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Current Trial Report

Spatially Fractionated Induction Radiotherapy to Widen the Therapeutic Window in Locally Advanced Non–Small-Cell Lung Cancer (SPARROW): Study Protocol of a Multicenter, Randomized, Open-Label Seamless Phase I/II Trial

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ABSTRACT

Background: Inoperable, locally advanced non–small-cell lung cancer (LA-NSCLC) remains associated with high rates of locoregional failure despite concurrent chemoradiotherapy and consolidation immunotherapy. Uniform dose escalation has failed to improve outcomes. We propose to address intra- and interindividual tumor heterogeneity by spatially fractionated radiotherapy (SFRT) and stereotactic body radiotherapy (SBRT).

Patients & Methods: SPARROW is a prospective, multicenter, open-label seamless phase I/II randomized clinical trial. In phase I, up to 32 patients with inoperable LA-NSCLC receive induction SFRT (Lattice or central boost, 1 × 18 Gy), followed by a 4-week interval and adaptive consolidation radiotherapy (25 × 2.4 Gy). Tumor volume reduction (primary endpoint), safety, and feasibility guide selection of the optimal SFRT approach. A "backup arm" allows SBRT of small primary tumors with mediastinal fractionated radiotherapy (25 × 2.4 Gy). In phase II, 100 patients are randomized (1:1) to this personalized treatment (induction SFRT or SBRT of the primary) versus standard fractionated radiotherapy (30-35 × 2 Gy). Both treatment arms employ intensity-modulated and adaptive radiation techniques. The primary endpoint is progression-free survival (PFS). Secondary and translational endpoints include overall survival, locoregional control, patient-reported outcomes, circulating tumor DNA and immune profiling.

Discussion: SPARROW investigates whether personalized and novel radiotherapy techniques can overcome tumor heterogeneity and radioresistance in LA-NSCLC. The embedded translational program aims to characterize potential antitumor immune responses. Thus, SPARROW could redefine dose concepts in radiation oncology beyond lung cancer.

Trial Registration: https://www.drks.de:DRKS00037163.

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Introduction

Patients with inoperable, locally advanced non–small-cell lung cancer (LA-NSCLC) receive definitive radiotherapy (RT) combined with chemotherapy and Durvalumab consolidation.[1] Despite this multimodal treatment, locoregional progression occurs frequently and is associated with dismal prognosis.[2]

The current standard-of-care (SOC) RT consists of 60-70 Gy in 30-35 fractions based on a homogeneous, "one-size-fits-all" paradigm established decades ago.[3] Attempts at uniform dose escalation have resulted in worse outcomes, likely due to increased cardiopulmonary toxicity.[4] Although PET-guided dose escalation strategies have been tolerated well, they could not consistently translate into survival gains.[5-7] Genomic radiosensitivity modeling suggests that even higher uniform dose escalation may be required for cure.[8] This highlights the narrow therapeutic window in LA-NSCLC. Furthermore, inoperable LA-NSCLC encompass a heterogeneous disease spectrum (UICC stage IIB-IIIC), where distinct anatomical constellations differ substantially in terms of RT feasibility.[2] While current advances in adaptive RT (ART) improve anatomical precision and may reduce toxicity,[9] they do not address the conceptual limitations of homogeneous, "one-size-fits-all" RT dose prescription.

Spatially fractionated radiotherapy (SFRT) represents an unconventional strategy that builds upon historical GRID concepts.[10] Instead of homogeneously irradiating the entire tumor, SFRT delivers high doses to selected intratumoral subvolumes, while maintaining low doses around.[10-12] Modern techniques such as Lattice RT or central boosts (CEBO) integrate intensity-modulated RT (IMRT) and image-guided RT (IGRT).[10-13] Such inhomogeneous dose distributions might work through direct cytotoxic effects but also immunogenic mechanisms, while sparing surrounding organs.[13,14] Early clinical experiences in bulky tumors have demonstrated encouraging tumor responses with favorable safety profiles.[10,11]

Stereotactic body radiotherapy (SBRT) delivers high inhomogeneous tumor doses in few fractions to small lung tumors. SBRT represents an effective standard treatment in early stage NSCLC and has shown promising results when combined with „classical" fractionated RT in selected LA-NSCLC settings.[2,15]

Therefore, we designed the SPARROW trial to assess whether individualized application of SFRT or SBRT in patients with LA-NSCLC can improve clinical outcomes and stimulate distinct antitumor immune responses.

