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Radiotherapy(R) Integration(I) Strategy for Small(S)-Cell Lung Cancer in Extensive(E) Stage (RISE) with up to 10 metastases- a study protocol of a randomized phase II trial

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Abstract

Background The current standard of care (SoC) for patients with extensive-disease small-cell lung cancer (ED-SCLC) is chemo-immunotherapy. The efficacy of radiotherapy (RT) for chest consolidation has been established for patients with ED-SCLC who have responded to chemotherapy. There is a lack of data on incorporating RT as chest consolidation and metastasis-directed therapy for ED-SCLC. The RISE (Radiotherapy for Extensive-Stage Small-Cell Lung Cancer) study aims to evaluate the effectiveness of different RT strategies for residual lesions for patients with ED-SCLC who receive chemo-immunotherapy.

Methods A total of 165 patients with ED-SCLC will be recruited, with 55 patients assigned to each of the three study arms. Patients with stabilization or partial regression, according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, during chemo-immunotherapy will be included.

• Arm I will serve as the control group, comprising patients who continue SoC of programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) immunotherapy (durvalumab or atezolizumab) following platinum-based chemo-immunotherapy.

• Arm II will receive the SoC with consolidative RT to the chest area and potentially, according to palliative indications to metastatic lesions, delivered in 30 Gy in 3-Gy fractions.

• Arm III will receive SoC with RT of 45 Gy in 3-Gy fractions to the chest area and stereotactic body radiotherapy (SBRT) with 24 Gy in 8-Gy fractions to the metastatic lesions.

Blood samples for circulating tumor DNA (ctDNA) will be collected before RT, during each week of treatment, and at the time of disease progression.

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The primary endpoint is progression-free survival (PFS) based on RECIST 1.1 or patient death. 1. Secondary endpoints are OS, treatment toxicity (frequency of G3 toxicity according to CTCAE v.5.0), area of progression (primary tumor localization/new lesions), Overall response rate (ORR), and the response rate in non-irradiated lesions.

Discussion The study population of patients with ED-SCLC has a poor prognosis. Dose-escalated chest RT and SBRT (for up to 10 metastases) administered with modern techniques offer the possibility to improve OS and PFS.

Trial registration Clinicaltrials.gov NCT06529081 (Registered 26th Jul 2024).

Keywords Lung cancer, Chemotherapy, Radiotherapy, Immunotherapy, Oligometastatic disease

Background

Extensive disease small cell lung cancer (ED-SCLC) continues to present a considerable therapeutic challenge. Worldwide, lung cancer accounts for nearly one in eight (12.4%) of all diagnosed cancers and one in five (18.7%) of cancer fatalities. Approximately 2.5 million new lung cancer cases were reported in 2022, comprising about 15.2% (1.572.045) in men and 9.4% (908.230) in women. Furthermore, there were around 1.8 million deaths attributed to lung cancer, representing 18.7% of all cancer-related deaths, 22.7% (1,233,241) in men and 13.6% (584,800) in women [1].

Small-cell lung cancer (SCLC) constitutes 15% of all lung cancer cases and is characterized by rapid growth and early spread to lymph nodes and distant organs [2]. Upon diagnosis, Most patients present with metastatic disease involving the liver, bones, bone marrow, central nervous system, and adrenal glands.

In ED, long-term survival is infrequent, even with the best available treatment options (chemo-immunotherapy and immunotherapy) [3]. The standard treatment for patients with ED-SCLC is chemo-immunotherapy. A phase III randomized trials have shown the OS benefit of chemo-immunotherapy (durvalumab or atezolizumab) over chemotherapy [3, 4]. Historically, the efficacy of radiation therapy for chest area consolidation (30 Gy/3 Gy) has been established for patients with ED-SCLC who have responded to chemotherapy [5]. Findings from the RTOG 0937 study indicate that irradiation of the thoracic region and extracerebral metastases after chemotherapy may be considered [6]. There is no prospective evidence to incorporate RT to chemio-immunotherapy. The decision to employ radiotherapy in patients receiving chemo-immunotherapy remains ambiguous. Without new clinical evidence, National Comprehensive Cancer Network (NCCN) v.3.2025 advises adapting previous clinical practices for patients receiving chemo-immunotherapy and exploring the possibility of consolidation radiotherapy. As a result, the NCCN suggests personalizing the fractionation method and total dose based on individual clinical circumstances [7]. These guidelines state that doses of 30 Gy/3 Gy and 45 Gy/3 Gy can be prescribed. The appropriate dosage for treatment needs to be better defined.

The *Radiotherapy for Extensive-Stage Small-Cell Lung Cancer (RISE)* trial aims to evaluate various radiotherapy approaches and dosages in patients diagnosed with histologically confirmed ED-SCLC after chemo-immunotherapy.

