
#10	'etoposide'/exp OR 'etopophos'/exp OR 'toposar'/exp OR 'vepesid'/exp OR 'irinotecan'/exp OR 'irrinotecan' OR 'camptothecin'/exp OR 'sn 38*' OR 'sn38*' OR 'amrubicin'/exp OR 'sm 5887'	155718
#11	'nivolumab'/exp OR 'bms 936558' OR 'bms936558' OR 'cmab 819' OR 'cmab819' OR 'mdx 1106' OR 'mdx1106' OR 'nivolumab' OR 'ono 4538' OR 'ono4538' OR 'opdivo'	42931

No.	Query	Results
#12	'pembrolizumab'/exp OR 'keytruda' OR 'lambrolizumab' OR 'mk 3475' OR 'mk3475' OR 'pembrolizumab' OR 'sch 900475' OR 'sch900475'	42812
#13	'ipilimumab'/exp OR 'bms 734016' OR 'bms734016' OR 'ipilimumab' OR 'mdx 010' OR 'mdx 101' OR 'mdx010' OR 'mdx101' OR 'strentarga' OR 'yervoy'	27418
#14	'atezolizumab'/exp OR 'atezolizumab' OR 'monoclonal antibody mpdl 3280a' OR 'monoclonal antibody mpdl3280a' OR 'mpdl 3280a' OR 'mpdl3280a' OR 'rg 7446' OR 'rg7446' OR 'tecentriq' OR 'tecntriq'	18205
#15	durvalumab OR imfinzi OR 'medi 4736' OR medi4736	12102
#16	tremelimumab OR ticilimumab OR 'cp 675' OR cp675 OR cp675206 OR 'cp 675206'	4818
#17	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	571845
Study design		
#18	'clinical trial'/de OR 'randomised controlled trial'/de OR 'controlled clinical trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de	2217723
#19	'open study' OR ('open label' NEAR/3 ('study' OR 'trial')) OR ('open-label' NEAR/3 ('study' OR 'trial'))	96959
#20	#18 OR #19	2152955
Combination		
#21	#5 AND #17 AND #20	2970
#22	'case study'/it OR 'case report'/it OR 'abstract report'/it OR 'conference proceeding'/it OR 'conference abstract'/it OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'review':ti,tt OR 'update review':ab OR 'we searched':ab OR 'short survey'/it OR 'comment':ti,ab	12192143
#23	#21 NOT #22	1400

No.	Query	Results
#24	'animal'/exp NOT 'human'/exp	6107003
#25	#23 NOT #24	1399
#21	#5 AND #17 AND #20	2970
Language		
#26	#25 AND [english]/lim	**1288**

Table 67 Search terms for Medline and Medline In-Process (searched via www.PubMed.com)

No.	Query	Results
Population		
#1	"small cell lung cancer"[MeSH Terms] OR "bronchial small cell carcinoma" OR "lung small cell cancer" OR "lung small cell carcinoma" OR "pulmonary small cell carcinoma" OR "small cell bronchial cancer" OR "small cell bronchial carcinoma" OR "small cell lung cancer" OR "small cell lung carcinoma" OR "small cell pulmonary cancer" OR "small cell pulmonary carcinoma" OR "extensive stage small cell lung cancer"	101,662
#2	((("small cell lung cancer"[Title/Abstract]) OR ("small cell lung carcinoma"[Title/Abstract]))) OR ("SCLC"[Title/Abstract] OR "ES-SCLC"[Title/Abstract])	101,084
#3	#1 OR #2	102,645
#4	((("non small cell lung carcinoma"[Title/Abstract]) OR ("non small cell lung neoplasm"[Title/Abstract])) OR ("non small cell lung cancer"[Title/Abstract])) OR (non small cell lung cancer[MeSH Terms])	102,282
#5	#3 NOT #4	15,828
Intervention and Comparators		
#6	"serplulimab"[All fields] OR "hlx 10"[All fields] OR "hansizhuang"[All fields]	39
#7	"carboplatin"[mh] OR carboplatin OR (cyclobutanedicarboxylato AND diammineplatinum) OR blastocarb OR boplatex OR carboplat OR carboplatino OR carbosin OR carbotec OR cycloplatin OR	74,657

No.	Query	Results
	diamminecyclobutanedicarboxylatoplatinum OR kemocarb OR oncocarbin OR paraplatin OR paraplatine OR platinum	
#8	"cisplatin"[mh] OR cisplatin OR "platinum diamminodichloride" OR "cis-platinum" OR "cis platinum" OR "cisplatinum" OR "dichlorodiammineplatinum" OR "cis-diamminedichloroplatinum" OR "cis diamminedichloroplatinum" OR "cis-dichlorodiammineplatinum" OR "platinol" OR "platidiam" OR "platino" OR biocisplatinum	91,831
#9	"paclitaxel"[mh] OR paclitaxel OR "abi 007" OR "abi007" OR "abraxane" OR "albumin bound paclitaxel" OR "albumin-bound paclitaxel" OR "anzatax" OR "apealea" OR "asotax" OR "biotax" OR "bms 181339" OR "bms181339" OR "bmy 45622" OR "bmy45622" OR "bristaxol" OR "britaxol" OR "coroxane" OR "dts 301" OR "dts301" OR "endotag 1" OR "formoxol" OR "genexol" OR "genexol pm" OR "hunxol" OR "ifaxol" OR "infinnium" OR "intaxel" OR "mbt 0206" OR "mbt0206" OR "medixel" OR "mitotax" OR "nab paclitaxel" OR "nanoparticle albumin bound paclitaxel" OR "nsc 125973" OR "nsc 673089" OR "nsc125973" OR "nsc673089" OR "oas pac 100" OR "oaspac100" OR "oncogel" OR "onxol" OR "pacitaxel" OR "paclitaxel nab" OR "pacxel" OR "padexol" OR "parexel" OR "paxceed" OR "paxene" OR "paxus" OR "pazenir" OR "praxel" OR "sb 05" OR "sb05" OR "taxocris" OR "taxol" OR "taxus" OR "taycovit" OR "yewtaxan"	52,049
#10	"etoposide"[mh] OR "etopophos" OR "toposar" OR "vepesid" OR "irinotecan"[mh] OR "irrinotecan"[mh] OR "camptothecin" OR "sn 38*" OR "sn38*" OR "amrubicin" OR "sm 5887"	34,884
#11	"nivolumab"[mh] OR "bms 936558" OR "bms936558" OR "cmab 819" OR "cmab819" OR "mdx 1106" OR "mdx1106" OR "nivolumab" OR "ono 4538" OR "ono4538" OR "opdivo"	10,578
#12	"pembrolizumab"[mh] OR "keytruda" OR "lambrolizumab" OR "mk 3475" OR "mk3475" OR "pembrolizumab" OR "sch 900475"	10,083
#13	"ipilimumab"[mh] OR "bms 734016" OR "bms734016" OR "ipilimumab" OR "mdx 010" OR "mdx 101" OR "mdx010" OR "mdx101" OR "yervoy"	5,962
#14	"atezolizumab"[mh] OR "atezolizumab" OR "monoclonal antibody mpdl 3280a" OR "monoclonal antibody mpdl3280a" OR "mpdl 3280a" OR "mpdl3280a" OR "rg 7446" OR "rg7446" OR "tecentriq"	3,592
#15	"durvalumab"[All fields] OR "imfinzi" OR "medi 4736" OR "medi4736"	1,814

