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Title

A single-arm phase II study of consolidation Serplulimab following hypofractionated radiotherapy with concurrent chemotherapy for patients with limited stage small cell lung cancer(ASTRUM-LC01)

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Abstract

Introduction With the inspiring results of PACIFIC trial in non-small cell lung cancer (NSCLC), and CAPIAN and IMpower133 trial in extensive-stage small cell lung cancer (SCLC), immunotherapy has increasingly gained attention. Serplulimab, a PD-1 inhibitor, showed great antitumor activity in ASTRUM-005 trial and has been recommended as first-line therapy in extensive-stage SCLC. Whether serplulimab following hypofractionation radiotherapy and chemotherapy could bring better outcomes in limited-stage SCLC remains to be answered.

Methods and analysis We designed a prospective multicenter single-arm phase II clinical trial to evaluate both the efficacy and safety of chemoradiotherapy and consolidation by serplulimab in limited-stage SCLC. Eligible patients will receive standard chemotherapy for 4 cycles and concurrent thoracic radiotherapy with total dose being 45Gy in 3 weeks and 3Gy dose per fraction. Prophylactic cranial irradiation is recommended for response patients. Serplulimab will be delivered afterwards every 3 weeks for up to 1 year. Based on sample size estimation, 55 patients will be enrolled in total.

Ethics and Dissemination Ethics approval was obtained from the Independent Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (22/236-3438).

Registration details This study was registered in ClinicalTrials.gov (NCT05443646).

Strengths and limitations of this study

Strengths

1. Serplulimab have reported the longest median overall survival time in extensive-stage small-cell lung cancer (SCLC) patients. This trial aimed at assessing drug efficacy in limited stage SCLC as consolidation therapy.
2. Hypofractionated radiotherapy was applied and might have additional benefits together with immunotherapy.

Limitations

1. Single-arm design without a control group.
2. Limited number of enrolled patients.

Introduction

Small cell lung cancer (SCLC) originates from epithelial cells with neuroendocrine differentiation. It accounts for 15%–20% of the total number of lung cancers[1]. SCLC is characterized by high malignancy, strong invasiveness, early metastasis, and rapid disease progression, with an extremely poor prognosis. According to the Veterans Administration Lung Study Group (VALSG) stage, SCLC can be further divided into limited stage and extensive stage. Approximately 30%-40% patients are initially diagnosed with limited-stage SCLC (LS-SCLC)(1). At present, surgery and chemotherapy with concurrent radiotherapy are standard treatment regimens for LS-SCLC. However, surgery is only applicable for a few patients with early SCLC, accounting for approximately 2%–5%. The combination of definitive thoracic radiotherapy and platinum-based chemotherapy followed by prophylactic cranial irradiation (PCI) in responsive patients has been the standard regimen in the past two decades. The median overall survival has been reported to be 25-30 months in recent years(2).

The progress of small cell lung cancer research was slow in the 20th century until the encouraging results of the Impower133 study(3) and CASPIAN study(4) shed light on the treatment of extensive-stage SCLC (ES-SCLC). Thereafter, more PD-1/PD-L1 inhibitors were proven to be effective as first-line treatment for ES-SCLC, including adebrelimab(5), pembrolizumab(6), serplulimab(7), etc. Among them, patients treated with serplulimab had the longest median overall survival time (OS) considering the absolute value (15.8 vs. 11.1 months for placebo group; hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.50–0.76; descriptive p<0.001). Subgroup analysis of OS by race showed similar trends to improved survival in Asians and non-Asians(7).

However, evidence of consolidation immunotherapy for LS-SCLC is limited. The STIMULI study, a phase II randomized controlled clinical study, failed to prove the superiority of consolidation immunotherapy consisting of nivolumab and ipilimumab(8). One possible reason for this may be the unexpectedly high rate of grade ≥3 adverse events (62% vs 25% in the experimental and observation arms, respectively).

A randomized, placebo-controlled phase III trial, the ADRIATIC study, investigating the efficiency of durvalumab with or without tremelimumab following concurrent chemoradiotherapy in LS-SCLC is ongoing. With the inspiring results of serplulimab in ES-SCLC, we hypothesized that serplulimab might show certain efficacy in LS-SCLC with acceptable toxicity profiles.

Moreover, the optimal radiotherapy fractionation for LS-SCLC has been under debate. The hyperfractionation regimen (45 Gy/1.5 Gy bid/3 weeks) has been the standard regimen according to the Intergroup 0096 study since 1999(9). A new phase II trial suggested that a higher dose of 60 Gy in 40 fractions may further improve survival. However, this twice-daily mode significantly increased the occurrence of grade ≥ 3 acute esophagitis compared with the once-daily mode (32% vs 16%, $p < 0.001$ in the Intergroup 0096 trial). The increased load to patients, physicians, and medical equipment of twice-daily radiotherapy is significantly limited in practice, and the once-daily schedule is more widely used(10). In the CONVERT trial and RTOG 0538 trial, the 66 Gy/70 Gy once-daily arm showed similar OS and toxicity to the 45 Gy twice-daily arm(11, 12). Recently, several retrospective and prospective phase II studies showed that hypofractionated radiotherapy regimens with total doses ranging from 40 Gy to 55 Gy were similarly effective as the 45 Gy twice-daily regimen, with similar incidences of grade ≥ 3 acute esophagitis and pneumonia(13-16). Both conventional and hypofractionated radiotherapy are recommended by the updated version of the National Comprehensive Cancer Network (NCCN) guidelines.

Additionally, a hypofractionated radiotherapy regimen may have a better synergistic effect with immunotherapy. Preclinical studies have suggested that a higher dose could remodel the tumor microenvironment by upregulating MHC-I expression, increasing CD8+ T-cell infiltration, and upgrading the ratio of proinflammatory macrophages(17-19). However, myeloid-derived suppressor cells and regulatory T cells accumulate as well, together with induction of the DNA exonuclease Trex1, which attenuates the immunogenicity of cancer cells(20-22). Thus, hypofractionated radiation could potentially lead to a greater response to immunotherapy as a tradeoff.

Survival has reached a plateau for patients with cytotoxic chemotherapy and

radiotherapy. With the development of immunotherapy in recent years, it is acknowledged that the combination of radiotherapy and immunotherapy has a synergistic effect. It has been proven that radiotherapy induces immunogenic death in tumor cells, promotes the release and presentation of tumor antigens, activates cytotoxic T lymphocytes, returns tumor cells to the tumor environment, activates the immunogenicity of the whole body, reconstructs the tumor microenvironment, and exerts a remote effect. In addition, immunotherapy normalizes tumor blood vessels, relieves anoxia of the tumor microenvironment, and makes tumors more sensitive to radiation(20).

Synergy between radiotherapy and immunotherapy has been confirmed and applied in clinical practice in recent years. Previous preclinical studies suggested that a higher irradiation dose might trigger cell death more effectively, upregulate the expression of immunogenetic cell surface markers, and better induce proinflammatory responses to enhance the clearance of tumor cells(17, 23, 24). Thus, hypofractionation might be a better complement to immunotherapy.

Based on previous evidence and urgent clinical needs, we designed this investigator-initiated multicenter phase II trial, the ASTRUM-LC01 study, to investigate the clinical efficacy and safety of serplulimab consolidation therapy after concurrent hypofractionated radiotherapy with chemotherapy in limited-stage small cell lung cancer.