Methods/design

The RISE trial is a phase II, randomized, non-blinded, three-arm trial conducted in four institutions. This research complies with the Helsinki Declaration and has been approved by the Bioethics Committee at the Medical University of Łódź (RNN/141/23/KE) and was registered in Clinicaltrials.gov identifier: NCT06529081. The study was funded by the Medical Research Agency Competition ABM/2032/1 (Competition for the head-to-head clinical trials – second edition). (2023/ABM/01/00040) [8].

This study aims to evaluate radiotherapy's efficacy as part of the combined treatment approach for patients diagnosed with ED-SCLC who are undergoing chemo-immunotherapy. The planned research aims to assess the impact of consolidative radiotherapy to the chest residual disease and, if present, up to 10 metastases following chemo-immunotherapy (during immunotherapy).

Three treatment arms have been implemented:

- Arm I: Continuation of the standard of care (SoC)—of programmed death-ligand 1 (PD-L1) or programmed death-1 (PD-1) immunotherapy (durvalumab or atezolizumab) after chemo-immunotherapy based on platinum compounds;
- Arm II: SoC, followed by consolidating radiotherapy of the chest area and possibly, according to palliative indications, metastases in doses of 30 Gy in 3 Gy fractions;
- Arm III: SoC, followed by consolidating radiotherapy in the total dose of 45 Gy in 3 Gy daily to the chest area and 24 Gy in 8 Gy fractions administered every 2–3 days for up to 10 metastatic lesions Fig. 1.

A total of 165 patients with ED-SCLC will be recruited, 55 for each of the three study arms.