No.	Query	Results
#16	"tremelimumab"[all fields] OR "ticilimumab" OR "cp 675" OR "cp675" OR "cp675206" OR "cp 675206"	594
#17	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	229,462
Study design		
#18	"clinical trial" OR "randomised controlled trial"[all fields] OR "controlled clinical trial"[all fields]	1,170,499
#19	"randomised"[tiab] OR "randomization"[mh:noexp] OR "rct" OR "placebo" OR randomly[tiab]	1,171,654
#20	((double[tiab] or single[tiab] or doubly[tiab] or singly[tiab]) AND (blind[tiab] or blinded[tiab] or blindly[tiab]))	212,433
#21	("open label study" OR "open label trial") OR ("open-label study" OR "open-label trial")	12,207
#22	"phase 2 clinical trial" OR "phase 3 clinical trial" OR "phase 4 clinical trial"	1,916
Combination		
#23	#18 OR #19 OR #20 OR #21 OR #22	1,785,927
#24	#5 AND #17 AND #23	1,296
Publication type		
#25	"case study"[tiab] OR "case reports"[pt] "chapter"[tiab] OR editorial[pt] OR letter[pt] OR comment[pt]	2,235,432
#26	review[pt] OR "update review"[tiab] OR "we searched"[tiab]	3,338,327
#27	#25 OR #26	5,537,966
#28	#23 NOT #27	1,162
#29	#23 NOT #27 Filters: Humans	1,088
Language		
#30	#23 NOT #27 Filters: Humans, English	**1,032**

Table 68 Search terms for Cochrane (searched via www.cochrane.com)

No.	Query	Results
Population		
#1	MeSH descriptor: [Small Cell Lung Cancer] explode all trees	624
#2	'small cell lung cancer' OR 'bronchial small cell cancer' OR 'bronchial small cell carcinoma' OR 'lung small cell cancer' OR 'lung small cell carcinoma' OR 'microcellular lung carcinoma' OR 'pulmonary small cell cancer' OR 'pulmonary small cell carcinoma' OR 'small cell bronchial cancer' OR 'small cell bronchial carcinoma' OR 'small cell cancer, lung' OR 'small cell lung cancer' OR 'small cell lung carcinoma' OR 'small cell pulmonary cancer' OR 'small cell pulmonary carcinoma'	20,172
#3	'small cell lung carcinoma' OR 'small cell lung neoplasm' OR 'sclc' OR 'es-sclc'	11,137
#4	("small-cell lung cancer"):ti,ab,kw	17,575
#5	#1 OR #2 OR #3 OR #4	20,244
#6	'non small cell lung cancer' OR 'lung non-small cell carcinoma cell line' OR 'non small cell lung carcinoma' OR 'non small cell lung neoplasm' OR 'nsclc'	18,108
#7	("non-small cell lung cancer"):ti,ab,kw	15,257
#8	#6 OR #7	18,108
#9	#5 NOT #8	2,798
Intervention and Comparators		
#10	MeSH descriptor: [Carboplatin] explode all trees	3,288
#11	carboplatin OR (cyclobutanedicarboxylato AND diammineplatinum) OR blastocarb OR boplatex OR carboplat OR carboplatino OR carbosin OR carbotec OR carplan OR cycloplatin OR diamminecyclobutanedicarboxylatoplatinum OR erbakar OR ercar OR ifacap OR kemocarb OR oncocarbin OR paraplatin OR paraplatine	8,873
#12	MeSH descriptor: [Cisplatin] explode all trees	6,393
#13	cisplatin OR 'platinum diamminodichloride' OR 'cis-platinum' OR 'cis platinum' OR 'cisplatinum' OR 'dichlorodiammineplatinum' OR 'cis-diamminedichloroplatinum' OR 'cis diamminedichloroplatinum' OR 'cis-	17,210

No.	Query	Results
	dichlorodiammineplatinum' OR 'platinol' OR 'platidiam' OR 'platino' OR biocisplatinum	
#14	MeSH descriptor: [Paclitaxel] explode all trees	5,067
#15	paclitaxel OR paclitaxel OR abi 007 OR abi007 OR abraxane OR 'albumin bound paclitaxel' OR 'albumin-bound paclitaxel' OR anzatax OR apealea OR asotax OR biotax OR 'bms 181339' OR bms181339 OR 'bmy 45622' OR bmy45622 OR bristaxol OR britaxol OR coroxane OR 'dts 301' OR dts301 OR 'endotag 1' OR formoxol OR genexol OR 'genexol pm' OR hunxol OR ifaxol OR infinnium OR intaxel OR 'mbt 0206' OR mbt0206 OR medixel OR mitotax OR 'nab paclitaxel' OR 'nanoparticle albumin bound paclitaxel' OR 'nsc 125973' OR 'nsc 673089' OR nsc125973 OR nsc673089 OR 'oas pac 100' OR oaspac100 OR oncogel OR onxol OR pacitaxel OR 'paclitaxel nab' OR pacxel OR padexol OR parexel OR paxceed OR paxene OR paxus OR pazenir OR praxel OR 'sb 05' OR sb05 OR taxocris OR taxol OR taxus OR taycovit OR yewtaxan	16,910
#16	MeSH descriptor: [Etoposide] explode all trees	2,157
#17	etoposide OR 'etopophos' OR 'toposar' OR 'vepesid'	4,741
#18	MeSH descriptor: [Irinotecan] explode all trees	1,316
#19	irinotecan OR 'irrinotecan' OR 'camptothecin' OR 'sn 38'	4,957
#20	amrubicin OR 'sm 5887'	121
#21	MeSH descriptor: [Nivolumab] explode all trees	945
#22	'bms 936558' OR 'bms936558' OR 'cmab 819' OR 'cmab819' OR 'mdx 1106' OR 'mdx1106' OR 'nivolumab' OR 'ono 4538' OR 'ono4538' OR 'opdivo'	3,120
#23	'pembrolizumab' OR 'keytruda' OR 'lambrolizumab' OR 'mk 3475' OR 'mk3475' OR 'pembrolizumab' OR 'sch 900475' OR 'sch900475'	3,229
#24	MeSH descriptor: [Ipilimumab] explode all trees	552
#25	'ipilimumab' OR 'bms 734016' OR 'bms734016' OR 'ipilimumab' OR 'mdx 010' OR 'mdx 101' OR 'mdx010' OR 'mdx101' OR 'strentarga' OR 'yervoy'	1,939
#26	'atezolizumab' OR 'atezolizumab' OR 'monoclonal antibody mpdl 3280a' OR 'monoclonal antibody mpdl3280a' OR 'mpdl 3280a' OR 'mpdl3280a' OR 'rg 7446' OR 'rg7446' OR 'tecentriq' OR 'tecntriq'	1,518

No.	Query	Results
#27	durvalumab OR imfinzi OR 'medi 4736' OR medi4736	1,278
#28	tremelimumab OR ticilimumab OR 'cp 675' OR cp675 OR cp675206 OR 'cp 675206'	564
#29	'serplulimab' OR 'hlx 10' OR 'hansizhuang'	32
#30	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	46,865
Combination		
#31	#9 AND #30	1,403
Publication Type		
#32	#9 AND #30 in Trials	**1,328**

H.1.2 Systematic selection of studies

Titles and abstracts of studies identified from the search strategy, where available, were screened by two reviewers independently, according to the pre-specified inclusion/exclusion criteria (Table 67). Articles, identified as potentially relevant based on titles and abstracts, were reviewed in full and selected similarly by two reviewers, independently and in parallel, based on the pre-specified study selection criteria. Any discrepancy was resolved by discussion. A third reviewer was involved if a decision agreement could not be reached between the two reviewers. Finally, all the included studies were extracted in a tabular summary.

