STILE

Stereotactic body radiotherapy with immunotherapy in early stage non-small cell lung cancer: tolerability and lung effects

Statistical Analysis Plan

Version 2.0, 30/07/2025

Protocol Title and CCR number:	Stereotactic body radiotherapy with immunotherapy in early stage non-small cell lung cancer: tolerability and lung effects (STILE) CCR4644
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Contents

List of Abbreviations

Abbreviation or special term	Explanation
CI	confidence interval
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DFS	Disease Free Survival
DLCO	diffusing capacity of lung for carbon monoxide
DR	Distant relapse
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FDG-PET	fluorodeoxyglucose (FDG)-positron emission tomography (PET)
FEV1	forced expiratory volume in one second
Gy	Gray
HRQoL	Health related quality of life
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
irAE	immune-related adverse events
IV	Intravenous therapy
LR	Local relapse
LRR	Loco-regional relapse
MDT	multidisciplinary team
NSCLC	Non-small-cell lung carcinoma
OS	Overall survival
PD-L1	Programmed death-ligand 1
PS2	Performance Status – grade 2
QLQ	Quality of Life Questionnaire
QOL	quality of life
RR	Regional relapse
SAP	Statistical Analysis Plan
SBRT	Stereotactic body radiation therapy
SD	standard deviation
TMG	Trial Management Group

Amendment history

Date	Version	Timing in relation to analysis	Brief description of change	Justification for change
29.11.2019	1.0	First draft prior to final analysis	N/A	N/A
30.07.2025	**2.0**	**Second draft prior to final analysis (post recruitment closure)**	• **Updates to study summary based on current protocol (v6.0)** • **Power calculation for n=29** • **Timing of analysis** • **Clarification of exploratory endpoints and methods.**	**Changes to the study since the original SAP drafted 5 years ago. Exploratory endpoints and methods were never originally specified.**

1. Trial Summary

Currently, no adjuvant systemic treatment post SBRT is offered to patients regardless of size or stage of the tumour in NSCLC. Immunotherapy, with its more favourable toxicity profile may provide a more attractive systemic adjuvant treatment in this population. Furthermore, the potential for radiotherapy to act as an in situ vaccine to prime the adaptive immune system makes immunotherapy an attractive option to target micrometastatic disease believed to be responsible for tumour relapse. While adjuvant immunotherapy trials post-surgical resection are on-going, it is necessary to assess the safety and tolerability of immunotherapy in the post SBRT patient population.

This study is primarily concerned with the acute toxicity of combining SBRT with nivolumab but safety data throughout the study treatment and until 100 days after the final nivolumab treatment will be collected and reported. The rationale for combining radiotherapy with immunotherapy is based on the concept that radiotherapy can be immune priming.

. Pneumonitis with nivolumab may be of particular concern for patients with poor lung reserve. In this study, frequent assessment of spirometry values may help to predict patients that are developing subclinical pneumonitis and prompt for early intervention.

The study will include subjects with histologically verified NSCLC deemed by a local MDT to have anatomical stage T1-3 [≤6cm] N0 M0 by means of CT and FDG-PET, amenable to radical treatment with SBRT and inoperable due to medical co-morbidity, being technically unresectable or patient declining surgery after offer of surgical assessment.

Patients will receive SBRT as per the study protocol; a total of 54 Gy if delivered in 3 fractions (2 weeks), 55 Gy if delivered in 5 fractions (2 weeks) or 60Gy if delivered in 8 fractions (3 weeks). Subjects will receive nivolumab as per the treatment schedule unless any withdrawal criteria are met. The first nivolumab infusion will be given after the final fraction of SBRT, within 24 hours and generally on the same day.

All subjects will receive nivolumab at 240 mg q2w for 13 cycles followed by 480mg q4w for 7 cycles as in IV infusion to complete 20 doses (a total of 1 year treatment if no delays are encountered).Dose interruptions are allowed up to a maximum of 12 weeks per dose for clinical reasons that do not meet withdrawal criteria. No dose reductions of nivolumab are allowed.

2. Study objectives

Research hypothesis

Nivolumab following SBRT for stage I-II NSCLC (T3 (≤5cm) N0M0 is a safe treatment and rates of pneumonitis at grade 3 or higher (CTCAE v.4) within 6 months of the final fraction of SBRT occur at a rate that does not exceed 20%.