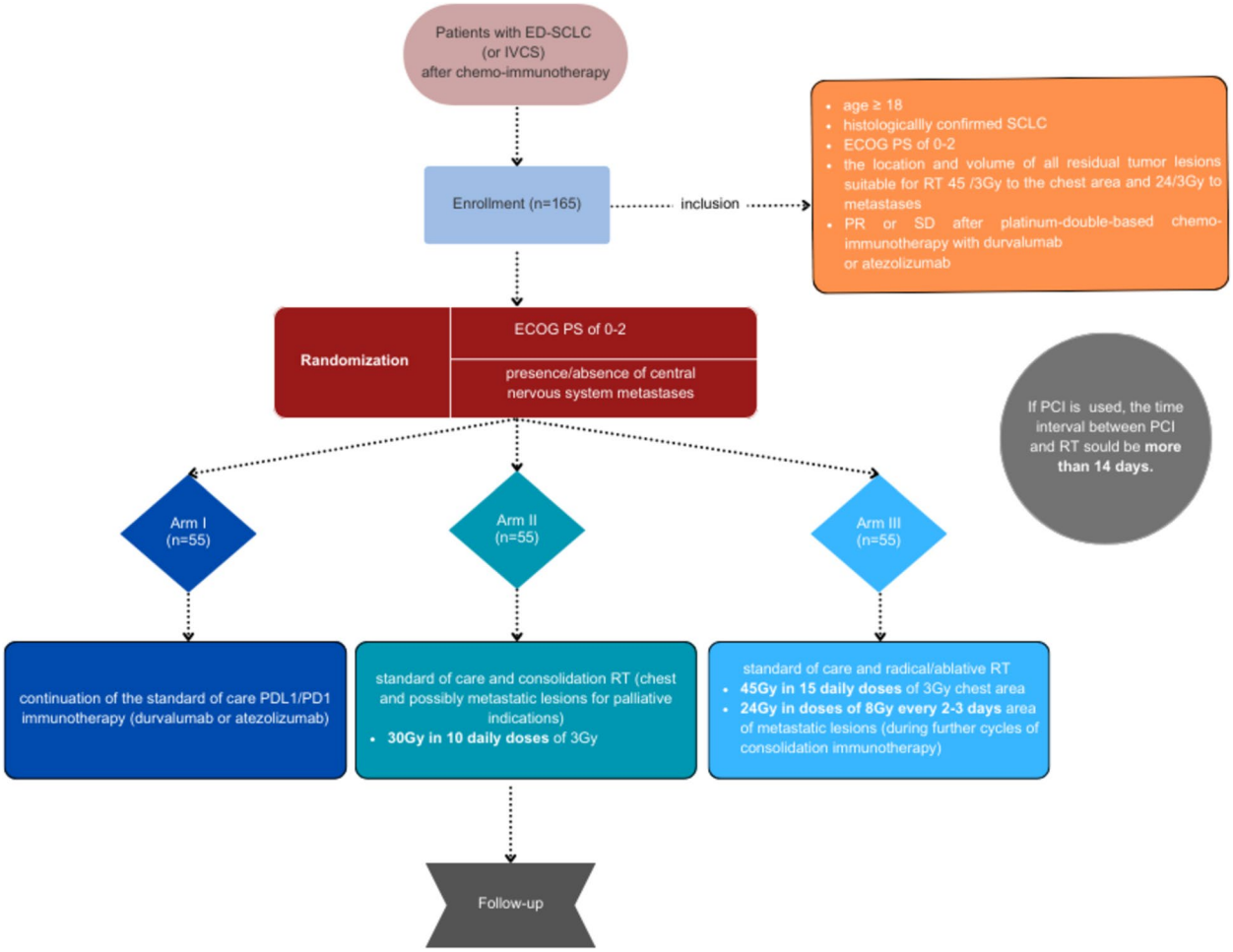

Fig. 1 The protocol schema of the RISE trial. ED-SCLC: Extensive-disease small-cell lung cancer; SCLC: Small-cell lung cancer; ECOG: Eastern Cooperative Oncology Group; PS: Performance status;; PR: Partial response; SD: Stable disease; PD-L1: Programmed death-ligand 1; PD-1: Programmed death-1; PCI: Prophylactic cranial irradiation; CS: Clinical Stage

The 10 ml blood sample will be collected before starting radiotherapy, during each week (maximum three samples), and at the time of disease progression. It will be prepared, stored, and used for circulating tumor DNA (ctDNA) testing. The ctDNA analysis data will be utilized as a potential marker to determine the time to progression and evaluate the benefits derived from the administered radiotherapy. The study schedule is presented in Table 1.

The patient will be offered the opportunity to participate in additional blood collection and biobanking for future research purposes.

Randomization

Stratified randomization will be conducted to ensure that a proportional number of participants with a specific characteristic, which may affect the treatment response, is assigned to each of the planned treatment groups. The factors considered are Eastern Cooperative Oncology Group(ECOG) Performance Status (PS) and the presence of brain metastases. The randomization procedure will be performed computationally with the blockrand R package. The block randomization for each stratification subgroup will be applied with permutation blocks of 3, 6, and 9. A sealed envelope method will be utilized between signing the consent to participate in the study and executing a CT for radiotherapy planning.

Study outcomes

Primary endpoints

The primary endpoint is progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or patient death.

The PFS was chosen as an adequate measure of the efficacy of the novel cancer therapy due to the lack of impact from subsequent lines of treatment on that endpoint (they are recommended in case of disease progression). The PFS

Table 1 Study schedule of the RISE trial

Study Procedure	Screening Visit	Treatment/Intervention Period				Follow up – every 6 weeks (+/- 7 days) CT scan/MR (head, chest, abdomen, pelvis) every 6 weeks																	
Visit	1	2	3[a]	4[a]	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Informed Consent (ICF)	X																							
Inclusion/Exclusion Criteria	X																							
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interview examintaion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X																							
Routine blood collection		X	X	X	X																			
Blood collection for ctDNA detection[b]		X	X	X	X																			
Radiotherapy		X	X	X	X																			
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Toxicities ≥ grade 2 (CTCAE v5.0)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 questionnaire	X				X	X	X		X		X		X		X		X		X		X		X	

ED-SCLC Extensive-disease small-cell lung cancer, *CT* Computed tomography, *MRI* Magnetic resonance imaging, *ICF* Informed consent form, *ctDNA* Circulating tumor DNA, *CTCAE* Common Terminology Criteria for Adverse Events, *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

[a] In the case of participants from Arm I and II, there will be one III/IV visit

[b] Visits 2-5 and additionally in case of progression

is the most relevant indicator for patients' quality of life and public health system burden; its extensions prevent symptomatic disease progression and disease and treatment-related complications. It measures extended time without additional medical procedures and needing third-party care. Based on previous studies where radiotherapy was applied to all disease foci in a similar patient population, the expected hazard ratio for the proposed study is 0.55.

Secondary endpoints

1. Overall survival (OS);
2. Treatment toxicity (frequency of G3 toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) v.5.0),
3. Area of progression (primary tumor localization [present at baseline]/new lesions);
4. Overall response rate (ORR);
5. The response rate in non-irradiated lesions.

The addition of radiotherapy to chemo-immunotherapy may result in additional toxicity, whose severity is below the expected benefits for patients. After enrolling one-third of the patients, a safety evaluation of the applied radiotherapy strategy and the potential significance of the intended endpoints is planned.