A comprehensive record of decisions was maintained for each article, with specific reasons for exclusion documented during the full-text review stage (e.g., not population of interest, no intervention of interest, no outcomes of interest, inappropriate study type, no language of interest).

A PRISMA flow chart was created to illustrate the number of studies/papers remaining at each stage, providing transparency and clarity regarding the study selection process (Figure 5).

Trials retrieved from the CT registries were only included if they have been completed, and all identified trials were crosschecked against the publications identified from the searches of electronic databases. Where results for the same study are reported in more than one publication, the relevant records were grouped by study.

In the data extraction stage of the SLR, each study was initially assigned to one of the two reviewers. The latter then undertook the extraction of data from the full-text studies, focusing on maintaining consistency and accuracy with the original source information. Once the initial extraction was complete, the second reviewer conducted a thorough review of a subset of the extracted data against the original articles (20% of manuscripts eligible after full-text review). For additional quality assurance, a third, independent reviewer was involved to adjudicate any discrepancies identified between the initial reviewer's data extraction and the second reviewer's verification.

When multiple articles were derived from the same study, only the latest article or the study with the most relevant and complete set of results and analysis relevant to the review was extracted.

Table 69 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adult patients with untreated ES-SCLC (naïve)	Studies including NSCLC patients; or ES-SCLC and NSCLC patients that do not stratify baseline characteristics and results for ES-SCLC patients Studies including LS-SCLC patients, or ES-SCLC and LS-SCLC patients that do not stratify baseline characteristics and results for ES-SCLC patients Studies including patients in the second or subsequent lines of therapy, that do not separately report results for line of treatment in ES-SCLC Other populations not listed under the inclusion criteria	
Intervention	Serplulimab + Carboplatin and Etoposide	Not applicable	
Comparators	Any regimens and/or targeted therapies	Studies including ChT regimens and/or targeted	

	recommended for the treatment of ES-SCLC by European Guidelines (ESMO and NICE guidelines ([28, 84])	therapies **not recommended** for the treatment of ES-SCLC
Outcomes	Efficacy: Overall Survival (OS) Progression Free Survival (PFS) Duration of Effect Event-Free Survival (EFS) Overall Response Rate (ORR) Complete Response Rate (CR) Duration of response (DoR) Safety: Adverse events Serious adverse events Mortality Time to treatment discontinuation HRQoL questionnaires	Studies that do not report on any of the outcomes listed under the inclusion criteria
Study design/publication type	Randomised Controlled Trials Open label extension studies Peer-reviewed published in journals or retrieved via hand searches Conference abstracts (published after 2021)	Non-randomised studies Case studies/ reports, observational studies (including prospective, retrospective, cross-sectional), reviews Interrupted/terminated studies Studies designed to determine the optimal dosing of a treatment Letters and editorials Conference abstracts (published in 2021 or earlier) Publications without full-text availability

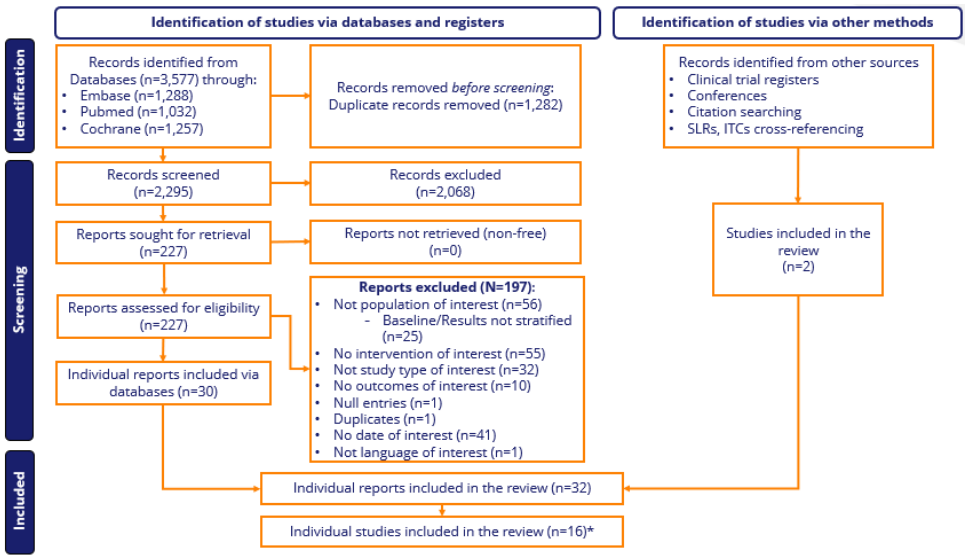
Language restrictions	English papers	Non-English papers (where translation is not provided)

Results

A total of 3,577 publications were identified through the electronic biomedical database searches. In addition, two relevant studies were added based on hand searches. Duplicates were identified and compared based on an exact match for author, year, title, and abstract. After removal of duplicates, 2,295 unique citations were obtained and screened.

After application of the pre-specified selection criteria and title, abstract and full text stages, **a total of 32 individual publications were included in this SLR** (Figure 5). Twenty-five were full publications and 7 were abstracts. Three of those abstracts corresponded to the CASPIAN study [52, 53, 86], three to ASTRUM-005 study [8, 50, 51] and one to Shimokawa 2021 [48].These 32 reports corresponded to 16 individual studies included in the review that reported efficacy, safety, and HRQoL results from CTs including untreated patients with ES-SCLC.

Figure 5. PRISMA Flow Diagram



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:** ITCs: Indirect Treatment Comparison; SLRs: Systematic Literature Review.

A summary of the study design characteristics of the 16 unique studies is outlined in Table 68. Four studies had multiple publications (JCOG1201 [48, 49] , and the ASTRUM-005 [5, 8, 50, 51], CASPIAN [52-59, 86], and IMpower133 [7, 9, 60, 61] studies). Ten studies (63%) were international, followed by six studies conducted in one single country, with four studies conducted exclusively in Asia-Pacific (APAC) (i.e., Noda et al., 2002 [87], Okamoto et al., 2007 [68], JCOG1201 [48, 49] each in Japan and Kim et al.,

2019 [67] in Korea) and two trials conducted in Germany (Schmittel et al., 2006 [63] and Schmittel et al., 2011 [66]). Regarding study design, all trials were RCTs, of which most trials (n=13) were phase 3, two were phase 2, and only one phase 2/3 ((Shimokawa et al., 2021 {Shimokawa, 2021 #2} and Shimokawa et al., 2023 [49]); Seven were open-label, and one was single-blinded (Quoix et al., 2005 [62]). Fifteen studies were two-arm, and one study was a three-arm trial (CASPIAN [52-59, 86],. Of note, Schmittel et al., 2006 [63] was the phase 2 trial preceding the Schmittel et al., 2011 [66] phase 3 trial.

All studies focused on untreated or chemo-naïve ES-SCLC patients only. The median sample size of the included studies was 347 patients, ranging from 70 (Schmittel et al., 2006 [63]) to 805 patients (CASPIAN [52-59, 86]). The median age of patients ranged between 37 (Hanna et al., 2006 [64]) and 80 years (Eckardt et al., 2007 [65], Schmittel et al., 2011 [66] and Kim et al., 2019 [67]). Two studies focused specifically on elderly patients with an average age of around 75 years old (Okamoto et al., 2007 [68], Shimokawa et al., 2023 [49]). Table 70 provides a breakdown of some of the key outcomes—OS, PFS, response rates, safety, DoR and HRQoL —reported in the studies.