Design

Patient Selection and Trial Design

SPARROW is a multicenter, open-label, prospective, seamless phase I/II trial (Figure 1). The trial enrolls patients with histologically proven NSCLC, available staging FDG-PET-CT and cerebral imaging, inoperable and locally-advanced tumors (stage II with positive lymph nodes (N1-2a) or stage III acc. UICC ninth edition), indication for definitive RT with sequential or simultaneous systemic treatment (eg, chemotherapy), age ≥ 18 years, ECOG score 0-2 and after written informed consent was obtained. Exclusion criteria are previous thoracic RT, acute toxicities from prior therapies and hemoptysis CTCAE ≥ grade 2. The SPARROW trial is planned to recruit at 4 German cancer clinics from 04/2026 until 06/2034 and was initially approved by the primary local ethics board (S325-2025). Thus, it will comply with the Helsinki declaration.

In phase I, 16 patients with large primary tumors or bulky lymph nodes eligible for spatially fractionated radiotherapy (SFRT) are randomized 1:1 to receive either Lattice RT or a central boost (CEBO) to the large tumor. SFRT is followed by a 4-week interval and subsequent consolidation radiotherapy (25 × 2.4 Gy) to all residual disease. Up to 16 additional patients with low volume disease will be treated with SBRT to the primary tumor and immediate fractionated mediastinal RT to involved lymph nodes (25 × 2.4 Gy). The best SFRT approach is selected for phase II. Phase II randomizes 100 patients 1:1 to individualized treatment (experimental arm) or SOC (control arm) stratified for T stage (T1-2 vs. T3-4), and PD-L1 tumor proportion score (TPS < 1%, 1-49%, ≥ 50%). The experimental arm reflects trial phase I and comprises induction SFRT followed by consolidation RT or SBRT plus mediastinal RT. The control arm consists of conventionally fractionated RT to the primary tumor and involved nodes (30-35 × 2 Gy). All patients will be followed-up for at least 3 years with clinical examinations thoracic imaging.

Objectives and Endpoints

The primary objective of phase I is to gain first insights into efficacy, safety and feasibility of induction SFRT. Thus, the primary endpoint is tumor volume reduction. The primary objective of phase II is to evaluate noninferiority of progression-free survival (PFS) as primary endpoint between individualized treatment and SOC. Secondary endpoints include overall survival (OS), local and distant tumor control, toxicity (CTCAE version 5.0), and patient-reported outcomes.

Statistical Methods

In phase I, the best SFRT approach will be chosen descriptively based on a go/no-go decision. Primarily, the mean log-transformed tumor volume FC should be < 0.9, ie, the approach should reach a predefined efficacy threshold above 10% tumor shrinkage. Secondly, an independent data safety monitoring board (DSMB) must confirm the safety based on continuous monitoring of adverse events (CTCAE). If Lattice and CEBO seem equivalent, then CEBO will be chosen because of clinical feasibility. In phase II, PFS will be compared between individualized treatment and SOC using cox proportional hazards models that adjust for center (random effect), T stage, and PD-L1 TPS. Hazard ratios with 95% CI are reported. Subgroup analyses will be specified in the statistical analysis plan. Secondary endpoints will be analyzed using appropriate regression models adjusting for the same variables.

No formal sample size calculation was performed, as the main purpose of this phase I/II study is to gain first insights into efficacy of SFRT. Instead, the proposed cohort sizes were estimated to yield adequate 95% CI for the go/no-go decision in phase I and the exploratory comparison in phase II. With a total sample size of 100 patients, the expected 95% CI for the HR of the PFS ranges from 0.61 to 1.63, assuming an annual recruitment rate of 30-35 patients and a 2-year PFS of 30%-40% in both groups (assumed HR = 1).

Radiation Treatment

SFRT delivers inhomogeneous dose distributions, applying focal high-dose regions within large tumors while maintaining lower peripheral doses. Phase I compares two different concepts. Lattice targets 1-2 cm spheres, so called vertices (Figure 2A), whereas CEBO targets the largest possible central tumor region (Figure 2B). Both deliver a single high-dose fraction of 18 Gy (maximum dose < 130%) to the target while complying with strict dose constraints outside. In case that dose constraint cannot be met, prescription dose may be reduced in 3-Gy-decrements to 12 Gy. SFRT is followed by a 4-week interval to allow tumor shrinkage and potential immune stimulation. Subsequent consolidation RT will focus on residual disease and apply moderately hypofractionated doses (25 × 2.4 Gy). If patients present with small volume disease, the primary will be treated with SBRT (eg, 3 × 15 Gy or 5 × 10 Gy) followed by immediate moderately hypofractionated RT to mediastinal lymph nodes (25 × 2.4 Gy). MRI/PET-based planning is mandatory to precisely identify tumor disease and involved lymph nodes. Modern IMRT, daily IGRT and offline or online ART are mandatory to comply with contemporary organ dose constraints.