Eligibility criteria

Inclusion criteria

- Age ≥ 18 years.
- Histopathological confirmation of SCLC.
- Primary clinical stage: extensive stage according to Veterans Administration Lung Study Group (VASLG) classification or stage IV according to TNM classification.
- ECOG-PS of 0–2.
- Partial Response (PR) or Stable Disease (SD) to platinum-based doublet chemotherapy with durvalumab or atezolizumab based on restaging (Computed Tomography (CT), or Magnetic Resonance Imaging (MRI) or Positron Emission Tomography/Computed Tomography (PET/CT)).
- The location and volume of all residual tumor lesions suitable for the safe delivery of RT at a total dose of 45 Gy in 3 Gy fractions to the chest area and 24 Gy in 8 Gy fractions to all metastases at the time of randomization.
- Clinical control of brain metastases (prior whole-brain irradiation at any stage is acceptable before randomization).
- Measurable residual disease after chemio-immunotherapy (according to RECIST 1.1) or in the case of Complete Response (CR)/PR, the presence of tumor lesions not classified as measurable.
- Up to 10 metastases at diagnosis.
- Absence of clinically significant and pharmacologically uncontrolled co-morbidities.
- Absence of active autoimmune diseases except for diabetes, hypothyroidism, psoriasis, eczema, lichen planus, and vitiligo.
- Adequate hematopoietic, renal, and hepatic function, allowing treatment with atezolizumab or durvalumab, according to the current Summary of Product Characteristics (SmPC).

- Signed written informed consent obtained by the investigators according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use/Good Clinical Practice (ICH/GCP) regulations.

Exclusion criteria

- Premenopausal women who do not accept the need for effective contraception during RT and/or chemotherapy/immunotherapy.
- Individuals excluded from participation in a medical experiment based on Article 23A(1) of the Act on the Profession of Physician and Pharmacist.
- Coexistence of other uncontrolled malignant neoplasms.
- Contraindications to the use of atezolizumab or durvalumab as specified in the SmPC.
- Grade 2 or greater CTCAE v.5.0 pneumonitis secondary to immunotherapy.
- Participation in another clinical trial during the study.
- Prior chest RT that precludes safe administration of RT according to the study protocol. Prior palliative RT to metastases is acceptable before study entry if clinically indicated as determined by the physician.
- Contraindications to RT according to the protocol.

Interventions

The radiotherapy standards outlined in this protocol are based on several key guidelines: the NCCN for SCLC, the European Society for Radiotherapy and Oncology (ESTRO) guidelines, and the American Society for Radiation Oncology (ASTRO) Clinical Practice Guideline [9–12]. The protocol should take precedence in discrepancies between these sources and the protocol.

Minimal technical requirements

The minimum technological standard for RT planning is three-dimensional conformal radiotherapy (3D-CRT) based on CT. More advanced technologies are recommended to minimize toxicity and increase treatment safety. These include four-dimensional computed tomography (4D-CT) and planning incorporating Fluorodeoxyglucose (FDG) PET/CT) images fused with CT. Other advanced imaging and treatment techniques include magnetic resonance imaging (MRI), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), image-guided radiotherapy (IGRT), and methods for compensating for respiratory motion. The IMRT or VMAT are preferred over 3D-CRT to reduce toxicity and dose/volume parameters of healthy tissue. Advanced computational methods, such as Monte Carlo model-based algorithms or heterogeneity correction algorithms that address complex anatomy and tissue inhomogeneities, are recommended to improve the accuracy of dose distribution. All data concerning the utilization of advanced RT planning and delivery will be prospectively collected.

Simulation

Simulation should be performed using CT scans taken while the patient is in the therapeutic position for RT and with appropriate immobilization devices. It is advisable to administer intravenous contrast (with or without oral contrast) whenever feasible, especially for patients with centrally located lung tumors and nodal disease. The pre-contrast (no contrast) phase will be utilized for planning purposes. During simulation, assessing and accounting for tumor and organ motion, especially respiratory-related motion, is crucial. Several methods can be used, with 4D-CT being the preferred approach. This involves taking CT scans during both the inspiratory and expiratory phases, as well as the deep inspiration breath-hold (DIBH) technique. Adaptive replanning should only be considered in rare cases involving substantial anatomical changes.

Imaging and fusion methods

The CT is the primary test used to determine the stage of patients and eligibility for the National Health Fund (NHF) for systemic therapy. When an FDG-PET/CT is performed before or after the implementation of systemic treatment, it is recommended that it is fused with CT for RT planning to improve the accuracy of determining the target volumes. An MRI is recommended to determine the target volumes and selected organs at risk (OARs) when planning SBRT, especially in the brain and spine.

Definition of target volumes and margins

The recommended target volumes for RT include the areas of only residual nodal and primary tumors located in the mediastinum and/or thorax. Radiotherapy to the primary involved nodal groups, as determined by initial imaging (CT or PET-CT) or histopathology, may be considered only if, in the investigator's opinion, it does not significantly increase the irradiation area.

– The v (GTV) encompasses the residual primary tumor area (GTVp) and residual nodal disease after chemotherapy (GTVn). This should be delineated on CT scans taken in the therapeutic position, using both lung and soft tissue windows. GTVp and GTVn must be contoured separately.