Table 70 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
Noda et al., 2002 [87]	Compare irinotecan + cisplatin with etoposide + cisplatin in patients with ES-SCLC	Multicentre, randomised, Phase 3 study	Median age: 63 Histologically confirmed SCLC; extensive disease (defined by distant metastasis, contralateral hilar-node metastasis, or both; those with pleural effusion alone were excluded); no prior radiotherapy, chemotherapy, or surgery; ECOG PS 0-2; adequate organ function; life	Intervention: Irinotecan + Cisplatin (n=75) Comparator: Etoposide + Cisplatin (n=77)	OS – time from randomisation to death. Enrolment began Nov 1995. First interim analysis Aug 1998. Second interim analysis Dec 1999. Study terminated Jan 1999.	PFS, complete response, ORR, toxicity. Follow-up period was the same as for primary outcome.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
			expectancy ≥3 months.				
Quoix et al., 2005 [62]	Evaluate the efficacy, safety and patient benefit profile of topotecan, in combination with cisplatin or etoposide, as first-line treatment of patients with ES-SCLC.	Randomised Phase II study[1]	Median age: 61 Histologically confirmed ES-SCLC; no prior chemotherapy or immunotherapy; either sex; adults; life expectancy ≥3 months.	Intervention: Topotecan + Cisplatin (n=41) Comparator: Topotecan + Etoposide (n=41)	RR Treatment duration depended upon response. Patients with complete/partial response continued treatment for at least 6 courses or until progression.	Survival, disease progression, safety (toxicity) Follow-up period was the same as for primary outcome.	NR
Schmittel et al., 2006 [63]	Investigate irinotecan/cisplatin versus etoposide/carboplatin in patients with ES-SCLC	Randomised Phase II/III trial	Median age: 59 (intervention), 63 (comparator) Pathologically proven ES-SCLC (malignant effusion	Intervention: Irinotecan + Cisplatin (n=35)	RR Median number of cycles administered in both treatment arms was 4 (16	PFS, safety. Follow-up period was the same as for primary outcome.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
			or supraclavicular lymph node metastases or visceral metastases); no prior chemotherapy; life expectancy ≥3 months; Karnofsky PS ≥60%; adequate organ function.	Comparator: Etoposide + Cisplatin (n=35)	week follow-up period).		
Eckardt et al., 2006 [65]	Compare oral topotecan/intravenous cisplatin with intravenous etoposide/cisplatin in patients with untreated ES-SCLC	Open-label, multicentre, randomised Phase III study	Mean age: 59.7 (intervention), 59.6 (comparator) Histologically or cytologically confirmed ES-SCLC with either measurable or non-measurable	Intervention: Topotecan + Cisplatin (n= 389) Comparator: Etoposide + Cisplatin (n=395)	OS – time from randomisation to death. All randomly assigned patients were to be observed for the full duration of survival[2]. Those	1-year survival rate, RR, time to response, response duration, time to progression, quality of life, safety.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
			disease; no prior chemotherapy; ECOG PS ≤2; adequate organ function; life expectancy ≥3 months.		patients who progressed wile on study were to be observed every 3 months. Patients who had not progressed on treatment or who subsequently received second-line therapy were assessed for disease status clinically or radiologically, PS, and QOL every 4 weeks following treatment until progression or for a maximum of 16 weeks and then	Follow-up period was the same as for primary outcome.	

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
					once every 3 months.		
Hanna et al., 2006 [64]	Determine if a modified weekly regimen of irinotecan plus cisplatin would provide superior survival with less toxicity than etoposide plus cisplatin	Randomised Phase III trial	Median age: 63 (intervention), 62 (comparator) Histopathologically or cytologically confirmed ES-SCLC; adequate organ function; ECOG PS 0-2; no prior systemic anticancer therapy for SCLC. Patients with known brain metastases were elgibile if asymptomatic and on a stable or tapering steroid	Intervention: Irinotecan + Cisplatin (n=216) Comparator: Etoposide + Cisplatin (n=106)	OS – time from randomisation to death. Tumour assessment was evaluated after every two cycles of therapy. The primary analysis was conducted 1.5 years after the last patient had been enroled and when the 220th patient death was recorded.	Antitumour efficacy as assessed by RR and time to progression, safety and tolerability. Follow-up period was the same as for primary outcome.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
			dose (if they were on steroids).				
Okamoto et al., 2007 [68] JCOG 9702	Compare the efficacy and safety or a carboplatin plus etoposide regimen vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with ES-SCLC	Multicentre, prospective, randomised Phase III trial	Median age: 74 (intervention), 73.5 (comparator) Untreated ES-SCLC; age ≥70 and ECOG PS 0-2 or age <70 and ECOG PS 3.	Intervention: Etoposide + Carboplatin (n=110) Comparator: split dose Etoposide + Cisplatin (n=110)	OS – time from randomisation to death. Both regimens were given in a 21-28 day cycle for four courses.	RR, safety, PFS. Follow-up period was the same as for primary outcome.	NR
Hermes et al., 2008 [88]	Evaluate the efficacy of irinotecan plus carboplatin compared with oral etoposide plus carboplatin	Binational, multicentre, open-label, randomised Phase III study	Median age: 67 (intervention), 68 (comparator) Histologically or cytologically confirmed ES-SCLC; adequate organ	Intervention: Irinotecan + Carboplatin (n=105) Comparator: Etoposide + Carboplatin (n=104)	OS – time from randomisation to death. Courses were repeated every 3	Quality of life, complete response rate. Follow-up period was the same as for primary outcome.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
			function; no previous systemic anticancer therapy.		weeks with four cycles planned.		
Lara et al., 2009 [89] SWOG S0124	Confirm the results of a Japanese trial in North American patients, and evaluate the status of select genomic DNA polymorphisms and correlate genotypic profiles with patient outcomes after chemotherapy	Randomised, Phase III trial	Median age: 62 (intervention), 63 (comparator) Histologically confirmed SCLC; extensive disease (defined by distant metastasis, contralateral hilar-node metastasis, or both; those with pleural effusion alone were excluded); no prior radiotherapy, chemotherapy, or surgery; Zubrod PS	Intervention: Irinotecan + Cisplatin (n=317) Comparator: Etoposide + Cisplatin (n=324)	OS – time from randomisation to death. Courses were repeated every four weeks (intervention arm) or three weeks (comparator arm) with four cycles planned.	PFS, safety. Follow-up period was the same as for primary outcome.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
			0-2; adequate organ function; life expectancy ≥3 months				
Zatloukal et al., 2010 [90]	Compare cisplatin in combination with irinotecan or etoposide in previously untreated ES-SCLC	Multicentre, open-label, international, randomised, two parallel-group Phase III study	Median age: 60 (intervention), 61 (comparator) Newly diagnosed histological or cytological proven ES-SCLC; WHO PS 0-1; adequate organ function; no previous radiotherapy (excluding that for bone metastasis on diagnosis) or surgery on the primary tumour	Intervention: Irinotecan + Cisplatin (n=202) Comparator: Etoposide + Cisplatin (n=203)	OS – time from randomisation to death. Treatment was repeated every 3 weeks and planned for a total of six cycles. Minimum follow-up of 13 months.	ORR, duration of response, duration of disease stabilisation, time to progression, safety. Follow-up period was the same as for primary outcome.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
			(other than palliative); no previous systemic chemotherapy or immunotherapy.				
Schmittel et al., 2011 [66]	Prove superiority of irinotecan over etoposide combined with carboplatin in ES-SCLC	Multicentre, randomised Phase III trial	Median age: 60 (intervention), 63 (comparator) Pathologically proven ES-SCLC defined as malignant effusion or contralateral supraclavicular lymph node metastases or distant metastases; no prior chemotherapy; adequate organ	Intervention: Irinotecan + Cisplatin (n=106) Comparator: Etoposide + Cisplatin (n=110)	PFS 6 months. Follow-up period was the same as for primary outcome.	OS, RR, toxicity.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
			function; life expectancy ≥3 months.				
Fink et al., 2012 [91]	Compare the safety and feasibility of an experimental arm topotecan-cisplatin with the standard arm physical examination in patients with ES-SCLC	Open-label, multicentre, randomised Phase III study	Mean age: 60.8 (intervention), 61.3 (comparator) Histologically or cytologically confirmed ES-SCLC; measurable or non-measurable disease; adequate organ function; ECOG PS <2; no symptomatic brain metastases.	Intervention: Topotecan + Cisplatin (n=346) Comparator: Etoposide + Cisplatin (n=334)	OS – time from randomisation to death. Patients without progressive disease were to receive six planned courses.	Time to disease progression, safety. Follow-up period was the same as for primary outcome.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
Kim et al., 2019 [67]	Compare the safety and efficacy of irinotecan plus cisplatin over etoposide plus cisplatin in chemotherapy-naive Korean patients with ES-SCLC	Randomised, multicentre Phase III trial	Median age: 66 (intervention), 65 (comparator) Histologically or cytologically confirmed ES-SCLC (defined as presence of distant metastasis, contralateral hilar lymph node involvement, or cytologically proven malignant pleural effusion); chemotherapy-naive; ECOG PS ≤2; adequate organ function; no	Intervention: Irinotecan + Cisplatin (n=173) Comparator: Etoposide + Cisplatin (n=189)	OS – time from start of treatment to death. Treatment in each arm was repeated every 3 weeks for a maximum of six cycles.	PFS Follow-up period was the same as for primary outcome.	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
			symptomic brain metastases.				
Shimokawa et al., 2021 [48], Shimokawa et al., 2023 [49] JCOG1201/TORG1528	Evaluate the efficacy and safety of carboplatin plus irinotecan compared with carboplatin plus etoposide in elderly Japanese patients with ES-SCLC	Randomised Phase II/III study	Median age: 75 (intervention), 76 (comparator) Histologically or cytologically proven ES-SCLC; no previous systemic chemotherapy; PS 0-2.	Intervention: Irinotecan + Carboplatin (n=129) Comparator: Etoposide + Carboplatin (n=129)	Phase II: ORR Phase III: OS	Safety (adverse events)	NR
Cheng et al., 2022 [5] , Cheng et al., 2022 [51], Cheng et al., 2022 ([50], Cheng et al., 2024 [8] **ASTRUM-005**	Evaluate the efficacy and adverse event profile of serplilumab plus chemotherapy compared with placebo plus	International, double-blind, placebo-controlled Phase 3 randomised clinical trial	Median age: 63 (intervention), 62 (comparator) Histologically or cytologically confirmed ES-SCLC; no previous	Intervention: Serplulimab + Carboplatin + Etoposide (n=389) Comparator: Placebo +	OS – time from randomisation to death. All patients were followed for a median of 12.3	PFS, ORR, duration of response, adverse events, relationship between PD-L1 expression and efficacy	22 Oct 2021 [44, 51] 13 Jun 2022 [50, 81] 13 Jun 2023[8]