Methods and analysis

Study design

ASTRUM-LC01 will be carried out as a multicenter single-arm phase II clinical trial (ClinicalTrials.gov identifier NCT05443646). Naïve LS-SCLC patients will receive concurrent chemoradiotherapy, PCI, and subsequent serplulimab therapy. The flowchart of this study is presented in Figure 1.

Research objectives

The primary objective of this trial was to evaluate improvements in PFS. PFS is defined as the time from the date of beginning of any antitumor therapy to the date of

any documented disease progression or death due to any cause.

The secondary objectives include evaluating overall survival (OS), objective response rate (ORR), time to treatment failure (TTF), and safety evaluation. OS is the period between the beginning of any antitumor therapy to any documented death due to any cause. ORR is the proportion of subjects achieving complete response (CR) and partial response (PR) as assessed by RECIST 1.1. TTF means time to disease progression, death, withdrawal due to adverse events, patient refusal to continue the study, or use of a new treatment from the very first date of treatment administration.

Participants

Detailed inclusion and exclusion criteria are presented in Table 1. Patients with histologically or cytologically confirmed SCLC and staged at a limited stage were considered potential participants. Patients must be 18-75 years of age, with a Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1, at least one evaluable lesion according to version 1.1 of the Response Evaluation Criteria in Solid Tumors, and no serious abnormalities in hematopoietic function or cardiac, hepatic, or renal function or immunodeficiency. Patients who were suitable for surgery but refused were included. Detection of PD-L1 expression levels is highly recommended but not essential. All patients will be informed of the potential benefit and risk of this trial. Informed consent signed by every participant is requested.

Treatments

All eligible patients will receive four cycles of chemotherapy after screening. The regimens are etoposide 100 mg/m^2 intravenously on days 1-3 in combination with cisplatin 75 mg/m^2 intravenously on day 1 (EP) or carboplatin AUC=5 every 3 weeks (EC). The selection of the regimen depends on the decision of the investigators. In cases of intolerance to chemotherapeutic agents, dose modifications are allowed twice according to the prescribing information for cisplatin/carboplatin and etoposide.

Thoracic radiation will be initiated after no later than two cycles of chemotherapy(25). It is planned to target the primary tumor and involved mediastinal lymph node regions. For simulation, 4D-CT simulation positioning and enhanced CT positioning image scanning should be performed as much as possible. The scanning

slice thickness was 0.3 cm. A total of 45 Gy in 15 fractions over 3 weeks will be delivered. PCI is routinely scheduled for patients without progression after chemoradiotherapy. 25Gy in 10 fractions over 2 weeks to the brain will be prescribed. Image guided-intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques are needed. Treatment plans should meet organ dose constraints, as listed in Table 2. Patients without disease progression will receive an intravenous infusion of 300 mg serplulimab every 3 weeks. Treatment with serplulimab should be continued until disease progression, intolerable toxicity, withdrawal of consent, or a maximum of 1 year.

Assessment

Treatment response will be assessed every 4 cycles during serplulimab treatment with chest CT and brain magnetic resonance imaging (MRI) and ultrasonic examination when necessary. Contrast-enhanced CT of the neck, thorax and abdomen is preferred. Brain CT or PET is allowed if MRI is contraindicated. Each CT and MRI scan needs to be reviewed by radiologists and radiation oncologists. Subsequent assessments and follow-up will be performed every 6 weeks during the first 48 weeks of treatment and every 9 weeks after 48 weeks.

Patients will be interviewed face to face during their routine hospital visits and by telephone 1-2 weeks after delivery. Adverse events will be evaluated at each visit. Grades of side effects using CTCAE 5.0 and their relationship with immunotherapy will be assessed by the research team members. Grade 2 pneumonia and grade 3 to 4 adverse effects will be managed by drug interruption and symptomatic treatment. Of note, dose reduction of serplulimab is not permitted.

Statistical considerations and analysis

The primary purpose of the phase II study was to evaluate the improvement in PFS for LS-SCLC patients. The study adopted the design of a superior test, and the sample size was calculated using historical data as a reference. The median PFS of LS-SCLC patients treated with standard CRT and PCI is approximately 15 months. The assumption of 80% power, a significance level of 10%, a hazard ratio of 0.65, an accrual period of 12 months, and a minimum follow-up of 27 months resulted in a

sample size of 50 individuals. Considering a maximum drop-out rate of 10%, a total of 55 patients will be recruited in ASTRUM-LC01.

All collected data will enter the computer. Measurement data will be described as the median, mean value and standard deviation. Enumeration data will be described as the number of cases and percentage. Kaplan–Meier survival analysis and Cox regression will be applied for survival analysis. The log-rank method will be used for comparison between subgroups. A value of 0.05 was set as the statistically significant standard in this trial.

Monitoring

The study group will review data about treatment efficacy and safety. Trial monitoring is planned every half-a-year, and the monitoring committee will modify the protocol if necessary. Trial progress will be monitored by the study group, same as safety and protocol compliance.

Discussion

Small cell lung cancer is a highly aggressive cancer with poor prognosis. Therefore, there is a great need to improve treatment efficacy, especially in the era of precision radiation and immunotherapy. Based on current evidence in NSCLC and extensive-stage SCLC, immunotherapy has shown high efficacy as first-line therapy or consolidation therapy in locally advanced NSCLC. Whether consolidation immunotherapy would bring added benefits to traditional concurrent chemoradiotherapy has attracted much attention worldwide. This clinical trial would help to answer this question. Improved survival with acceptable toxicity is expected and hopefully further ameliorates the treatment paradigm.

Ethics and dissemination

This study received ethical approval from the Independent Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (22/236-3438). This protocol has been accepted for poster presentation at the European Lung Cancer Congress (ELCC) 2024. Investigators

will obtain written consent from patients willing to participate in the trial.

List of abbreviation

CI: confidence interval

CR: complete response

EC: etoposide and carboplatin

ECOG PS: Eastern Cooperative Oncology Group performance status

EP: etoposide and cisplatin

ES-SCLC: extensive-stage small cell lung cancer

HR: hazard ratio

IMRT: image guided-intensity modulated radiation therapy

LS-SCLC: limited-stage small cell lung cancer

MRI: magnetic resonance imaging

ORR: objective response rate

OS: overall survival

PCI: prophylactic cranial irradiation

PFS: Progression-free survival

PR: partial response

SCLC: Small cell lung cancer

TTF: time to treatment failure

VALSG: Veterans Administration Lung Study Group

VMAT: volumetric modulated arc therapy

Authors' Contributions

The study was designed by YW, LD, JC and NB. YW and JC developed the statistical analysis plan. YW and LD were major contributors in writing the manuscript. LD, JW, TZ, JC and XZ perform the research and monitor progress. JC, XZ and NB modified the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Serplulimab in this trial will be provided by Shanghai Henlius Biotech, Inc., for free. This had no influence on the trial design, statistical analysis, or publication.

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Figure Legends & Tables

Figure 1 Flowchart of the ASTRUM-LC01 study. SCLC: Small cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; PCI: Prophylactic cranial irradiation; PFS: Progression-free survival; OS: Overall survival; ORR: Objective response rate; DCR: TTF: Time to treatment failure.