- The Clinical Target Volume (CTV) expands upon the GTV by adding a motion-related margin and an additional 5 mm margin in all directions to account for the tumor's microscopic spread. The CTV should also be adjusted manually to conform to natural anatomical barriers.
- To create the Planning Target Volume (PTV), a margin should be applied around the CTV, considering geometric uncertainties per the current recommendations from the International Commission on Radiation Units and Measurements (ICRU) (https://www.icru.org/current-activities-of-icru/radiation-therapy/). The size of the PTV margin should account for potential alignment errors, patient movement, and tumor movement, with an individualized range of 5–8 mm, depending on the treatment center's standards.

Organs at risk definitions and margins

Selected OARs have to be contoured for chest irradiation:

- The lungs (both individually and combined, excluding the CTV or GTV),
- The entire heart, including the pericardial sac,
- The esophagus, from the annulus to the gastroesophageal junction,
- The spinal canal (as Planning Risk Volume (PRV) for the spinal cord).

The central bronchial tree and chest wall do not need to be delineated at doses of either 30 Gy/3 Gy or 45 Gy/3 Gy, depending on the allocation to the study arms.

If 4D CT is used for planning, the OARs should be assessed in the average phase of CT.

In cases where SBRT is employed, it is advisable to define OARs within 5 cm of the PTV to ensure that all OARs listed in Table 2 can be evaluated. Creating planning risk volume (PRV) for the spinal cord and brainstem is recommended, with the margins determined according to the center's standards, typically 1 to 3 mm [13].

Dose-volume constraints for organs at risk

The area for planning non-stereotactic radiotherapy should cover 95% of the dose on 98% of the PTV volume. A 95–105% isodose should cover the PTV area. For SBRT, 100% of the dose in the PTV should cover 100% of the volume, with a maximum dose (Dmax) of at least 120%.

If the following dose-volume recommendations in OARs cannot be met, PTV/CTV/GTV coverage should be limited below the recommendations formulated above.

The dose constraints were adapted from Timmerman et al. [14] Table 2.

Statistical analysis and sample size estimation

The sample size for the study was estimated using the log-rank test under the following assumptions: power of 1-β = 0.80; statistical significance level α = 0.1; minimum expected hazard ratio for the study group vs. control group HR = 0.55; estimated percentage of censored observations CR = 0.05; planned follow-up period [months] FU = 24. An equal ratio of sample sizes in the groups was assumed. The estimation was conducted in two stages. In the first stage, the number of adverse events was estimated at 99 (assuming HR = 0.55). Subsequently, based on the estimated number of adverse events, an assumed censoring rate of 0.05, and an assumed median time to progression in the control group of approximately 5.5 months, the number of patients was estimated at $N = 165$. The sample size estimation was performed in R v.4.0.2 based on Schoenfeld's equation for estimating sample size for Cox proportional hazards models [15].

Primary and secondary endpoints analysis

Survival analysis will be conducted based on Kaplan–Meier estimators and Cox proportional hazards regression models. Differences in continuous variables between study groups will be assessed using Student's t-test and ANOVA with post-hoc tests for parametric data or Mann–Whitney U test and Kruskal–Wallis test with post-hoc tests for non-parametric data. The distribution of data will be examined with the Shapiro–Wilk test. Given this Phase II study's nature, the accepted statistical significance alpha level is set at 0.1. Furthermore, data from the proposed research may be corroborated with those from published studies mentioned in the protocol to create a meta-analysis. A prospective sample size estimation for the following assumptions, HR 0.55, and observation time of 24 months was made.

Security analysis

The safety analysis will be performed based on the population for the safety analysis, i.e., 33%—54 recruited patients. Radiotherapy-related toxicity assessment will be conducted once 66% – 109 patients have been recruited. The analysis will include reported SAEs based on CTCAE v.5.0. Adverse events concerning arm, severity, and relationship to the procedures will be summarized.

Ethics

The study will follow the protocol and ethical principles in the Declaration of Helsinki, with the GCP guidelines and with Polish law. The Ethics Committee will receive annual and periodic product safety reports during development and will be informed of the discontinuation/completion of the study following the regulations.