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
	chemotherapy as first-line treatment in patients with ES-SCLC		systemic therapy; 1 or more measurable lesions; ECOG PS 0-1; adequate organ function; life expectancy of ≥12 weeks; no symptomatic brain metastases.	Carboplatin + Etoposide (n=196)	months (range, 0.2-24.8 months) [44]. At interim analysis, the median follow-up duration was 12.3 months [51] an extended follow-up duration of 31.6 months [8] median follow-up duration was 19.7 months[50].	Tumour responses were assessed at screening, every 6 weeks for the first 48 weeks, and every 9 weeks thereafter. Treatment-emergent adverse events were recorded throughout the trial and for 90 days after the last dose was received.	
Paz-Ares et al., 2019 [54], Goldman et al., 2020 [55], Hotta et al., 2021 [57], Alt et al., 2021	Assess durvalumab, with or without tremelimumab, in combination with etoposide plus	Randomised, open-label, sponsor-blind Phase III study	Median age: 62 (intervention), 63 (comparator A), 63 (comparator B)	Intervention: Durvalumab + Platinum-Etoposide (n=268)	OS – time from randomisation to death.	PFS, OR, OS at 18 months, PFS at 6 and 12 months, safety.	11 Mar 2019 [52, 54, 55] 27 Jan 2020 [52, 56, 59]

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
[52], Goldman et al., 2021 [56], Garassino et al., 2021 [52], Paz-Ares et al., 2022 [58], Paz-Ares et al., 2022 [86], Goldman et al., 2022 [53], Paz-Ares et al., 2024 [59] **CASPIAN**	either cisplatin or carboplatin in treatment-naive patients with ES-SCLC		Treatment-naive histologically or cytologically confirmed ES-SCLC; WHO PS 0-1; measurable disease; adequate organ function; no symptomatic brain metastases.	Comparator: A: Platinum + Etoposide (n=269) B: Durvalumab + Tremelimumab + Platinum-Etoposide (n=268)	The median duration of follow-up for overall survival in censored patients was 14.2 months [54] the median follow-up for overall survival in censored patients was 25.1 months (IQR 22·3–27·9), reflecting an additional 11 months of follow-up compared with the interim analysis. [58] The biomarker analyses reported here were based on		22 Mar 2021 [58]

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
					data from the updated analysis of CASPIAN with a median follow-up of 25.1 months [59]		
Horn et al., 2018 [9], Nishio et al., 2019 [60], Mansfield et al., 2020 [61], Liu et al., 2021 [7] **IMpower13**	Evaluate atezolizumab plus carboplatin and etoposide in treatment-naive patients with ES-SCLC	Double-blind, placebo-controlled Phase III trial	Median age: 64 Histologically or cytologically confirmed ES-SCLC; measurable disease; ECOG PS 0-1; no previous systemic treatment for ES-SCLC.	Intervention: Atezolizumab + Carboplatin + Etoposide (n=201) Comparator: Carboplatin + Etoposide (n=202)	OS – time from randomisation to death, investigator-assessed PFS. Median follow-up of 22.9 months (updated analysis).[92] At a median follow-up of **13.9 months**, the median overall survival was 12.3 months in the atezolizumab group	Investigator-assessed ORR, duration of response. Tumour assessments were conducted at screening, every 6 weeks for the first 48 weeks, and every 9 weeks thereafter until disease progression.	24 Apr 2018 [9, 60, 61] 19 Jan 2019 (additional 9m months after the primary analysis) [7]

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
					and 10.3 months in the placebo group [9] The median follow-up duration for Japanese patients was **16.5 months** (range, 5.3-17.8 months) in the atezolizumab group and 15.3 months (range, 0.5-16.6 months) in the placebo group. The median duration of treatment was 4.7 months (range, 2.0-16.6 months) and 3.3 months (range, 0.0-15.2 months) in the atezoli[1]zumab		

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Data cut-off (DCO)
					and placebo groups, respectively [60]		

Notes: [1]All scans were subjected to review by at least one independent assessor blinded to treatment; [2]Final analysis was performed after all randomly assigned patients had at least 1 year of follow-up after random assignment, which occurred approximately 30 months after study start | **Abbreviations** ECOG PS: Eastern Cooperative Oncology Group Performance Status; ES-SCLC, extended stage small cell lung cancer; NR: Not Reported; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-Free Survival; RR, response rate; WHO PS, World Health Organisation Performance Status

H.1.3 Excluded fulltext references

[Please provide in a list or table the references that were excluded during fulltext screening along with a short reason. If using an existing, locally adapted SLR, please fill in the references originally included in the SLR but excluded in the current application.]

