Serplulimab (Hetronifly®) with carboplatin and etoposide for the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC)

General information [1]

Drug description

The active substance of Hetronifly® is serplulimab, an antineoplastic monoclonal antibody. By blocking the binding of PD-1 to PD-L1 and PD-L2, serplulimab potentiates T-cell responses, including anti-tumour responses.

Indication

Serplulimab (Hetronifly®) in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with ES-SCLC.

Incidence

In Austria, in 2022, a total of 5,203 persons were newly diagnosed with cancer of the lung, bronchia and trachea. The age-standardised[1] incidence rate was 68.0 per 100,000 men and 45.8 per 100,000 women [2].
Small cell lung cancer (SCLC)accounts for about 12-15% of lung carcinomas. 60-70% of patients with SCLC are first diagnosed in the extensive disease stage [3].

Current treatment [3]

The algorithm for the first-line therapy in stage IV SCLC is displayed in the Appendix.

Regulatory status

EMA [1]	FDA
Approval status for this indication: On 19 September 2024, the CHMP adopted a positive opinion, recommending granting a marketing authorisation for Hetronifly®. The full indication is: ❖ Hetronifly® in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with ES-SCLC. **Other indications**: none ✓ **Orphan status**	**Approval status for this indication**: not approved In March 2022, the FDA granted an orphan designation to serplulimab for the treatment of SCLC [4]. **Other indications**: none

Marketing authorisation applicant [1]

The marketing authorisation applicant for Hetronifly® is Henlius Europe GmbH.

Costs

Currently, there is no cost information available.

Posology

[1] European Standard Population 2013.

Currently, there is no EMA EPAR Product Information available for Hetronifly®.

Warnings and precautions

Currently, there is no EMA EPAR Product Information available for Hetronifly®.

Study characteristics [5]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
ASTRUM-005 NCT04063163	585 (2:1)	4.5 mg/kg of serplulimab + IV carboplatin and etoposide every 3 weeks for up to 12 weeks	placebo + IV carboplatin and etoposide every 3 weeks for up to 12 weeks	OS[2]	12.3 months (range, 0.2-24.8 months)	double-blind, placebo-controlled, phase 3 randomised clinical trial	PD-L1	Shanghai Henlius Biotech, Inc.	ASTRUM-005 [5]

Inclusion criteria[3]

- Aged ≥ 18 years and ≤ 75 years when signing the ICF.
- Histologically or cytologically diagnosed with ES-SCLC.
- No prior systemic therapy for ES-SCLC (including systemic chemotherapy, molecular targeted therapy, biological therapy, and other investigational therapies, etc.).
- Patients who have received chemoradiotherapy for previous limited-stage SCLC must be treated with curative intent and have a treatment-free interval of at least 6 months from the last course of chemotherapy, radiotherapy, or chemoradiotherapy to the diagnosis of extensive-stage SCLC.
- At least one measurable lesion as assessed by the IRRC according to RECIST v1.1 within 4 weeks prior to randomisation.
- Every effort should be made to provide tumour tissues that meet the requirements for determining PD-L1 expression levels. Subjects are assessed for randomisation for an evaluable PD-L1 expression category (negative, positive, or not available) by the central laboratory.
- Prior antineoplastic therapy must have been ≥ 2 weeks from the first dose in this study, with treatment-related AEs resolved to NCI-CTCAE Grade ≤ 1.
- An ECOG PS score of 0 or 1.
- An expected survival ≥ 12 weeks.

Exclusion criteria

- Histologically or cytologically confirmed mixed SCLC.
- Other active malignancies within 5 years or at the same time.
- Patients who are preparing for or have received an organ or bone marrow transplant.
- Pleural or pericardial effusion requiring clinical intervention or ascites.
- Patients with known or documented active CNS metastases and/or carcinomatous meningitis at screening.
- Subjects with spinal cord compression that has not been radically treated with surgery and/or radiotherapy.
- Patients with myocardial infarction within half a year before the first dose of the study drug poorly controlled arrhythmia.
- Class III to IV cardiac insufficiency according to NYHA classification or an LVEF < 50% by cardiac colour Doppler.
- Subject has uncontrolled or symptomatic hypercalcemia.
- Subject with peripheral neuropathy ≥ Grade 2 by CTCAE.
- HIV infection, positive test for HIV antibody.
- Active pulmonary tuberculosis.
- Subjects with previous and concurrent interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis and severe impaired pulmonary function that may interfere with the detection and management of suspected drug-related pulmonary toxicity as judged by the investigator.
- Hepatitis B or Hepatitis C co-infection.