Table 2 Dose constraints for OARs applied in the RISE trial

Radiotherapy schema	Organ at Risk	Volume (cm^3)	Max dose in critical volume (Gy)	Max point dose (≤ 0.035 cm^3) (Gy)
30 Gy/3 Gy	Lung (right and left)	1500 cm^3 for mens and 950 cm^3 for females	15	
			V-16 Gy < 37%	
	Heart/pericardium	< 15 cm^3	36.6	42.5
	Esophagus(avoid circumferential irradiation)	< 5 cm^3	40	48
	Spinal cord	< 5 cm^3	31	36
45 Gy/3 Gy	Lung (right and left)	1500 for males and 950 for females	16.5	
			V-18 Gy < 37%	
	Heart/pericardium	< 15 cm^3	42	48.9
	Esophagus	< 5 cm^3	45	54
	Spinal cord	< 5 cm^3	39	42
SBRT: 24 Gy/8 Gy	Optic pathway	< 0,2 cm^3	15,3	17,4
	Cochlea		14.4	
	Brainstem (not medulla)	< 0,5 cm^3	15.9	23,1
	Spinal cord and medulla	< 0,35 cm^3	15,9	22,5
	Cauda equina	< 5 cm^3	21,9	25,5
	Sacral plexus	< 5 cm^3	22,5	25,5
	Esophagus	< 5 cm^3	27,9	32,4
	Brachial plexus	< 3 cm^3	22	26
	Peripheral (named) nerve	< 2 cm length	25,5	30,6
	Heart/pericardium	< 15 cm^3	24	30
	Great vessels	< 10 cm^3	39	45
	Trachea and large bronchus	< 5 cm^3	39	43
	Bronchus, smaller airways	< 0,5 cm^3	25,8	30
	Rib	< 5 cm^3	40	50
	Skin	< 10 cm^3	31	33
	Stomach	< 5 cm^3	22,5	30
	Bile duct		36	
	Duodenum	< 5 cm^3	22,5	30
	Jejunum/ileum	< 30 cm^3	20,7	28,5
	Colon	< 20 cm^3	28,8	
	Rectum	< 3,5 cm^3	43	47
		< 20 cm^3	30,3	
	Ureter		40	
	Bladder wall	< 15 cm^3	17	33
	Penile bulb	< 3 cm^3	25	
	Femoral heads	< 10 cm^3	24	
	Renal hilum/vascular trunk	15 cm^3	19,5	
	Lung (right and left)	1500 for males and 950 for females	10,8	
	Lung (right and left)	V-11,4 Gy < 37%		
	Liver	700	17,7	
	Renal cortex (right and left)	200	14,7	

Discussion

The RISE study aims to evaluate radiotherapy strategies in combination with chemoimmunotherapy for patients with ED-SCLC. Despite advances in systemic therapies, a median progression-free survival (PFS) of 5.1–5.2 months is reported in key trials on chemo-immunotherapy [3, 15]. Furthermore, local control of preexisting tumor sites remains inadequate. The most common patterns of disease progression in ED-SCLC involve failure within the thoracic region. Isolated progression to only the extra-thoracic region was observed in 11% of patients receiving chemo-immunotherapy. In comparison, 68% of patients progressed within the thoracic region [16]. The addition of radiotherapy reduces the risk of thoracic progression. It may be a valuable option for those patients, with a gain in oncological outcomes comparable to adding IO to chemotherapy [16].

Consolidative thoracic radiotherapy in palliative doses 30 Gy in 10 fractions has been shown to improve intrathoracic local control, 6 months PFS, and 2-year OS in ED-SCLC patients receiving chemotherapy [5]. The escalation of thoracic radiotherapy doses beyond palliative levels, such as 45 Gy in 15 fractions, may offer additional benefits. Evidence from RTOG 0937 suggests that those higher doses and metastasis-directed radiotherapy prolong PFS with acceptable toxicity. These findings support exploring dose escalation to improve long-term outcomes [7]. However, both mentioned trials failed to meet the primary endpoint of one-year OS improvement and were negative from the methodological point of view. Radiotherapy treatment volumes in both trials encompassed the primary extent of nodal involvement and post-chemotherapy tumor [5, 7]. The most recently presented trial as a conference abstract does not support the practice of dose escalation following chemotherapy [17]. The extent of radiotherapy target volumes must be carefully considered to mitigate risks such as cardiotoxicity and radiation-induced lymphopenia, which has been associated with poorer survival outcomes for lung cancer treatment and is directly connected with doses in the heart and lungs [18–21].

Furthermore, radiation-induced lymphopenia may fully diminish the survival advantage of the addition of immunotherapy [22]. Limiting the radiotherapy target volume to avoid extensive irradiation of lymphocyte-rich areas may enhance the safety profile of the treatment while preserving its efficacy. In the RISE trial, thoracic radiotherapy target volume encompasses only residual nodal and tumor disease. In the dose escalation arm, metastasis-directed therapy after chemo-immunotherapy is additionally used. Ongoing phase II/III studies (NRG-LU007/RAPTOR, TRIPLEX, TRESURE) assess the addition of radiotherapy to chemo-immunotherapy but not its optimal dosing/fractionation strategy. In some with available protocols, the radiotherapy thoracic target volumes are more extensive than ours [23–25]. Metastasis-directed therapy, facilitated by modern delivery techniques SBRT, has demonstrated minimal toxicity, with grade 3 adverse events being sporadic [26]. We also prioritize OARs dose constraints over PTV coverage to minimize potential toxicity.