H.1.4 Quality assessment

Assessment of risk of bias (RoB) is regarded as an essential component of an SLR on the effects of an intervention. The quality appraisal process was conducted collaboratively by two reviewers to ensure a comprehensive and unbiased evaluation. Initially, one reviewer undertook the appraisal, methodically assessing each study against the predefined criteria. Subsequently, a second reviewer reviewed these appraisals to confirm accuracy and consistency. Discrepancies between reviewers were resolved through discussion, and if necessary, consultation with a third independent reviewer was sought.

To guarantee the transparency and accountability of the quality appraisal process, each judgment made during the assessment of risk of bias was documented in Microsoft Excel®.

The quality of studies included in this SLR were assessed according to the criteria outlined in the latest version of the Cochrane risk-of-bias tool (RoB 2) [93].

H.1.5 Unpublished data

Data on file: [3, 69, 70, 77].

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Accord Healthcare Ltd (Accord) sought Alira Health to perform a systematic literature review (SLR) to identify and synthesize evidence on economic evaluations, healthcare resource utilization (HCRU) and associated costs related to the of untreated extensive-stage small-cell lung cancer (ES-SCLC). The selection of treatments to be included in the SLR was based on European treatment guidelines recommendations.

An SLR was carried out to ensure that the identification of studies was comprehensive, accurate, and unbiased. This methodical approach ensured that each study was evaluated for its relevance, scientific integrity, and validity by two independent reviewers. Any discrepancy was resolved through discussion. A third reviewer was consulted if an agreement was not reach between the two other reviewers.

SLR methodology followed guidance from the Centre for Reviews and Dissemination (CRD) guidance [94]. Consistent with CRD guidance, the data selection process complied with the National Institute for Health and Care Excellence (NICE) guidance [82] and Cochrane methodology [83] for undertaking systematic reviews.

Research objectives and research questions

The aim was to conduct a SLR to synthesize the available evidence on the economic and humanistic burden associated with ES-SCLC in treatment-naïve patients and of all relevant and available interventions recommended by European Guidelines (European Society for Medical Oncology [ESMO] and NICE). This SLR aimed to answer the following narrow research questions:

- What are the comprehensive economic implications of treating ES-SCLC (see Appendix J)?
- What impact do treatments for ES-SCLC have on the quality of life of patients?

Table 71 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	2010-2024	07.05.2024
MEDLINE	Embase.com and PubMed.gov	2010-2024	07.05.2024

Database	Platform	Relevant period for the search	Date of search completion
The Cochrane Library, including CENTRAL	Cochranelibrary.com	2010-2024	07.05.2024

Abbreviations: CENTRAL, CENTRAL, Cochrane Central Register of Controlled Trials.

In addition to the searches through electronic databases, hand searches were conducted to capture data from recent studies or Health Technology Assessments (HTAs) not yet published or not captured by the electronic database registries. Searches for conference proceedings were limited to the last **three years** as it is assumed that studies are usually published within two to three years following presentation to a conference.

Table 72 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
HTAi	https://htai.org/	Hand search	07.05.2024
SMDM	https://smdm.org/	Hand search	07.05.2024
IASL	https://www.iaslc.org/	Hand search	07.05.2024
ISPOR	www.ispor.org	Hand search	07.05.2024
CEA	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Hand search	07.05.2024
RePEc	http://repec.org/	Hand search	07.05.2024
INAHTA	https://database.inahta.org/	Hand search	07.05.2024
NIHR	https://www.nihr.ac.uk/)	Hand search	07.05.2024

Abbreviations: CEA, Cost-Effectiveness Analysis Registry; Health Technology Assessment International; IASL, International Association for the Study of Lung Cancer; INAHTA, International HTA database; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NIHR, National Institute for Health and Care Research; RePEc, Research Papers in Economics.

Table 73 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to	dd.mm.yyyy

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
			search in the congress material:	
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

Table 74 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO Annual Meeting	https://www.asco.org/meetings	Hand search	-	07.05.2024
ECCO Congress	https://www.europeancancer.org/	Hand search	-	07.05.2024
ESMO Congress	https://www.esmo.org/meetings/esmo-congresses)	Hand search	-	07.05.2024
ELCC	https://www.esmo.org/meetings/past-meetings/european-lung-cancer-congress-2020	Hand search	-	07.05.2024

Abbreviations: ASCO, American Society of Clinical Oncology; ECCO, European Cancer Organisation; ESMO, European Society for Medical Oncology; ELCC, European Lung Cancer Congress.

Established HTA agencies' websites were consulted, including but not limited to:

- United Kingdom (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, National Authority for Health)
- Germany: *Gemeinsamer Bundesausschuss* (G-BA, Federal Joint Committee) and *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesenis* (IQWiG, Institute for Quality and Efficiency in Health Care)
- Sweden: Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU, Statens beredning för medicinsk och social utvärdering)
- Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)

- Australia: Pharmaceutical Benefits Advisory Committee (PBAC)
- United States: Institute for Clinical and Economic Review (ICER)

SLRs 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.

I.1.1 Search strategies

For health-state utility values and quality-of-life data, studies were selected if published between 2010 and 2024.

Table 75 Search strategy for EMBASE (searched via www.embase.com)

No.	Query	Results
Population		
#1	small cell lung cancer'/exp OR 'bronchial small cell cancer' OR 'bronchial small cell carcinoma' OR 'lung small cell cancer' OR 'lung small cell carcinoma' OR 'microcellular lung carcinoma' OR 'pulmonary small cell cancer' OR 'pulmonary small cell carcinoma' OR 'small cell bronchial cancer' OR 'small cell bronchial carcinoma' OR 'small cell cancer, lung' OR 'small cell lung cancer' OR 'small cell lung carcinoma' OR 'small cell pulmonary cancer' OR 'small cell pulmonary carcinoma' OR "extensive stage small cell lung cancer"	218339
#2	'small cell lung cancer':ab,ti OR 'small cell lung carcinoma':ab,ti OR 'small cell lung neoplasm':ab,ti OR 'sclc':ab,ti OR 'es-sclc' OR (('small cell lung' NEAR/3 cancer):ab,ti) OR (('small cell lung' NEAR/3 carcinoma):ab,ti) OR (('small cell lung' NEAR/3 neoplasm):ab,ti)	156920
#3	#1 OR #2	219605
#4	'non small cell lung cancer'/exp OR 'lung nonâ€•small cell carcinoma cell line':ab,ti OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung neoplasm':ab,ti OR 'nsclc':ab,ti OR ((non NEAR/2 'small cell lung'):ab,ti)	244250
#5	#3 NOT #4	26878
Study type: Economic studies		
#6	'socioeconomics'	174201
#7	'costs benefit analysis' OR 'cost-benefit analysis' OR 'costs effectiveness analysis' OR 'cost miniization analysis' OR 'budget impact analysis' OR	456561