Table 1 Inclusion criteria and exclusion criteria.

Inclusion criteria	**Exclusion criteria**
Age 18-75 years.	Histologically or cytologically confirmed mixed SCLC.
Histologically or cytologically confirmed SCLC.	Suitable for surgery.
Limited stage SCLC.	Patients with other active malignancies within 5 years or at the same time. Localized tumors that have been cured such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder carcinoma, prostate carcinoma in situ, cervical carcinoma in situ, and breast cancer in situ are acceptable.

Score of Eastern Cooperative Oncology Group performance status (ECOG PS) being 0 or 1.	Patients with pleural, pericardial effusions, or ascites requiring clinical intervention.
Without previous anti-tumor treatment history	Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN).
Without serious abnormalities in hematopoietic function or cardiac, hepatic, or renal function, or immunodeficiency.	Patients with peripheral neuropathy ≥ grade 2 by CTCAE.
Expected survival of at least 3 months	Patients with human immunodeficiency virus (HIV), Hepatitis B or C infection.
Voluntarily participate in this clinical study and signed the informed consent form.	Patients with active pulmonary tuberculosis, previous and current interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis, and severe impaired pulmonary function as judged by the investigator.
	Subjects with known active or suspected autoimmune diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy are allowed to be enrolled.

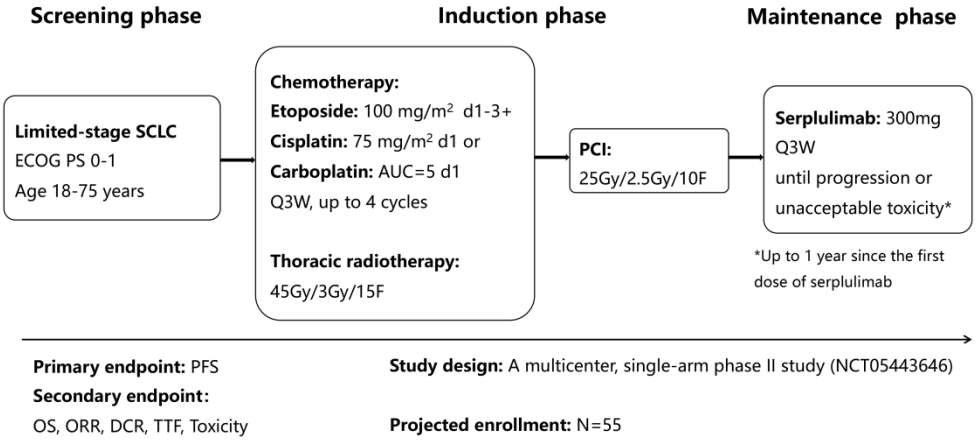
Table 2 Organ at risk dose constrains.

Organ at risk		
Lung	V20 < 25%	mean lung dose ≤ 15 Gy
Spinal cord PRV*	Dmax< 42Gy	
Esophagus	Dmax< 50 Gy	mean dose < 34 Gy
Heart	V30 < 50%	

Hippocampus	Dmax < 9 Gy	
Hippocampus PRV**	Dmax < 12 Gy	

*5 mm expansion outside the spinal cord to form planning organ-at-risk volume (PRV)

** 2 mm expansion outside hippocampus to form PRV



Flowchart of the ASTRUM-LC01 study.

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ASTRUM-LC01 Study Protocol: A Single-arm Phase II Study of Consolidation Serplulimab Following Hypofractionated Radiotherapy with Concurrent Chemotherapy for Patients with Limited Stage Small Cell Lung Cancer

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology, Immunology (including allergy)
Keywords:	Respiratory tract tumours < ONCOLOGY, Immunology < THORACIC MEDICINE, RADIOTHERAPY

Strengths and limitations of this study

Strengths: This study applies the first PD-1 monoclonal antibody which is effective in extensive-stage SCLC, serplulimab, to the consolidation therapy of limited-stage SCLC following hypofractionated radiotherapy and concurrent chemotherapy.

Limitations: The single-arm design and reliance on historical controls may limit the generalizability of the trial's findings.

Title

ASTRUM-LC01 Study Protocol: A Single-arm Phase II Study of Consolidation Serplulimab Following Hypofractionated Radiotherapy with Concurrent Chemotherapy for Patients with Limited Stage Small Cell Lung Cancer

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Introduction

Small cell lung cancer (SCLC) originates from epithelial cells with neuroendocrine differentiation. It accounts for 15%–20% of the total number of lung cancers[1]. SCLC is characterized by high malignancy, strong invasiveness, early metastasis, and rapid disease progression, with an extremely poor prognosis. According to the Veterans Administration Lung Study Group (VALSG) stage, SCLC can be further divided into limited stage and extensive stage. Approximately 30%-40% patients are initially diagnosed with limited-stage SCLC (LS-SCLC)[1]. At present, surgery and chemotherapy with concurrent radiotherapy are standard treatment regimens for LS-SCLC. However, surgery is only applicable for a few patients with early SCLC, accounting for approximately 2%–5%. The combination of definitive thoracic radiotherapy and platinum-based chemotherapy followed by prophylactic cranial irradiation (PCI) in responsive patients has been the standard regimen in the past two decades. The median overall survival has been reported to be 25-30 months in recent years[2].

The progress of small cell lung cancer research was slow in the 20th century until the encouraging results of the Impower133 study[3] and CASPIAN study[4] shed light on the treatment of extensive-stage SCLC (ES-SCLC). Thereafter, more PD-1/PD-L1 inhibitors were proven to be effective as first-line treatment for ES-SCLC[5-7]. Among them, patients treated with serplulimab, the first PD-1 inhibitor showed efficacy as first-line systematic treatment according to the ASTRUM-005 trial, had the longest median overall survival time (OS) considering the absolute value (15.8 vs. 11.1 months for placebo group; hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.50–0.76; descriptive p<0.001). Subgroup analysis of OS by race showed similar trends to improved survival in Asians and non-Asians[7].

However, evidence of consolidation immunotherapy for LS-SCLC is limited. The STIMULI study, a phase II randomized controlled clinical study, failed to prove the superiority of consolidation immunotherapy consisting of nivolumab and ipilimumab[8]. One possible reason for this may be the unexpectedly high rate of grade

≥3 adverse events (62% vs 25% in the experimental and observation arms, respectively). A randomized, placebo-controlled phase III trial, the ADRIATIC study, which investigating the efficiency of durvalumab following concurrent chemoradiotherapy in LS-SCLC, was ongoing when we designed this trial[9]. It has recently represented a significant advancement in both median PFS (16.6 months vs. 9.2 months, p=0.02) and OS (55.9 months vs. 33.4 months, p=0.01)[10] . These results suggested the importance of correct combination of immunotherapy and traditional chemoradiotherapy. With the inspiring results of serplulimab in ES-SCLC, we hypothesized that serplulimab might show promising efficacy in LS-SCLC with acceptable toxicity profiles.