Current NCCN SCLC v.3.2025 guidelines [9]. suggest adapting consolidative radiotherapy practices to chemo-immunotherapy regimens, but data on optimal dosing and fractionation strategies are lacking. Data on safety and efficacy comes from retrospective studies [27]. The RISE study addresses these gaps by evaluating the feasibility, safety, and efficacy of incorporating thoracic radiotherapy in ED-SCLC treatment while considering strategies to limit irradiation volume. Interim safety analysis will be conducted after enrolling 33% of the planned cohort to ensure the approach meets safety and efficacy criteria.

Trial status

At the time of publication, RISE was open to recruitment in one center. The remaining centers are in the activation process. Trial recruitment began in September 2024, with the first patient enrolled on 24th September 2024, and the estimated recruitment end date is July 2027. The current RISE protocol is Version 1.1, 22th May 2024.

Trial sponsor

Copernicus Memorial Hospital. Funding under the Medical Research Agency Competition ABM/2032/1 (Competition for the head-to-head clinical trial – second edition). (2023/ABM/01/00040).

Abbreviations

AE	Adverse Events
ASTRO	The Amercian Society for Radiation Oncology
CT	Computed tomography
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse EventsCS: Clinical Stage
ctDNA	Circulating Tumor DNA
DIBH	Deep Inspiration Breath-Hold
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
ED	Extensive Disease
ESTRO	The European Society for Radiotherapy and Oncology
FDG	Fluorodeoxyglucose
GTV	Gross Tumor Volume
GY	Grey
ICRU	International Commission on Radiation Units and Measurements
IMRT	Intensity Modulated Radiation Therapy
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
SCLC	Small Cell Lung Cancer
SmPC	Summary of Product Characteristics
SoC	Standard of Care
ORR	Objective Response Rate
OS	Overall Survival

PFS	Progression-free Survival
PRV	Planning Risk Volume
PTV	Planning Target Volume
OaR	Organs at Risk
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
VMAT	Volumetric Modulated Arc Therapy

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Authors' contributions
Ł.K.: Conceptualization, Methodology, Writing - Original Draft Preparation, Supervision, Funding Acquisition. J. F.: Supervision, Writing - Review & Editing. D. T.: Data Curation, Writing - Review & Editing. E. S.: Validation, Writing - Review & Editing. P. C.: Validation, Writing - Review & Editing. M. M.: Investigation, Data Curation. M. L-H.: Investigation, Writing - Review & Editing. M. O.: Data Analysis, Visualization. K. G.-K.: Writing - Review & Editing, Resources. A. A.: Supervision, Writing - Review & Editing. I. C.: Investigation, Writing - Review & Editing. B. Z.: Investigation, Writing - Review & Editing. M. K.-M.: Investigation, Writing - Review & Editing. W. K.: Data Curation, Writing - Review & Editing. N. J.: Data Curation, Writing - Review & Editing. K. R.: Data Curation, Writing - Review & Editing. M. B.: Investigation, Validation, Data Analysis, Writing - Original Draft, Writing - Review & Editing, Resources.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This research complies with the Helsinki Declaration and has been approved by Medical University of Lodz Ethics committee.
Trial registration: Clinicaltrials.gov identifier: NCT06529081; Registered 26 July 2024. A signature of the informed consent will be obtained from all patients before inclusion in the study.

Consent for publication
Not applicable. No patient-level information in this manuscript.