No.	Query	Results
	'cost consequence analysis' OR 'cost utility' OR 'cost of illness' OR 'cost control' OR 'economic aspect' OR 'financial management'	
#8	'health care cost' OR 'healthcare cost$' OR 'healthcare financing' OR 'health economics' OR 'drug cost$' OR 'cost of drugs' OR 'cost near/2 treatment' OR 'employer health* cost$' OR 'hospital cost$' OR 'health expenditure$'	431363
#9	'direct cost'/exp OR 'indirect cost'/exp OR 'productivity' OR 'resource use' OR 'resource utilization'	170279
#10	'economic burden' OR 'economic evaluation'	59039
#11	#6 OR #7 OR #8 OR #9 OR #10	1101642
#12	#5 AND #11	316
Publication date (Economic: 2019-2024)		
#13	#12 AND (2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py)	114
Study type: Humanistic studies		
#14	'quality of life' OR 'quality adjusted life year' OR 'health related quality of life' OR 'european quality of life 5 dimensions questionnaire' OR 'euroqol-5 dimension' OR 'eq-5d' OR 'european quality of life 5 dimensions 3 level questionnaire' OR 'health state utility value' OR 'health state utility'	854099
#15	#5 AND #14	949
Publication date (QoL: 2010-2024)		
#16	#15 AND (2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py)	598
Combination		
#17	#13 OR #16	664
Publication type		
#18	'case study'/it OR 'case report'/it OR 'abstract report'/it OR 'conference proceeding'/it OR 'conference abstract'/it OR 'chapter'/it OR 'editorial'/it	12238709

No.	Query	Results
	OR 'letter'/it OR 'note'/it OR 'review'/it OR 'review':ti,tt OR 'update review':ab OR 'we searched':ab OR 'short survey'/it OR 'comment':ti,ab	
#19	#17 NOT #18	237
#20	'animal'/exp NOT 'human'/exp	6120557
#21	#19 NOT #20	236
Language		
#22	#21 AND [english]/lim	**216**

Table 76 Search strategy for Medline and Medline In-Process (searched via www.PubMed.com)

No.	Query	Results
Population		
#1	small cell lung cancer [MeSH Terms] OR "bronchial small cell carcinoma" OR "lung small cell cancer" OR "lung small cell carcinoma" OR "pulmonary small cell carcinoma" OR "small cell bronchial cancer" OR "small cell bronchial carcinoma" OR "small cell lung cancer" OR "small cell lung carcinoma" OR "small cell pulmonary cancer" OR "small cell pulmonary carcinoma"	102,292
#2	((("small cell lung cancer"[Title/Abstract]) OR ("small cell lung carcinoma"[Title/Abstract]))) OR ("SCLC"[Title/Abstract] OR "ES-SCLC"[Title/Abstract])	101,719
#3	#1 OR #2	103,282
#4	((("non small cell lung carcinoma"[Title/Abstract]) OR ("non small cell lung neoplasm"[Title/Abstract])) OR ("non small cell lung cancer"[Title/Abstract])) OR (non small cell lung cancer[MeSH Terms])	102,881
#5	#3 NOT #4	15,905
Study type: Economic studies		
#6	socioeconomics[mh]	521,830
#7	'cost* benefit analysis' OR 'cost-benefit analysis' OR 'cost* effectiveness analysis' OR 'cost minimization analysis' OR 'budget impact analysis' OR	1,098,409

No.	Query	Results
	'cost consequence analysis' OR 'cost utility' OR 'cost of illness' OR 'cost control' OR 'economic aspect' OR 'financial management'	
#8	'health care cost' OR 'healthcare cost*' OR 'healthcare financing' OR 'health economics' OR 'drug cost*' OR "cost of drugs" OR "cost of treatment" OR 'employer healthcare cost*' OR 'hospital cost*' OR 'health expenditure*'	2,028,987
#9	"direct cost" OR "indirect cost" OR "productivity" OR "resource use" OR "resource utilization"	122,661
#10	'economic burden' OR 'economic evaluation'	229,278
#11	#6 OR #7 OR #8 OR #9 OR #10	2,871,134
#13	#11 AND #5; Filter: from 2019 – 2024, English, Humans	122
Publication type		
#14	"case study"[tiab] OR "case reports"[pt] "chapter"[tiab] OR editorial[pt] OR letter[pt] OR comment[pt]	1,678,160
#15	review[pt] OR "update review"[tiab] OR "we searched"[tiab]	2,240,687
Study type: Humanistic studies		
#16	#14 OR #15	3,890,107
#17	#13 NOT #16	108
Publication date (QoL: 2010-2024)		
#18	'quality of life' OR 'quality adjusted life year' OR 'health related quality of life' OR 'european quality of life 5 dimensions questionnaire' OR 'euroqol-5 dimension' OR 'eq-5d' OR 'european quality of life 5 dimensions 3 level questionnaire' OR 'health state utility value' OR 'health state utility'	1,169,906
Combination		
#19	#5 AND #18; Filter: from 2010 - 2024	318
Publication type		
#20	#5 AND #18; Filter: from 2010 – 2024, English, Humans	246

No.	Query	Results
#21	"case study"[tiab] OR "case reports"[pt] "chapter"[tiab] OR editorial[pt] OR letter[pt] OR comment[pt]	1,678,160
#22	review[pt] OR "update review"[tiab] OR "we searched"[tiab]	2,240,687
#23	#21 OR #22	3,890,107
#24	#20 NOT #23	193

Table 77 Search strategy for Cochrane (searched via www.cochrane.com)

No.	Query	Results
#1	MeSH descriptor: [Small Cell Lung Carcinoma] explode all trees	632
#2	'small cell lung cancer' OR 'bronchial small cell cancer' OR 'bronchial small cell carcinoma' OR 'lung small cell cancer' OR 'lung small cell carcinoma' OR 'microcellular lung carcinoma' OR 'pulmonary small cell cancer' OR 'pulmonary small cell carcinoma' OR 'small cell bronchial cancer' OR 'small cell bronchial carcinoma' OR 'small cell cancer, lung' OR 'small cell lung cancer' OR 'small cell lung carcinoma' OR 'small cell pulmonary cancer' OR 'small cell pulmonary carcinoma' OR 'extensive stage small cell pulmonary cancer'	20289
#3	'small cell lung carcinoma' OR 'small cell lung neoplasm' OR 'sclc' OR 'es-sclc'	11197
#4	("small-cell lung cancer"):ti,ab,kw	17678
#5	#1 OR #2 OR #3 OR #4	20361
#6	'non small cell lung cancer' OR 'lung non-small cell carcinoma cell line' OR 'non small cell lung carcinoma' OR 'non small cell lung neoplasm' OR 'nsclc'	18212
#7	("non-small cell lung cancer"):ti,ab,kw	15349
#8	#6 OR #7	18212
#9	#5 NOT #8	2812
Study type: Economic studies		