Moreover, the optimal radiotherapy fractionation for LS-SCLC has been under debate. The hyperfractionation regimen (45 Gy/1.5 Gy bid/3 weeks) has been the standard regimen according to the Intergroup 0096 study since 1999[11]. A new phase II trial suggested that a higher dose of 60 Gy in 40 fractions may further improve survival. However, this twice-daily mode significantly increased the occurrence of grade ≥ 3 acute esophagitis compared with the once-daily mode (32% vs 16%, $p < 0.001$ in the Intergroup 0096 trial). The increased load to patients, physicians, and medical equipment of twice-daily radiotherapy is significantly limited in practice, and the once-daily schedule is more widely used[12]. In the CONVERT trial and RTOG 0538 trial, the 66 Gy/70 Gy once-daily arm showed similar OS and toxicity to the 45 Gy twice-daily arm[13,14]. Recently, several retrospective and prospective phase II studies showed that hypofractionated radiotherapy regimens with total doses ranging from 40 Gy to 55 Gy were similarly effective as the 45 Gy twice-daily regimen, with similar incidences of grade ≥ 3 acute esophagitis and pneumonia[15-18]. Both conventional and hypofractionated radiotherapy are recommended by the updated version of the National Comprehensive Cancer Network (NCCN) guidelines.

Additionally, a hypofractionated radiotherapy regimen may have a better synergistic effect with immunotherapy. Preclinical studies have suggested that a higher dose could remodel the tumor microenvironment by upregulating MHC-I expression, increasing CD8+ T-cell infiltration, and upgrading the ratio of proinflammatory macrophages[19-21]. However, myeloid-derived suppressor cells and regulatory T

cells accumulate as well, together with induction of the DNA exonuclease Trex1, which attenuates the immunogenicity of cancer cells[22-24]. Thus, hypofractionated radiation could potentially lead to a greater response to immunotherapy as a tradeoff.

Survival has reached a plateau for patients with cytotoxic chemotherapy and radiotherapy. With the development of immunotherapy in recent years, it is acknowledged that the combination of radiotherapy and immunotherapy has a synergistic effect. It has been proven that radiotherapy induces immunogenic death in tumor cells, promotes the release and presentation of tumor antigens, activates cytotoxic T lymphocytes, returns tumor cells to the tumor environment, activates the immunogenicity of the whole body, reconstructs the tumor microenvironment, and exerts a remote effect. In addition, immunotherapy normalizes tumor blood vessels, relieves anoxia of the tumor microenvironment, and makes tumors more sensitive to radiation[22].

Synergy between radiotherapy and immunotherapy has been confirmed and applied in clinical practice in recent years. Previous preclinical studies suggested that a higher irradiation dose might trigger cell death more effectively, upregulate the expression of immunogenetic cell surface markers, and better induce proinflammatory responses to enhance the clearance of tumor cells[19,25,26]. Thus, hypofractionation might be a better complement to immunotherapy.

Based on previous evidence and urgent clinical needs, we designed this investigator-initiated multicenter phase II trial, the ASTRUM-LC01 study, to investigate the clinical efficacy and safety of serplulimab consolidation therapy after concurrent hypofractionated radiotherapy with chemotherapy in limited-stage small cell lung cancer.

Methods and analysis

Study design

ASTRUM-LC01 will be carried out as a multicenter single-arm phase II clinical trial (ClinicalTrials.gov identifier NCT05443646). Naïve LS-SCLC patients will receive concurrent chemoradiotherapy, PCI, and subsequent serplulimab therapy. The

flowchart of this study is presented in Figure 1.

Research objectives

The primary objective of this trial was to evaluate improvements in PFS. PFS is defined as the time from the date of beginning of any antitumor therapy to the date of any documented disease progression or death due to any cause.

The secondary objectives include evaluating overall survival (OS), objective response rate (ORR), time to treatment failure (TTF), and safety evaluation. OS is the period between the beginning of any antitumor therapy to any documented death due to any cause. ORR is the proportion of subjects achieving complete response (CR) and partial response (PR) as assessed by RECIST 1.1. TTF means time to disease progression, death, withdrawal due to adverse events, patient refusal to continue the study, or use of a new treatment from the very first date of treatment administration.

Participants

Detailed inclusion and exclusion criteria are presented in Table 1. Patients with histologically or cytologically confirmed SCLC and staged at a limited stage were considered potential participants. Patients must be aged 18-75 years, with an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1, at least one evaluable lesion according to version 1.1 of the Response Evaluation Criteria in Solid Tumors, and no serious abnormalities in hematopoietic function or cardiac, hepatic, or renal function or immunodeficiency. Patients who were suitable for surgery but refused were included. Detection of PD-L1 expression levels is highly recommended but not essential. All patients will be informed of the potential benefit and risk of this trial. Informed consent signed by every participant is requested.

Treatments

All eligible patients will receive four cycles of chemotherapy after screening. The regimens are etoposide 100 mg/m^2 intravenously on days 1-3 in combination with cisplatin 75 mg/m^2 intravenously on day 1 (EP) or carboplatin AUC=5 every 3 weeks (EC). The selection of the regimen depends on the decision of the investigators. In cases of intolerance to chemotherapeutic agents, dose modifications are allowed twice according to the prescribing information for cisplatin/carboplatin and etoposide.

Thoracic radiation will be initiated no later than two cycles after chemotherapy[27]. It is planned to target the primary tumor and involved mediastinal lymph node regions. For simulation, 4D-CT simulation positioning and enhanced CT positioning image scanning should be performed as much as possible. The scanning slice thickness was 0.3 cm. A total of 45 Gy in 15 fractions over 3 weeks will be delivered. PCI is routinely scheduled for patients without progression after chemoradiotherapy. 25Gy in 10 fractions over 2 weeks to the brain will be prescribed. Image guided-intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques are needed. Treatment plans should meet organ dose constraints, as listed in Table 2. Patients without disease progression will receive an intravenous infusion of 300 mg serplulimab every 3 weeks. Treatment with serplulimab should be continued until disease progression, intolerable toxicity, withdrawal of consent, or a maximum of 1 year.

Assessment

Treatment response will be assessed every 4 cycles during serplulimab treatment with chest CT and brain magnetic resonance imaging (MRI) and ultrasonic examination when necessary. Contrast-enhanced CT of the neck, thorax and abdomen is preferred. Brain CT or PET is allowed if MRI is contraindicated. Each CT and MRI scan needs to be reviewed by radiologists and radiation oncologists. Subsequent assessments and follow-up will be performed every 6 weeks during the first 48 weeks of treatment and every 9 weeks after 48 weeks.

Patients will be interviewed face to face during their routine hospital visits and by telephone 1-2 weeks after delivery. Adverse events will be evaluated at each visit. Grades of side effects using CTCAE 5.0 and their relationship with immunotherapy will be assessed by the research team members. Grade 2 pneumonia and grade 3 to 4 adverse effects will be managed by drug interruption and symptomatic treatment. Of note, dose reduction of serplulimab is not permitted.

Statistical considerations and analysis

The primary purpose of the phase II study was to evaluate the improvement in PFS for LS-SCLC patients. The study adopted the design of a superior test, and the

sample size was calculated using historical data as a reference. The median PFS of LS-SCLC patients treated with standard CRT and PCI is approximately 15 months. The assumption of 80% power, a significance level of 10%, a hazard ratio of 0.65, an accrual period of 12 months, and a minimum follow-up of 27 months resulted in a sample size of 50 individuals. Considering a maximum drop-out rate of 10%, a total of 55 patients will be recruited in ASTRUM-LC01. The sample size calculation was performed using the Power Analysis and Sample Size (PASS) software, version 15.