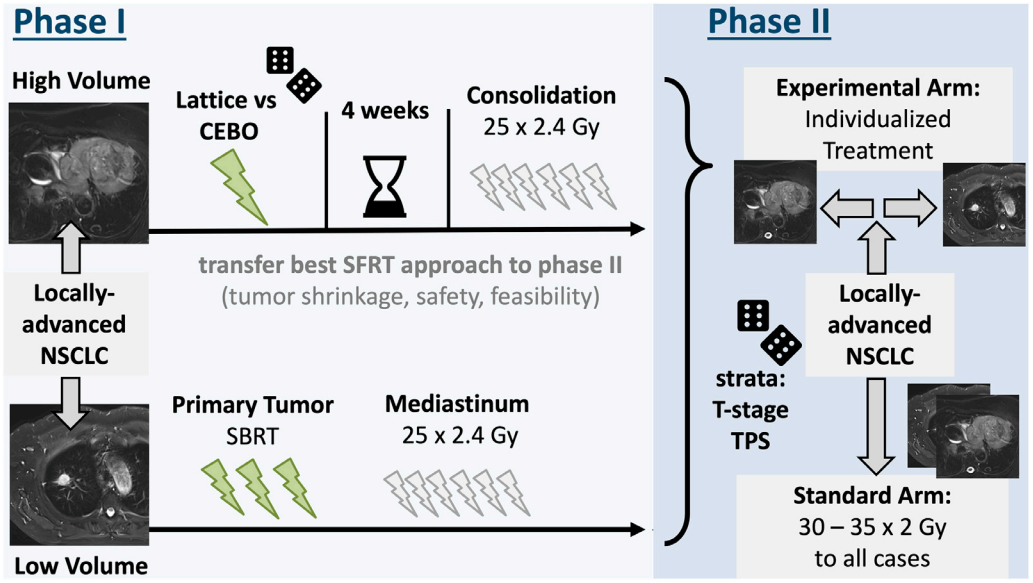


Figure 1. SPARROW trial design. Dices represent randomization steps (1:1). NSCLC = non–small-cell lung cancer; CEBO = central tumor boost; SBRT = stereotactic body radiotherapy; Gy = gray; TPS = Tumor proportion score, reflecting tumor programmed death-ligand 1 (PD-L1) expression.

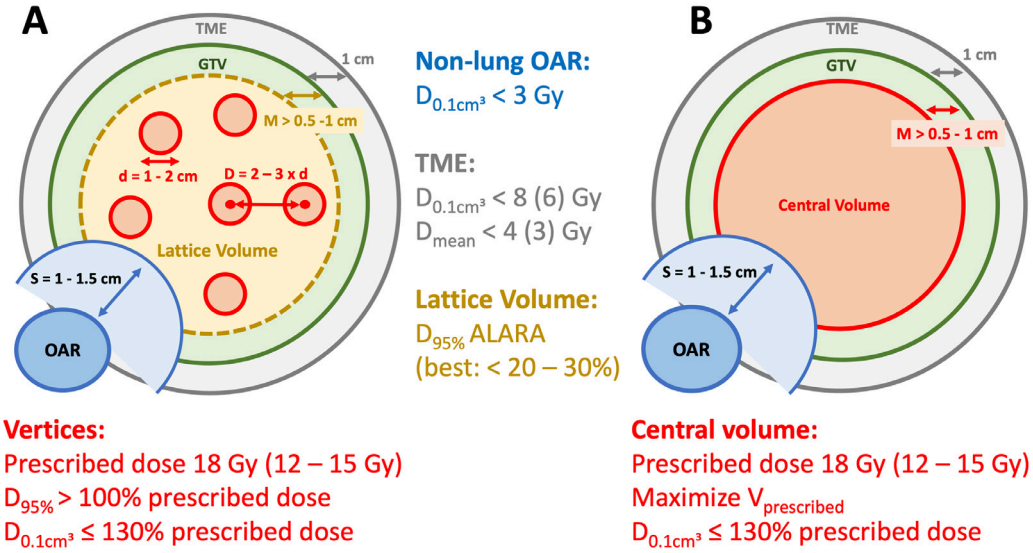


Figure 2. Geometries of different spatially fractionated radiotherapy approaches. (A) Lattice. (B) Central boost to the tumor (CEBO).