No.	Query	Results
#10	MeSH descriptor: [Cost of Illness] explode all trees	1185
#11	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	11411
#12	MeSH descriptor: [Cost-Effectiveness Analysis] explode all trees	115
#13	'cost* benefit analysis' OR 'cost-benefit analysis' OR 'cost* effectiveness analysis' OR 'cost minimization analysis' OR 'budget impact analysis' OR 'cost consequence analysis' OR 'cost utility' OR 'cost of illness' OR 'cost control' OR 'economic aspect' OR 'financial management'	62703
#14	'health care cost' OR 'healthcare cost*' OR 'healthcare financing' OR 'health economics' OR 'drug cost*' OR "cost of drugs" OR "cost of treatment" OR 'employer healthcare cost*' OR 'hospital cost*' OR 'health expenditure*'	79721
#15	"direct cost" OR "indirect cost" OR "productivity" OR "resource use" OR "resource utilization"	11029
#16	#10 OR #11 OR #12 OR #13 OR #14 OR #15	99653
#17	#9 AND #16	209
#18	#9 AND #16 with Publication Year from 2019 to 2024, in Trials	24
Source	Pubmed	9
	Embase	16
	CT.gov	4
	ICTRP	2
	CINAHL	NR
Study type: Humanistic studies		
	MeSH descriptor: [Quality of Life] explode all trees	43875
	'quality of life' OR 'quality adjusted life year' OR 'health related quality of life' OR 'european quality of life 5 dimensions questionnaire' OR 'euroqol-5 dimension' OR 'eq-5d' OR 'european quality of life 5 dimensions 3 level questionnaire' OR 'health state utility value' OR 'health state utility'	187735
	#19 OR #20	179961

No.	Query	Results
	#9 AND #21	468
	#9 AND #21 with Publication Year from 2010 to 2024, in Trials	153
Source	Pubmed	42
	Embase	89
	CT.gov	14
	ICTRP	35
	CINAHL	NR

Titles and abstracts of studies identified from the search strategy, where available, were screened by two reviewers independently, according to the pre-specified inclusion/exclusion criteria. Articles, identified as potentially relevant based on titles and abstracts, were reviewed in full and selected similarly – by two reviewers, independently and in parallel, based on the pre-specified study selection criteria. Any discrepancy was resolved by discussion. A third reviewer was involved if a decision agreement could not be reached between the two reviewers. Finally, all the included studies were extracted in a tabular summary.

A comprehensive record of decisions was maintained for each article, with specific reasons for exclusion documented during the full-text review stage (e.g., not population of interest, no intervention of interest, no outcomes of interest, inappropriate study type, no language of interest).

A PRISMA flow chart was created to illustrate the number of studies/papers remaining at each stage, providing transparency and clarity regarding the study selection process.

Table 78 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with untreated ES-SCLC (naïve)	Patients with NSCLC Studies that do not separately report results by line of treatment in ES-SCLC Studies including squamous and non-squamous patients that

		do not stratify results for squamous patients Other populations not listed under the inclusion criteria
Intervention	Serplulimab + Carboplatin and Etoposide	Not applicable
Comparators	Any regimens and/or targeted therapies recommended for the treatment of ES-SCLC by European Guidelines (ESMO and NICE guidelines ({Dingemans, 2021 #34;Scottish Intercollegiate Guidelines Network, #104})[1]	Studies including chemotherapy regimens and/or targeted therapies not recommended for the treatment of ES-SCLC
Outcomes	Humanistic Burden: QoL for either patients and/or caregivers Health state utility values (HSUV) Economic Burden: Economic evaluations (i.e., cost-consequence, cost-minimization, cost-effectiveness, cost-utility, cost-benefit, cost-consequence, and budget impact analysis) Direct costs and resources use (e.g., medication, diagnostics, long-term care) Indirect costs and resource use (e.g., productivity, transportation, support costs)	Other economic and QoL outcomes No costs or resource utilization reported, studies only reporting efficacy, safety
Study design/publication type	Primary research literature, systematic reviews, and economic model reports	Case studies/reports, Randomized Controlled Trials (RCTs), reviews
Language restrictions	English	Non-English papers (where translation is not provided)
Publication type	Peer-reviewed published in journals or retrieved via hand searches	Letters and editorials

		Conference abstracts (published in 2021 or earlier)
Publication date	HSUV and QoL: 2010-2024 Economic outcomes: 2019-2024 (March)	Studies published before 2019 or 2010, for the economic and humanistic burden searches, respectively
Geography	Not restricted	Not restricted

Notes: 1 At the time of writing the NICE ES-SCLC guidelines, some immunotherapy regimens had not yet received approval or reimbursement in UK. In this case, decisions regarding the recommendation for use of these therapies will be driven by reimbursement status as determined by the national HTA agency of the UK.
Abbreviations: ESMO: European Society for Medical Oncology; ES-SCLC: Extensive-Stage Small Cell Lung Cancer; HSUV: Health-State Utility Values; NICE: National Institute for Health and Care Excellence; NSCLC: Non-Small Cell Lung Cancer; QoL: Quality of Life; RCT: Randomized Controlled Trial; SCLC: Small Cell Lung Cancer.

Literature search results included in the model/analysis:

N/A

I.1.2 Quality assessment and generalizability of estimates

The CHEERs checklist developed by the 2022 ISPOR task force is the preferred guidance on reporting health economic research and is recognized by bodies such as PRISMA for its role in SLRs (Husereau et al., 2022 [95]).

CHEERs checklist includes a set of 28 items that cover various aspects of economic evaluations to ensure that economic evaluations are reported with sufficient detail and clarity. Checklist items are subdivided into seven main categories:

- Title: Clearly state that the study is an economic evaluation.
- Abstract: Summarize the economic evaluation's objectives, methods, results, and conclusions.
- Introduction:
  - Background and Objectives: Explain the study's context, the rationale for the economic evaluation, and its objectives.
- Methods:
  - Target Population and Subgroups: Describe the population being studied.
  - Setting and Location: Specify the study's setting and location.
  - Study Perspective: Clarify the perspective (e.g., societal, healthcare system) from which the evaluation is conducted.
  - Comparators: Identify the alternatives compared in the evaluation.
  - Time Horizon: Define the time period over which costs and outcomes are evaluated.

- Discount Rate: If applicable, report the discount rate used for future costs and outcomes.
- Choice of Health Outcomes: Specify the health outcomes used (e.g., quality-adjusted life years).
- Measurement of Effectiveness: Explain how the effectiveness of interventions was measured.
- Measurement and Valuation of Preference-Based Outcomes: Describe methods used to value outcomes.
- Estimation of Resources and Costs: Detail how resource use and costs were estimated.
- Currency, Price Date, and Conversion: Report the currency used, the price date, and any conversions.
- Analytic Methods: Describe the methods used for analysing the data.

- Results:
  - Study Parameters: Present key parameters and assumptions used in the model.
  - Incremental Costs and Outcomes: Report the difference in costs and outcomes between alternatives.
  - Characterizing Uncertainty: Describe how uncertainty was handled and present the results of sensitivity analyses.
  - Characterizing Heterogeneity: Discuss variations in results across different subgroups or scenarios.
- Discussion:
  - Study Findings, Limitations, Generalizability, and Current Knowledge: Interpret the findings in the context of existing knowledge, discuss limitations, and consider the generalizability of results.
- Other:
  - Source of Funding: Disclose funding sources and their potential influence.
  - Conflicts of Interest: Declare any conflicts of interest.

The checklist judgement uses three judgment categories to evaluate the quality of reporting in economic evaluations: ‘Yes’, ‘No’, ‘Partially reported’ or ‘Not reported’

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

Not applicable, a Health economic model is not used in this application.

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