All collected data will enter the computer. Measurement data will be described as the median, mean value and standard deviation. Enumeration data will be described as the number of cases and percentage. Kaplan–Meier survival analysis and Cox regression will be applied for survival analysis. The log-rank method will be used for comparison between subgroups. A value of 0.05 was set as the statistically significant standard in this trial.

Monitoring

The study group will review data about treatment efficacy and safety. Trial monitoring is planned every half-a-year, and the monitoring committee will modify the protocol if necessary. Trial progress will be monitored by the study group, same as safety and protocol compliance.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Discussion

Small cell lung cancer is a highly aggressive cancer with poor prognosis. Therefore, there is a great need to improve treatment efficacy, especially in the era of precision radiation and immunotherapy. Based on current evidence, immunotherapy has shown high efficacy as consolidation therapy in locally advanced NSCLC. The landscape of ES-SCLC treatment has also been significantly impacted by the increasing evidences of combining immunotherapy and chemotherapy in first line. Whether consolidation

immunotherapy would bring added benefits to traditional concurrent chemoradiotherapy in LS-SCLC has attracted much attention worldwide. This clinical trial was therefore designed to answer this question.

Serplulimab, a novel humanized monoclonal anti-PD-1 antibody, has emerged as a promising agent in this context. The ASTRUM-005 study demonstrated that serplulimab was the first PD-1 antibody to show positive results in the first-line treatment of ES-SCLC with advanced survival data, marking a milestone in the immunotherapy exploration process and the history of SCLC treatment[7]. Meanwhile, ≥grade 3 adverse effect of serplulimab was similar to other drugs. Hence, we expect improved survival with acceptable toxicity in this trial, with great confidence.

The optimal duration of consolidation remains controversial. At the initiation of this trial in 2022, the only trial with results published, STIMULI trial, adopted a similar design as the classic PACIFIC trial[8]. Its failure was considered to be mainly due to treatment toxicity. The GEMSTONE-301 study and the recently published ADRIATIC study have opted for a longer duration of 2 years, and both significantly prolonged survival versus placebo[9,28]. But the 2-year consolidation therapy in GEMSTONE-301 trial did not demonstrate survival benefits beyond the PACIFIC pattern. Taking both the potential benefits of extended therapy and the costs into consideration, our study set the duration of serplulimab consolidation therapy to 1 year. But whether extended exposure to immunotherapy consolidation could potentially enhance its therapeutic effects will need further investigation.

Different from conventional or hyperfractionated RT in ADRIATIC trial, hypofractionated thoracic radiation was scheduled during CRT in our study. This cost-effective regimen is permitted and recommended by NCCN guideline. Synergistic effect of RT and immunotherapy might be dose-dependent as mentioned before. Further research is necessary to define the precise parameters for combining RT with immunotherapy to achieve the best clinical outcomes.

There are some limitations of this trial. The single-arm design with small sample size may limit the generalizability of the findings. Also, since only Chinese patients

will be enrolled, the applicability of the results to other regions with different healthcare systems and patient populations.

In summary, this trial design comprehensively optimized treatment paradigm with the expectation of further improving the prognosis of LS-SCLC patients.

Ethics and dissemination

This study received ethical approval from the Independent Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (22/236-3438). This protocol has been accepted for poster presentation at the European Lung Cancer Congress (ELCC) 2024. Investigators will obtain written consent from patients willing to participate in the trial.

List of abbreviation

CI: confidence interval

CR: complete response

EC: etoposide and carboplatin

ECOG PS: Eastern Cooperative Oncology Group performance status

EP: etoposide and cisplatin

ES-SCLC: extensive-stage small cell lung cancer

HR: hazard ratio

IMRT: image guided-intensity modulated radiation therapy

LS-SCLC: limited-stage small cell lung cancer

MRI: magnetic resonance imaging

ORR: objective response rate

OS: overall survival

PCI: prophylactic cranial irradiation

PFS: Progression-free survival

PR: partial response

SCLC: Small cell lung cancer

TTF: time to treatment failure

VALSG: Veterans Administration Lung Study Group

VMAT: volumetric modulated arc therapy

Authors' Contributions

The study was designed by YW, LD, JC and NB. YW and JC developed the statistical analysis plan. YW and LD were major contributors in writing the manuscript. LD, JW, TZ, JC and XZ perform the research and monitor progress. JC, XZ and NB modified the manuscript. All authors read and approved the final manuscript. NB acted as guarantor.

Competing interests

The authors declare that they have no competing interests.

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Serplulimab in this trial will be provided by Shanghai Henlius Biotech, Inc., for free. This had no influence on the trial design, statistical analysis, or publication.

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Figure Legends & Tables

Figure 1 Flowchart of the ASTRUM-LC01 study. SCLC: Small cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; PCI: Prophylactic cranial irradiation; PFS: Progression-free survival; OS: Overall survival; ORR: Objective response rate; DCR: TTF: Time to treatment failure.

Table 1 Inclusion criteria and exclusion criteria.

Inclusion criteria	Exclusion criteria

Aged 18-75 years.	Histologically or cytologically confirmed mixed SCLC.
Histologically or cytologically confirmed SCLC.	Suitable for surgery.
Limited stage SCLC.	Patients with other active malignancies within 5 years or at the same time. Localized tumors that have been cured such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder carcinoma, prostate carcinoma in situ, cervical carcinoma in situ, and breast cancer in situ are acceptable.
Score of Eastern Cooperative Oncology Group performance status (ECOG PS) being 0 or 1.	Patients with pleural, pericardial effusions, or ascites requiring clinical intervention.
Without previous anti-tumor treatment history	Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN).
Without serious abnormalities in hematopoietic function or cardiac, hepatic, or renal function, or immunodeficiency.	Patients with peripheral neuropathy ≥ grade 2 by CTCAE.
Expected survival of at least 3 months	Patients with human immunodeficiency virus (HIV), Hepatitis B or C infection.
Voluntarily participate in this clinical study and signed the informed consent form.	Patients with active pulmonary tuberculosis, previous and current interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis, and severe impaired pulmonary function as judged by the investigator.

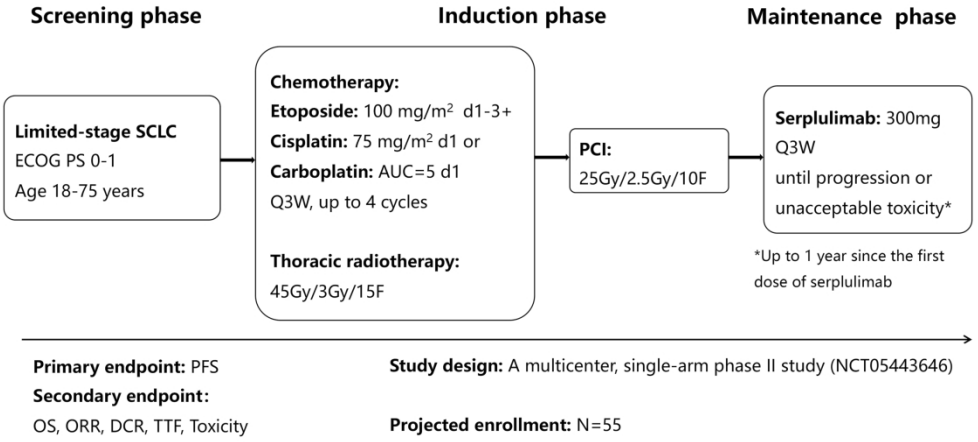
	Subjects with known active or suspected autoimmune diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy are allowed to be enrolled.