Patient characteristics at baseline (n) Number of patients overall: 389 vs. 196

- Age <65 years: 235 vs. 119
- Age >65 years: 154 vs. 77
- Male sex: 317 vs. 164
- Race:
  - Asian: 262 vs. 139
  - Non-Asian: 127 vs. 57
- ECOG PS score:
  - 0: 71 vs. 32
  - 1: 318 vs. 164
- Smoking history:
  - Never: 81 vs. 35
  - Current: 102 vs. 48
  - Former: 206 vs. 113
- Brain metastases
  - No: 339 vs. 168
  - Yes: 50 vs. 28
- PD-L1 expression level:
  - TPS <1%: 317 vs. 152
  - TPS ≥1%: 62 vs. 34
  - Not evaluable or not available: 10 vs. 10

[2] According to the study protocol, PFS assessed by IRRC according to RECIST v1.1 was defined as primary endpoint.
[3] For detailed in- and exclusion criteria, please see trial protocol.

❖ Subjects with prior denosumab use that can and agree to switch to bisphosphonate therapy for bone metastases starting prior to randomisation and throughout treatment. ❖ Normal major organ functions as defined by the following criteria (no blood transfusions, or treatment with albumin, recombinant human thrombopoietin or colony-stimulating factor within 14 days prior to the first dose in this study): • Absolute neutrophil count ≥ 1.5×109/L • Lymphocyte ≥ 0.5×109/L • Platelet ≥ 100×109/L • Haemoglobin ≥ 90 g/L Liver function • Total bilirubin ≤ 1.5×upper limit of normal (ULN). For patients with Gilbert's syndrome, total bilirubin ≤ 3 × ULN is acceptable. • Alanine transaminase ≤ 2.5×ULN; ≤ 5 × ULN for patients with liver metastases • Aspartic transaminase ≤ 2.5×ULN; ≤ 5 × ULN for patients with liver metastases • Alkaline phosphatase ≤ 2.5×ULN; ≤ 5.0 × ULN for patients with liver or bone metastases • Creatinine ≤ 1.5×ULN; In case of > 1.5 × ULN, creatinine clearance ≥ 50 mL/min (calculated from Cockcroft-Gault formula). • Activated partial prothrombin time ≤ 1.5×ULN • International normalised ratio ≤ 1.5×ULN ❖ Female patients must meet one of the following conditions: • Menopause or • Surgically sterilised or • With child-bearing potential, but must: o have a negative serum pregnancy test within 7 days prior to first dose, and o agree to use contraception with an annual failure rate of < 1% or to remain abstinent from obtaining informed consent to at least 120 days after the last dose of trial medication and at least 150 days after the last dose of chemotherapy medication and o not breastfeed ❖ Male patients must: agree to abstinence or take contraception measures as defined in protocol.	❖ Known active or suspected autoimmune diseases. ❖ Treatment with live vaccines within 28 days prior to study drug administration; inactivated viral vaccines for seasonal influenza are allowed. ❖ Subjects requiring treatment with systemic corticosteroids or other immunosuppressive drugs within 14 days prior to the first dose or during the study. ❖ Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration. ❖ Major surgery within 28 days prior to the first dose of the study drug. ❖ Radical radiation therapy within 3 months prior to study medications. ❖ The subject has previously received other antibodies/drugs against immune checkpoints, such as PD-1, PD-L1, CTLA4, etc. ❖ Participation in any other ongoing clinical studies, or less than 14 days from the end of the previous clinical study treatment to the start of this trial. ❖ Known history of severe allergy to any monoclonal antibody. ❖ Known hypersensitivity to carboplatin or etoposide. ❖ Pregnant or lactating women. ❖ Known history of psychotropics abuse or drug abuse. ❖ In the judgment of the investigator, the subject has any other factors that may lead to a premature discontinuation.	
Efficacy (I vs. C)		**Safety** (I vs. C, n=389 vs. 196)
Data cutoff for the interim analysis: 22 October 2021; median follow-up 12.3 months		