Translational Program

SPARROW incorporates longitudinal peripheral immune-phenotyping (PBMC subsets, cytokines), circulating tumor DNA (ctDNA) assessments, and multiparametric MRI. These data are correlated with clinical outcomes to substantiate the hypothesized immunogenic effects and to refine imaging-based definition of tumor subvolumes in SFRT.

Discussion

The SPARROW trial addresses a fundamental limitation in the management of LA-NSCLC: the reliance on “one-size-fits-all”, homogeneous RT concepts in a biologically and anatomically heterogeneous disease. Previous attempts at uniform radiation dose escalation have failed to improve clinical outcomes, which underscores the narrow therapeutic window of conventional RT.[4,8] SPARROW represents the first prospective clinical trial that approaches inoperable LA-NSCLC with different RT concepts tailored to the anatomical disease spread. By integrating induction SFRT or SBRT into a personalized treatment framework together with modern IMRT and ART, the trial seeks to intensify intratumoral dose and stimulate immune responses while maintaining OAR protection.

Previous and ongoing trials in selected cases with low volume disease suggest improved locoregional control when combining SBRT with fractionated RT.[2,15] However, SBRT is challenging in large tumors close to sensitive OAR. Early clinical studies have found encouraging results when treating bulky tumors with SFRT,[10,11] but clinical outcome data remains limited. Moreover, different SFRT approaches have not yet been standardized and sufficiently characterized clinically. Hence, the SPARROW trial will investigate and compare two frequently applied SFRT techniques, Lattice and central tumor boosts (here termed CEBO), in a standardized, prospective setting. Advanced MRI and imaging biomarkers will be explored to better define biologically distinct subregions within bulky tumors and refine target selection for spatial dose escalation.[13] Importantly, SPARROW is among the first prospective trials to

investigate the theoretically proposed immunogenic effects of SFRT in-vivo.[14] Longitudinal immune phenotyping of PBMC and ctDNA analyses may clarify whether SFRT induces response signatures distinct from conventional fractionation and potentially more comparable to SBRT. Thus, patients who receive SBRT and / or fractionated RT may serve as comparison. In this context, we chose a moderately hypofractionated approach to consolidative and/or mediastinal RT to minimize interference with potential immune stimulation.

Limitations of this trial include the moderate sample size, with both trial phases aiming for descriptive rather than confirmatory results. Moreover, systemic treatment is only partly standardized so that consecutive heterogeneity may result.

Conclusions

The SPARROW trial combines novel RT techniques with modern adaptive techniques to improve outcomes in patients with locally advanced NSCLC. In specific, SPARROW will characterize the clinical outcomes and potentially distinct antitumor immune responses after spatially fractionated RT, which might redefine RT paradigms beyond NSCLC.

Ethical Approval

The SPARROW trial was approved by the local ethics board of the Medical Faculty at Heidelberg University (coordinating trial center, IRB number: S-325/2025) and is currently evaluated by the local ethic boards at the trial centers in Düsseldorf, Ludwigshafen and Stuttgart.

Disclosure

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CRediT authorship contribution statement

Sebastian Regnery: Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Conceptualization. **Markus Ehle:** Writing – review & editing, Investigation. **David Neugebauer:** Writing – review & editing, Methodology, Conceptualization. **Lukas Gerke:** Writing – review & editing, Investigation. **Rasmus Schindehütte:** Writing – review & editing, Investigation. **Lukas Bauer:** Writing – review & editing, Investigation. **Stephan Mende:** Writing – review & editing, Investigation. **Marietta Kirchner:** Writing – review & editing, Methodology, Formal analysis. **Alexandra Balzer:** Writing – review & editing, Methodology, Formal analysis. **Aoife Gahlawat:** Writing – review & editing, Investigation. **Amir Abdollahi:** Writing – review & editing, Investigation. **Daniel Kazdal:** Writing – review & editing, Investigation. **Albrecht Stenzinger:** Writing – review & editing, Investigation. **Juliane Hörner-Rieber:** Writing – review & editing, Investigation. **Matthias Uhl:** Writing – review & editing, Investigation. **Kynann Aninditha:** Writing – review & editing, Investigation. **Marc Münter:** Writing – review & editing, Investigation. **Thomas Welzel:** Writing – review & editing, Investigation. **Jürgen Debus:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Fabian Weykamp:** Writing – review & editing, Supervision, Investigation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2026.07.008.

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