Table 2 Organ at risk dose constrains.

Organ at risk		
Lung	V20 < 25%	mean lung dose ≤ 15 Gy
Spinal cord PRV*	Dmax< 42Gy	
Esophagus	Dmax< 50 Gy	mean dose < 34 Gy
Heart	V30 < 50%	
Hippocampus	Dmax < 9 Gy	
Hippocampus PRV**	Dmax < 12 Gy	

*5 mm expansion outside the spinal cord to form planning organ-at-risk volume (PRV)

** 2 mm expansion outside hippocampus to form PRV



Flowchart of the ASTRUM-LC01 study.

253x142mm (300 x 300 DPI)

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ASTRUM-LC01 Study Protocol: A Single-arm Phase II Study of Consolidation Serplulimab Following Hypofractionated Radiotherapy with Concurrent Chemotherapy for Patients with Limited Stage Small Cell Lung Cancer

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology, Immunology (including allergy)
Keywords:	Respiratory tract tumours < ONCOLOGY, Immunology < THORACIC MEDICINE, RADIOTHERAPY

Title

ASTRUM-LC01 Study Protocol: A Single-arm Phase II Study of Consolidation Serplulimab Following Hypofractionated Radiotherapy with Concurrent Chemotherapy for Patients with Limited Stage Small Cell Lung Cancer

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Abstract

Introduction With the inspiring results of PACIFIC trial in non-small cell lung cancer (NSCLC), and CAPIAN and IMpower133 trial in extensive-stage small cell lung cancer (SCLC), immunotherapy has increasingly gained attention. Serplulimab, a PD-1 inhibitor, showed great antitumor activity in ASTRUM-005 trial and has been recommended as first-line therapy in extensive-stage SCLC. Whether serplulimab following hypofractionation radiotherapy and chemotherapy could bring better outcomes in limited-stage SCLC remains to be answered.

Methods and analysis We designed a prospective multicenter single-arm phase II clinical trial to evaluate both the efficacy and safety of chemoradiotherapy and consolidation by serplulimab in limited-stage SCLC. Eligible patients will receive standard chemotherapy for 4 cycles and concurrent thoracic radiotherapy with total dose being 45Gy in 3 weeks and 3Gy dose per fraction. Prophylactic cranial irradiation is recommended for response patients. Serplulimab will be delivered

afterwards every 3 weeks for up to 1 year. Based on sample size estimation, 55 patients will be enrolled in total.

Ethics and Dissemination Ethics approval was obtained from the Independent Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (22/236-3438).

Registration details This study was registered in ClinicalTrials.gov (NCT05443646).

Strengths and limitations of this study

1. This trial will be the first prospective study to assess hypofractionated radiotherapy combined with concurrent chemotherapy, followed by consolidation PD-1 inhibitor in limited-stage small-cell lung cancer.
2. This multicenter single-arm prospective study provides a defined treatment protocol and is helpful to obtained informed consent from participants, which is particularly important for promoting clinical research in China.
3. The efficacy evaluation will be completed separately by a blinded independent imaging center and the investigators.
4. The limited sample size may restrict the ability to detect rare adverse events.

Word count: 2246 words.

Introduction

Small cell lung cancer (SCLC) originates from epithelial cells with neuroendocrine differentiation. It accounts for 15%–20% of the total number of lung cancers[1]. SCLC is characterized by high malignancy, strong invasiveness, early metastasis, and rapid disease progression, with an extremely poor prognosis. According to the Veterans Administration Lung Study Group (VALSG) stage, SCLC can be further divided into limited stage and extensive stage. Approximately 30%-40% patients are initially diagnosed with limited-stage SCLC (LS-SCLC)[1]. At present, surgery and chemotherapy with concurrent radiotherapy are standard treatment regimens for LS-SCLC. However, surgery is only applicable for a few patients with early SCLC, accounting for approximately 2%–5%. The combination of definitive thoracic radiotherapy and platinum-based chemotherapy followed by prophylactic cranial irradiation (PCI) in responsive patients has been the standard regimen in the past two decades. The median overall survival has been reported to be 25-30 months in recent years[2].

The progress of small cell lung cancer research was slow in the 20th century until the encouraging results of the Impower133 study[3] and CASPIAN study[4] shed light on the treatment of extensive-stage SCLC (ES-SCLC). Thereafter, more PD-1/PD-L1 inhibitors were proven to be effective as first-line treatment for ES-SCLC[5-7]. Among them, patients treated with serplulimab, the first PD-1 inhibitor showed efficacy as first-line systematic treatment according to the ASTRUM-005 trial, had the longest median overall survival time (OS) considering the absolute value (15.8 vs. 11.1 months for placebo group; hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.50–0.76; descriptive p<0.001). Subgroup analysis of OS by race showed similar trends to improved survival in Asians and non-Asians[7].

However, evidence of consolidation immunotherapy for LS-SCLC is limited. The STIMULI study, a phase II randomized controlled clinical study, failed to prove the superiority of consolidation immunotherapy consisting of nivolumab and ipilimumab[8]. One possible reason for this may be the unexpectedly high rate of grade

≥3 adverse events (62% vs 25% in the experimental and observation arms, respectively). A randomized, placebo-controlled phase III trial, the ADRIATIC study, which investigating the efficiency of durvalumab following concurrent chemoradiotherapy in LS-SCLC, was ongoing when we designed this trial[9]. It has recently represented a significant advancement in both median PFS (16.6 months vs. 9.2 months, p=0.02) and OS (55.9 months vs. 33.4 months, p=0.01)[10] . These results suggested the importance of correct combination of immunotherapy and traditional chemoradiotherapy. With the inspiring results of serplulimab in ES-SCLC, we hypothesized that serplulimab might show promising efficacy in LS-SCLC with acceptable toxicity profiles.

Moreover, the optimal radiotherapy fractionation for LS-SCLC has been under debate. The hyperfractionation regimen (45 Gy/1.5 Gy bid/3 weeks) has been the standard regimen according to the Intergroup 0096 study since 1999[11]. A new phase II trial suggested that a higher dose of 60 Gy in 40 fractions may further improve survival. However, this twice-daily mode significantly increased the occurrence of grade ≥ 3 acute esophagitis compared with the once-daily mode (32% vs 16%, $p < 0.001$ in the Intergroup 0096 trial). The increased load to patients, physicians, and medical equipment of twice-daily radiotherapy is significantly limited in practice, and the once-daily schedule is more widely used[12]. In the CONVERT trial and RTOG 0538 trial, the 66 Gy/70 Gy once-daily arm showed similar OS and toxicity to the 45 Gy twice-daily arm[13,14]. Recently, several retrospective and prospective phase II studies showed that hypofractionated radiotherapy regimens with total doses ranging from 40 Gy to 55 Gy were similarly effective as the 45 Gy twice-daily regimen, with similar incidences of grade ≥ 3 acute esophagitis and pneumonia[15-18]. Both conventional and hypofractionated radiotherapy are recommended by the updated version of the National Comprehensive Cancer Network (NCCN) guidelines.