Median OS: 15.4 months (95% CI, 13.3 months-NE) vs. 10.9 months (95% CI, 10.0-14.3 months); HR 0.63 (95% CI, 0.49-0.82); p< .001) Estimated OS rate at 1 year: 60.7% (95% CI, 54.9%-66.0%) vs. 47.8% (95% CI, 39.6%-55.6%) Estimated OS rate at 2 years: 43.1% (95% CI, 34.1%-51.7%) vs. 7.9% (95% CI, 0.7%-27.2%) <u>Assessments by the IRRC:</u> Median PFS: 5.7 months (95% CI, 5.5-6.9 months) vs. 4.3 months (95% CI, 4.2-4.5 months); HR 0.48 (95% CI, 0.38-0.59) ORR: 80.2% (95% CI, 75.9%-84.1%) vs. 70.4% (95% CI, 63.5%-76.7%) Median duration of response among patients with complete or partial tumour response: 5.6 months (95% CI, 4.2-6.8 months) vs. 3.2 months (95% CI, 2.9-4.2 months) <u>Assessments by the Investigators:</u> Median PFS: 5.5 months vs. 4.3 months; HR, 0.58 (95% CI, 0.48-0.71) The assessments of tumour response and duration of response by the investigators were consistent with the committee's assessments. <u>Prespecified Subgroup Analyses and Post Hoc Analyses</u> HR for overall survival consistently favoured the serplulimab group across the prespecified subgroups. Median OS in patients with brain metastases: 13.9 months (95% CI, 9.0 months-NE) vs. 10.0 months (95% CI, 7.2-12.7 months); HR 0.61 (95% CI, 0.33-1.13). Median OS in patients without brain metastases: 15.6 months (95% CI, 13.3 months-NE) vs. 11.3 months (95% CI, 10.0-14.6 months); HR 0.62 (95% CI, 0.47-0.82). Median OS in patients with a tumour proportion score of < 1% for PD-L1 expression level: 15.0 months vs. 10.5 months; HR 0.58 (95% CI, 0.44-0.76). Median OS in patients with a tumour proportion score of ≥1%: NR vs. 12.9 months; HR 0.92 (95% CI, 0.44-1.89). Subsequent treatment received after the first incidence of disease progression: 44.2% vs. 43.4% Patients who completed the trial: 42.1% Patients still receiving study treatment at the time of data cutoff: 24.9% vs. 11.7% **<u>Extended follow-up results (abstract data); data cutoff 13 June 2023 [6]:</u>** Median OS: 15.8 vs.11.1 months; stratified HR 0.61, 95% CI 0.50–0.74 Subgroup analysis by race: prolonged median OS in Asians (unstratified HR 0.61, 95% CI 0.48–0.77) and non-Asians (all were White; unstratified HR 0.57, 95% CI 0.39–0.83). Estimated OS rate at 3 years: 24.6% (95% CI 19.5–30.1) vs. 9.8% (95% CI 5.6–15.4)	TEAEs: 95.6% vs. 97.4% TEAEs of grade ≥3: 82.5% vs. 80.1% TRAEs (related to serplulimab or placebo). 69.9% vs. 56.1% TRAEs grade ≥3: 33.2% vs. 27.6% TEAEs leading to treatment discontinuation: 8.0% vs. 7.7% TRAES leading to treatment discontinuation: 4.9% vs. 4.1% Death due to TEAEs: 7.7% vs. 10.2% Death due to AEs attributed to serplulimab: n=3[4] (0.8%) Death due to AEs attributed to placebo: n=1[5] (0.5%)[6] Immune-related AEs: 37.0% vs. 18.4% Immune-related AEs grade ≥3: 9.5% vs. 5.6% Infusion-related reactions: 1.8% vs. 0.5% Pneumonia: 8.2% vs. 8.2% TRAE of pneumonia grade ≥3: 1% vs. 1% Pneumonia with an immune-mediated mechanism: 0.8% vs. 0.5% Immune-related pneumonia grade ≥3: n=1 vs. n=1
Patient-reported outcomes [6]	
❖ By-visit longitudinal changes in all domains of the 3 questionnaires were comparable between arms.	