Competing interests
The authors declare no competing interests.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
2. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primer. 2021;7(1):3.
3. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–9.
4. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):51–65.
5. Slotman BJ, Van Tinteren H, Praag JO, Knegjens JL, El Sharouni SY, Hatton M, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet. 2015;385(9962):36–42.
6. Gore EM, Hu C, Sun AY, Grimm DF, Ramalingam SS, Dunlap NE, et al. Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extracranial irradiation for extensive-disease small cell lung cancer (ED SCLC): NRG Oncology RTOG 0937. J Thorac Oncol. 2017;12(10):1561–70.
7. NCCN Clinical Practice Guidelines in Oncology. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Small Cell Lung Cancer Version 3.2025 — October 29, 2024. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Cited 2024 Dec 21.
8. Kitala, Diana et al. Medical research agency: 5 years of reshaping the clinical trials ecosystem in Poland. Lancet Reg Health Eur. 48:101175.
9. Ganti AKP, Loo BW, Bassetti M, Blakely C, Chiang A, D'Amico TA, et al. Small cell lung cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19(12):1441–64.
10. Guckenberger M, Andratschke N, Belka C, Bellut D, Cuccia F, Dahele M, et al. ESTRO clinical practice guideline: stereotactic body radiotherapy for spine metastases. Radiother Oncol. 2024;190:109966.
11. Simone CB, Bogart JA, Cabrera AR, Daly ME, DeNunzio NJ, Detterbeck F, et al. Radiation therapy for small cell lung cancer: an ASTRO clinical practice guideline. Pract Radiat Oncol. 2020;10(3):158–73.
12. Le Pechoux C, Faivre-Finn C, Ramella S, McDonald F, Manapov F, Putora PM, et al. ESTRO ACROP guidelines for target volume definition in the thoracic radiation treatment of small cell lung cancer. Radiother Oncol. 2020;152:89–95.
13. Respiratory small cell lung cancer thoracic EBRT with or without chemotherapy 2023 V.1), , eviQ Cancer Treatments Online, Cancer Institute NSW, viewed 29th October 2024, https://www.eviq.org.au/radiation-oncology/respiratory/4292-respiratory-small-cell-lung-cancer-thoracic-e#organs-at-risk.
14. Timmerman R. A story of hypofractionation and the table on the wall. Int J Radiat Oncol Biol Phys. 2022;112(1):4–21.
15. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394(10212):1929–39.
16. Kim D, Kim HJ, Wu HG, Lee JH, Kim S, Kim TM, et al. Intrathoracic progression is still the most dominant failure pattern after first-line chemo-immunotherapy in extensive-stage small-cell lung cancer: implications for thoracic radiotherapy. Cancer Res Treat. 2024;56(2):430–41.
17. Zhang X, Yu J, Zhu H, Meng X, Li M, Jiang L, et al. Consolidative thoracic radiotherapy for extensive stage small cell lung cancer. Oncotarget. 2017;8(13):22251–61.
18. Kuncman Ł, Pajdziński M, Smółka K, Bilski M, Socha J, Stando R, et al. Early lymphocyte levels and low doses radiation exposure of lung predict lymphopenia in radiotherapy for lung cancer. Front Immunol. 2024;15:1426635.

19. Walls GM, Bergom C, Mitchell JD, Rentschler SL, Hugo GD, Samson PP, et al. Cardiotoxicity following thoracic radiotherapy for lung cancer. Br J Cancer . 2024; Available from: https://www.nature.com/articles/s41416-024-02888-0. Cited 2024 Dec 23.
20. Jin JY, Hu C, Xiao Y, Zhang H, Paulus R, Ellsworth SG, et al. Higher radiation dose to the immune cells correlates with worse tumor control and overall survival in patients with stage III NSCLC: A secondary analysis of RTOG0617. Cancers. 2021;13(24):6193.
21. Abravan A, Faivre-Finn C, Kennedy J, McWilliam A, Van Herk M. Radiotherapy-related lymphopenia affects overall survival in patients with lung cancer. J Thorac Oncol. 2020;15(10):1624–35.
22. Jing W, Xu T, Wu L, Lopez PB, Grassberger C, Ellsworth SG, et al. Severe radiation-induced lymphopenia attenuates the benefit of durvalumab after concurrent chemoradiotherapy for NSCLC. JTO Clin Res Rep. 2022;3(9):100391.
23. NRG-LU007: The RAPTOR Study for ES-SCLC. Available from: https://www.nrgoncology.org/RAPTOR. Cited 2024 Dec 21.
24. Bozorgmehr F, Christopoulos P, Chung I, Cvetkovic J, Feißt M, Krisam J, et al. Protocol of the TREASURE study: Thoracic RadiothErapy with Atezolizumab in Small cell lUng canceR Extensive disease – a randomized, open-label, multicenter phase II trial. BMC Cancer. 2022;22(1):1011.
25. Ishii H, Azuma K, Shimose T, Yoshioka H, Kurata T, Shingu N, et al. Phase II study of durvalumab (MEDI 4736) plus carboplatin and etoposide in elderly patients with extensive stage small cell lung cancer: study protocol of turtle study (LOGIK 2003). Thorac Cancer. 2023;14(1):105–7.
26. Alongi F, Nicosia L, Ricardi U, Scorsetti M, Greto D, Balermpas P, et al. Acute toxicity in patients with oligometastatic cancer following metastasis-directed stereotactic body radiotherapy: an interim analysis of the E2-RADIatE OligoCare cohort. Radiother Oncol. 2024;199:110466.
27. Yao Y, Li B, Song R, Yang L, Zou B, Wang L. Efficacy and safety of thoracic radiotherapy in extensive-stage small-cell lung cancer patients receiving first-line immunotherapy plus chemotherapy: a propensity score matched multicentre retrospective analysis. Radiat Oncol. 2024;19(1):25.

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