Additionally, a hypofractionated radiotherapy regimen may have a better synergistic effect with immunotherapy. Preclinical studies have suggested that a higher dose could remodel the tumor microenvironment by upregulating MHC-I expression, increasing CD8+ T-cell infiltration, and upgrading the ratio of proinflammatory macrophages[19-21]. However, myeloid-derived suppressor cells and regulatory T

cells accumulate as well, together with induction of the DNA exonuclease Trex1, which attenuates the immunogenicity of cancer cells[22-24]. Thus, hypofractionated radiation could potentially lead to a greater response to immunotherapy as a tradeoff.

Survival has reached a plateau for patients with cytotoxic chemotherapy and radiotherapy. With the development of immunotherapy in recent years, it is acknowledged that the combination of radiotherapy and immunotherapy has a synergistic effect. It has been proven that radiotherapy induces immunogenic death in tumor cells, promotes the release and presentation of tumor antigens, activates cytotoxic T lymphocytes, returns tumor cells to the tumor environment, activates the immunogenicity of the whole body, reconstructs the tumor microenvironment, and exerts a remote effect. In addition, immunotherapy normalizes tumor blood vessels, relieves anoxia of the tumor microenvironment, and makes tumors more sensitive to radiation[22].

Synergy between radiotherapy and immunotherapy has been confirmed and applied in clinical practice in recent years. Previous preclinical studies suggested that a higher irradiation dose might trigger cell death more effectively, upregulate the expression of immunogenetic cell surface markers, and better induce proinflammatory responses to enhance the clearance of tumor cells[19,25,26]. Thus, hypofractionation might be a better complement to immunotherapy.

Based on previous evidence and urgent clinical needs, we designed this investigator-initiated multicenter phase II trial, the ASTRUM-LC01 study, to investigate the clinical efficacy and safety of serplulimab consolidation therapy after concurrent hypofractionated radiotherapy with chemotherapy in limited-stage small cell lung cancer.

Methods and analysis

Study design

ASTRUM-LC01 will be carried out as a multicenter single-arm phase II clinical trial (ClinicalTrials.gov identifier NCT05443646). Naïve LS-SCLC patients will receive concurrent chemoradiotherapy, PCI, and subsequent serplulimab therapy. The

flowchart of this study is presented in Figure 1.

Research objectives

The primary objective of this trial was to evaluate improvements in PFS. PFS is defined as the time from the date of beginning of any antitumor therapy to the date of any documented disease progression or death due to any cause.

The secondary objectives include evaluating overall survival (OS), objective response rate (ORR), time to treatment failure (TTF), and safety evaluation. OS is the period between the beginning of any antitumor therapy to any documented death due to any cause. ORR is the proportion of subjects achieving complete response (CR) and partial response (PR) as assessed by RECIST 1.1. TTF means time to disease progression, death, withdrawal due to adverse events, patient refusal to continue the study, or use of a new treatment from the very first date of treatment administration.

Participants

Detailed inclusion and exclusion criteria are presented in Table 1. Patients with histologically or cytologically confirmed SCLC and staged at a limited stage were considered potential participants. Patients must be aged 18-75 years, with an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1, at least one evaluable lesion according to version 1.1 of the Response Evaluation Criteria in Solid Tumors, and no serious abnormalities in hematopoietic function or cardiac, hepatic, or renal function or immunodeficiency. Patients who were suitable for surgery but refused were included. Detection of PD-L1 expression levels is highly recommended but not essential. All patients will be informed of the potential benefit and risk of this trial. Informed consent signed by every participant is requested.

Treatments

All eligible patients will receive four cycles of chemotherapy after screening. The regimens are etoposide 100 mg/m^2 intravenously on days 1-3 in combination with cisplatin 75 mg/m^2 intravenously on day 1 (EP) or carboplatin AUC=5 every 3 weeks (EC). The selection of the regimen depends on the decision of the investigators. In cases of intolerance to chemotherapeutic agents, dose modifications are allowed twice according to the prescribing information for cisplatin/carboplatin and etoposide.

Thoracic radiation will be initiated no later than two cycles after chemotherapy[27]. It is planned to target the primary tumor and involved mediastinal lymph node regions. For simulation, 4D-CT simulation positioning and enhanced CT positioning image scanning should be performed as much as possible. The scanning slice thickness was 0.3 cm. A total of 45 Gy in 15 fractions over 3 weeks will be delivered. PCI is routinely scheduled for patients without progression after chemoradiotherapy. 25Gy in 10 fractions over 2 weeks to the brain will be prescribed. Image guided-intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques are needed. Treatment plans should meet organ dose constraints, as listed in Table 2. Patients without disease progression will receive an intravenous infusion of 300 mg serplulimab every 3 weeks. Treatment with serplulimab should be continued until disease progression, intolerable toxicity, withdrawal of consent, or a maximum of 1 year.

Assessment

Treatment response will be assessed every 4 cycles during serplulimab treatment with chest CT and brain magnetic resonance imaging (MRI) and ultrasonic examination when necessary. Contrast-enhanced CT of the neck, thorax and abdomen is preferred. Brain CT or PET is allowed if MRI is contraindicated. Each CT and MRI scan needs to be reviewed by radiologists and radiation oncologists. Subsequent assessments and follow-up will be performed every 6 weeks during the first 48 weeks of treatment and every 9 weeks after 48 weeks.

Patients will be interviewed face to face during their routine hospital visits and by telephone 1-2 weeks after delivery. Adverse events will be evaluated at each visit. Grades of side effects using CTCAE 5.0 and their relationship with immunotherapy will be assessed by the research team members. Grade 2 pneumonia and grade 3 to 4 adverse effects will be managed by drug interruption and symptomatic treatment. Of note, dose reduction of serplulimab is not permitted.

Statistical considerations and analysis

The primary purpose of the phase II study was to evaluate the improvement in PFS for LS-SCLC patients. The study adopted the design of a superior test, and the

sample size was calculated using historical data as a reference. The median PFS of LS-SCLC patients treated with standard CRT and PCI is approximately 15 months. The assumption of 80% power, a significance level of 10%, a hazard ratio of 0.65, an accrual period of 12 months, and a minimum follow-up of 27 months resulted in a sample size of 50 individuals. Considering a maximum drop-out rate of 10%, a total of 55 patients will be recruited in ASTRUM-LC01. The sample size calculation was performed using the Power Analysis and Sample Size (PASS) software, version 15.

All collected data will enter the computer. Measurement data will be described as the median, mean value and standard deviation. Enumeration data will be described as the number of cases and percentage. Kaplan–Meier survival analysis and Cox regression will be applied for survival analysis. The log-rank method will be used for comparison between subgroups. A value of 0.05 was set as the statistically significant standard in this trial.

Monitoring

The study group will review data about treatment efficacy and safety. Trial monitoring is planned every half-a-year, and the monitoring committee will modify the protocol if necessary. Trial progress will be monitored by the study group, same as safety and protocol compliance.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Discussion

Small cell lung cancer is a highly aggressive cancer with poor prognosis. Therefore, there is a great need to improve treatment efficacy, especially in the era of precision radiation and immunotherapy. Based on current evidence, immunotherapy has shown high efficacy as consolidation therapy in locally advanced NSCLC. The landscape of ES-SCLC treatment has also been significantly impacted by the increasing evidences of combining immunotherapy and chemotherapy in first line. Whether consolidation

immunotherapy would bring added benefits to traditional concurrent chemoradiotherapy in LS-SCLC has attracted much attention worldwide. This clinical trial was therefore designed to answer this question.