[4] Acute coronary syndrome, pyrexia, and decreased platelet count.
[5] Thrombocytopenia.
[6] All 4 TRAEs leading to death were immune-related.

- Least square mean (LSM) changes from baseline to week 18 in QLQ-C30 functional and symptom domains, QLQ-LC13 symptom domains, and EQ-5D-5L VAS were similar and generally improved in both arms, with more pronounced and persistent amelioration in "pain in other parts" symptom domain for the serplulimab arm (difference in LSM change 26.37; 95% CI 211.59 to 21.15; p = 0.0170).
- Time to deterioration was similar between arms: median, NR vs. NR for global health status/quality of life (HR 0.90, 95% CI 0.59–1.39), physical functioning (HR 1.01, 95% CI 0.61–1.65), and role functioning (HR 1.17, 95% CI 0.74–1.87).

ESMO-MCBS version 1.1 [7]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	≤12 months	OS: +4.7 months	0.61 (0.50–0.74)	HR≤0.65 AND gain ≥3 months	4	-	Improved	+1[7]	5
Adapted	NC	2A	≤12 months	OS: +4.7 months	0.61 (0.50–0.74)	HR≤0.65 AND gain ≥3 months	4	+18.6% immune-related AEs	improved	+1[8]/-1[9]	4

Risk of bias (RCT) [8]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	low risk	yes[10] high risk	yes[11] high risk	High risk

Ongoing trials [9]

NCT number/trial name	Description	Estimated study completion date
NCT05468489 / ASTRIDE	A randomised, open-label study of serplulimab plus chemotherapy (carboplatin-etoposide) in comparison with atezolizumab plus chemotherapy in previously untreated US patients with ES-SCLC.	12/2025

Available assessments

- In July 2023, NIHR published a Health Technology Briefing "Serplulimab with chemotherapy for treating previously untreated extensive stage small-cell lung cancer" [10].
- No assessments were found via G-BA, NICE and ICER.

Other aspects and conclusions

- In September 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for serplulimab (Hetronify®), indicated in combination with carboplatin and etoposide for the first-line treatment of adult patients with ES-SCLC. Hetronify® is currently **not approved by the FDA**.
- **ASTRUM-005 (NCT04063163)** is an international, **double-blind, phase 3** randomised clinical trial evaluating the efficacy and adverse event profile of serplulimab plus chemotherapy compared with placebo plus chemotherapy as first-line treatment in patients with extensive-stage SCLC. Eligible patients were ≥18 years old, had histologically or cytologically confirmed extensive-stage SCLC, and had not previously received systemic therapy for extensive-stage SCLC. Patients must have had 1 or more measurable lesions assessed using RECIST version 1.1, an ECOG PS Scale score of 0 or 1, adequate organ function, and a life expectancy of 12 weeks or longer. Key exclusion criteria included mixed-stage SCLC, active CNS metastases or carcinomatous meningitis, and autoimmune diseases.
- According to the trial protocol, **PFS was the predefined primary endpoint. At the request of the FDA and the EMA, a protocol amendment changed the primary outcome** from PFS to OS. Extended follow-up results showed a **median OS of 15.8 months in the serplulimab arm compared to 11.1 months in the placebo arm** (stratified HR 0.61, 95% CI 0.50–0.74).