Serplulimab, a novel humanized monoclonal anti-PD-1 antibody, has emerged as a promising agent in this context. The ASTRUM-005 study demonstrated that serplulimab was the first PD-1 antibody to show positive results in the first-line treatment of ES-SCLC with advanced survival data, marking a milestone in the immunotherapy exploration process and the history of SCLC treatment[7]. Meanwhile, ≥grade 3 adverse effect of serplulimab was similar to other drugs. Hence, we expect improved survival with acceptable toxicity in this trial, with great confidence.

The optimal duration of consolidation remains controversial. At the initiation of this trial in 2022, the only trial with results published, STIMULI trial, adopted a similar design as the classic PACIFIC trial[8]. Its failure was considered to be mainly due to treatment toxicity. The GEMSTONE-301 study and the recently published ADRIATIC study have opted for a longer duration of 2 years, and both significantly prolonged survival versus placebo[9,28]. But the 2-year consolidation therapy in GEMSTONE-301 trial did not demonstrate survival benefits beyond the PACIFIC pattern. Taking both the potential benefits of extended therapy and the costs into consideration, our study set the duration of serplulimab consolidation therapy to 1 year. But whether extended exposure to immunotherapy consolidation could potentially enhance its therapeutic effects will need further investigation.

Different from conventional or hyperfractionated RT in ADRIATIC trial, hypofractionated thoracic radiation was scheduled during CRT in our study. This cost-effective regimen is permitted and recommended by NCCN guideline. Synergistic effect of RT and immunotherapy might be dose-dependent as mentioned before. Further research is necessary to define the precise parameters for combining RT with immunotherapy to achieve the best clinical outcomes.

There are some limitations of this trial. The single-arm design with small sample size may limit the generalizability of the findings. Also, since only Chinese patients

will be enrolled, the applicability of the results to other regions with different healthcare systems and patient populations.

In summary, this trial design comprehensively optimized treatment paradigm with the expectation of further improving the prognosis of LS-SCLC patients.

Ethics and dissemination

This study received ethical approval from the Independent Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (22/236-3438). This protocol has been accepted for poster presentation at the European Lung Cancer Congress (ELCC) 2024. Investigators will obtain written consent from patients willing to participate in the trial.

List of abbreviation

CI: confidence interval

CR: complete response

EC: etoposide and carboplatin

ECOG PS: Eastern Cooperative Oncology Group performance status

EP: etoposide and cisplatin

ES-SCLC: extensive-stage small cell lung cancer

HR: hazard ratio

IMRT: image guided-intensity modulated radiation therapy

LS-SCLC: limited-stage small cell lung cancer

MRI: magnetic resonance imaging

ORR: objective response rate

OS: overall survival

PCI: prophylactic cranial irradiation

PFS: Progression-free survival

PR: partial response

SCLC: Small cell lung cancer

TTF: time to treatment failure

VALSG: Veterans Administration Lung Study Group

VMAT: volumetric modulated arc therapy

Authors' Contributions

The study was designed by YW, LD, JC and NB. YW and JC developed the statistical analysis plan. YW and LD were major contributors in writing the manuscript. LD, JW, TZ, JC and XZ perform the research and monitor progress. JC, XZ and NB modified the manuscript. All authors read and approved the final manuscript. NB acted as guarantor.

Competing interests

The authors declare that they have no competing interests.

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Figure Legends & Tables

Figure 1 Flowchart of the ASTRUM-LC01 study. SCLC: Small cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; PCI: Prophylactic cranial irradiation; PFS: Progression-free survival; OS: Overall survival; ORR: Objective response rate; DCR: TTF: Time to treatment failure.

Table 1 Inclusion criteria and exclusion criteria.

Inclusion criteria	Exclusion criteria

Aged 18-75 years.	Histologically or cytologically confirmed mixed SCLC.
Histologically or cytologically confirmed SCLC.	Suitable for surgery.
Limited stage SCLC.	Patients with other active malignancies within 5 years or at the same time. Localized tumors that have been cured such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder carcinoma, prostate carcinoma in situ, cervical carcinoma in situ, and breast cancer in situ are acceptable.
Score of Eastern Cooperative Oncology Group performance status (ECOG PS) being 0 or 1.	Patients with pleural, pericardial effusions, or ascites requiring clinical intervention.
Without previous anti-tumor treatment history	Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN).
Without serious abnormalities in hematopoietic function or cardiac, hepatic, or renal function, or immunodeficiency.	Patients with peripheral neuropathy ≥ grade 2 by CTCAE.
Expected survival of at least 3 months	Patients with human immunodeficiency virus (HIV), Hepatitis B or C infection.
Voluntarily participate in this clinical study and signed the informed consent form.	Patients with active pulmonary tuberculosis, previous and current interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis, and severe impaired pulmonary function as judged by the investigator.

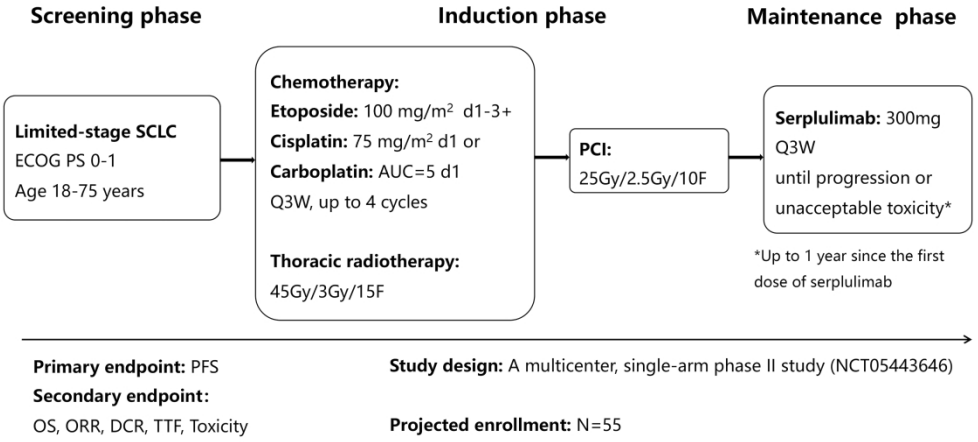
	Subjects with known active or suspected autoimmune diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy are allowed to be enrolled.

Table 2 Organ at risk dose constrains.

Organ at risk		
Lung	V20 < 25%	mean lung dose ≤ 15 Gy
Spinal cord PRV*	Dmax< 42Gy	
Esophagus	Dmax< 50 Gy	mean dose < 34 Gy
Heart	V30 < 50%	
Hippocampus	Dmax < 9 Gy	
Hippocampus PRV**	Dmax < 12 Gy	

*5 mm expansion outside the spinal cord to form planning organ-at-risk volume (PRV)

** 2 mm expansion outside hippocampus to form PRV



Flowchart of the ASTRUM-LC01 study.

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