[7] Upgrade due to QoL improvement.
[8] Upgrade due to QoL improvement.
[9] Toxicity adjustment.
[10] According to the trial protocol, "PFS assessed by IRRC according to RECIST v1.1" was defined as primary endpoint. A protocol amendment (protocol version 3.0 dated April 8, 2020) was made at the request of the FDA and the EMA that changed the primary outcome from PFS to OS. The sample size calculation was based on OS. The initial sample size calculation was based on PFS; sample size was recalculated.
[11] Industry-funded.

- Analyses of **PROs** showed LSM changes from baseline to week 18 in QLQ-C30 functional and symptom domains, QLQ-LC13 symptom domains, and EQ-5D-5L VAS were **similar and generally improved** in both arms. Time to deterioration was similar between arms.
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit of **5 and 4**, respectively.
- The **ASTRUM-005 trial's risk of bias was considered high. Although conducted in a randomised and double-blind way, the trial´s risk is increased by the change of primary endpoint due to** protocol amendment and its industry-funded background.
- One **ongoing** phase 3 trial, assessing serplulimab plus chemotherapy (carboplatin-etoposide) in comparison with atezolizumab plus chemotherapy in previously untreated US patients with ES-SCLC, was identified via ClinicalTrials.gov.
- **Final analysis results** for efficacy, safety and PROs of the ASTRUM-005 trial are required. **Concerns** are raised due to the subsequent protocol amendment to change the primary endpoint.

First published: 11/2024

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS= central nervous system, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EMA=European Medicines Agency, EPAR=European Public Assessment Report, EQ-5D-5L= EuroQol Group 5-Dimension 5-Level questionnaire, ES-SCLC=extensive stage small cell lung cancer, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, EU=European Union, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, ICF=informed consent, Int.=intention, IRRC=Independent Radiology Review Committee, IV=intravenous, LSM= Least square mean, MG=median gain, n=number of patients, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, NE=not evaluable, NICE=National Institute for Health Care Excellence, NR=not reached, NYHA=New York Heart Association ORR=objective response rate, OS=overall survival, PD-1=Programmed cell death-ligand 1, PD-L1=Programmed cell death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QLQ-C30=Quality of Life Questionnaire, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, SCLC=small cell lung cancer, ST=standard treatment, ULN=upper limit of normal, VAS=visual analogue scale

References:

[1] European Medicines Agency (EMA). Medicines. Hetronifly. [cited 2024-11-18]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/hetronifly.

[2] Statistik Austria. Krebserkrankungen. Krebsinzidenz nach ausgewählten Lokalisationen und Geschlecht. [cited 2024-11-18]. Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen.

[3] Onkopedia, Wolf M and et al. Onkopedia guidelines. Small-Cell Lung Cancer (SCLC). [cited 2024-11-18]. Available from: https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/small-cell-lung-cancer-sclc/@@guideline/html/index.html#ID0E5DBG.

[4] U.S. Food and Drug Administration (FDA). Orphan Drug Designations and Approvals. [cited 2024-11-18]. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=869822.

[5] Cheng Y, Han L, Wu L and 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 doi:101001/jama202216464.

[6] Cheng Y and 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. 2024 ASCO Annual Meeting2024.

[7] Cherny NI, Dafni U, Bogaerts J and et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.

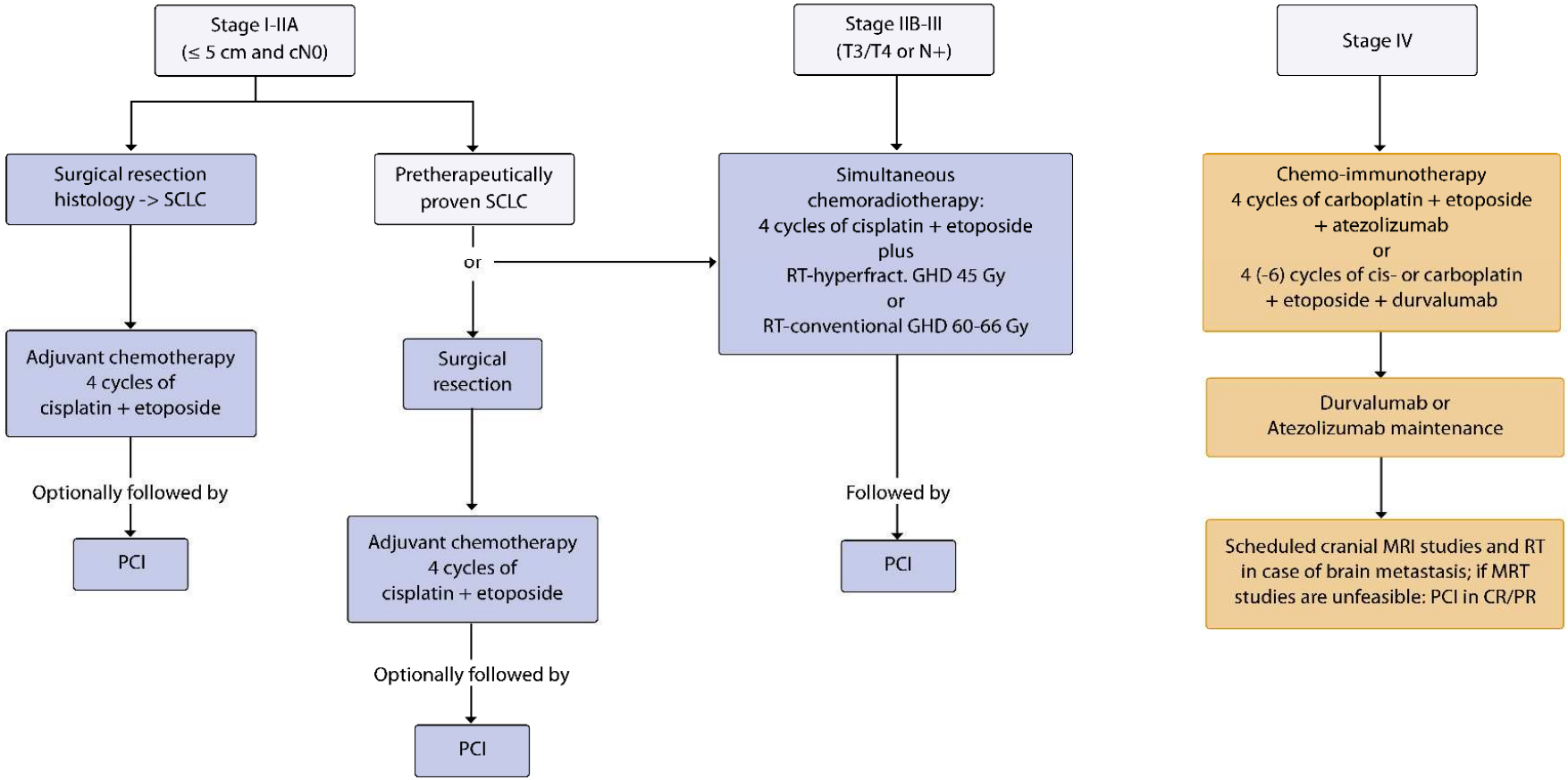
[8] European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015) Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf.

[9] U.S. National Library of Medicine and ClinicalTrials.gov. [cited 2024-11-19]. Available from: https://clinicaltrials.gov/.

[10] National Institute for Health Research (NIHR). Serplulimab with chemotherapy for treating previously untreated extensive stage small-cell lung cancer. [cited 2024-11-19]. Available from: https://io.nihr.ac.uk/wp-content/uploads/2023/07/30372-Serplulimab-Chemotherapy-for-Small-Cell-Lung-Cancer-V1.0-JUL2023-NON-CONF.pdf.

Appendix:

Treatment structure for small-cell lung cancer (SCLC)



Legend:

curative intention; palliative intention;

SCLC = small-cell lung cancer, OP = surgery, PCI = prophylactic cranial irradiation; RT = radiation (radiotherapy); GHD = total therapeutic dose, hyperfraction RT = hyperfractionated radiotherapy 2 x daily, RT-conventional = conventional fractionated radiotherapy 1 x daily, Gy = Gray, CR = complete remission, NC = no change, PR = partial remission, MRI = magnetic resonance imaging.