Study objectives

Primary Objective:

To assess the lung toxicity of nivolumab after stereotactic body radiotherapy (SBRT) for early stage NSCLC (T1-3 (≤6cm) N0M0).

Secondary Objectives:

1. To assess the overall safety of nivolumab after SBRT
2. To assess the tolerability of nivolumab after SBRT
3. To assess local, local-regional and distant disease relapse rates at 3, 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if available) post SBRT
4. To assess the overall survival rates at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if available) post SBRT
5. To assess the disease free survival (DFS) rates at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if available) post SBRT
6. To measure health related quality of life (HRQoL)

Exploratory Objectives:

1. To describe the relationship between lung function and the tolerability of nivolumab after SBRT
2. To assess relapse rates and survival rates in relation to tumour PD-L1 status
3. To assess relapse rates and survival rates according to squamous versus non-squamous histology
4. To assess tumour biology and immune function changes with treatment

3. Study Methods

3.1 Study design

This is a single arm, multi-centre, phase Ib/II open label study of nivolumab administered on completion of SBRT to patients with early stage NSCLC.

3.2 Randomisation

This is not a randomised study.

3.3 Sample Size

The study will recruit 31 patients. Assuming that the observed rate (grade ≥ 3) of pneumonitis is around 10%, with 31 patients we would be able to estimate this with a one-sided 95% confidence interval (CI) of 9% width. The table below demonstrates the widths of the 95% CIs given different rates of pneumonitis. Any patient that has enrolled on the study but does not receive at least 1 dose of nivolumab will be replaced. Recruitment may continue until 31 patients have received at least one dose of nivolumab unless any study discontinuation criteria are met.

Table 1a: Upper bound of a one-sided 95% Confidence interval according to observed proportion assuming 31 patients

Observed proportion	Upper Bound of 95% C.I.
0.070	0.145
0.100	0.189
0.130	0.229
0.150	0.255

The upper limit of the CI should ideally exclude a rate of 20% for this treatment to be deemed acceptable however it is acknowledged that with a total of 31 patients if the observed rate of pneumonitis is higher than 10% then we would consider that the drug might exceed the toxic response rate of 20%.

Recruitment closed at n=29 evaluable patients (at least one dose of Nivolumab following final fraction of SBRT), which was agreed as sufficient based on the below calculation:

Table 1b: Upper bound of a one-sided 95% Confidence interval according to observed proportion assuming 29 patients

Observed proportion	Upper Bound of 95% C.I.
0.070	0.148
0.100	0.192
0.130	0.233
0.150	0.259

3.4 Framework

The study aims to establish whether Nivolumab following SBRT is a safe treatment and rates of pneumonitis at grade 3 or higher within 6 months of the final fraction of SBRT occur at a rate that does not exceed 20%. A pneumonitis rate that exceeds 20% will be deemed unacceptable and will lead to a rejection of the null hypothesis.

3.5 Statistical Interim Analysis and stopping guidance

Due to the low number of patients in this study no interim analysis is planned however accumulating data will be monitored regularly by an Independent Data Monitoring Committee (IDMC). No formal decision rules for early stopping will be used. Safety data will be reviewed. Details are outlined in a separate DMC charter. A Trial Management Group (TMG) will also be set up.

Although no formal early stopping is planned, stopping due, to efficacy or to futility, or due to safety or external evidence will be considered. Stopping will be based on the recommendations from the IDMC and endorsed by the TMG.

The first IDMC meeting was held in Oct 2018 after the first 5 enrolled patients with ECOG PS 0-1, who were evaluable for IDMC purposes (i.e. those who had reached 3 months follow up from their 1st dose of nivolumab) were available. Further patients of PS <2 could enrol while awaiting the outcome of the IDMC meeting. The IDMC was satisfied with the safety data from the initial 5 patients, and recommended escalation to include recruitment of patients with ECOG performance status of 2.

The study protocol specified that the IDMC will perform the next safety review when the first 5 patients enrolled with ECOG PS2 have reached 3 months follow up after their 1st dose of nivolumab or have withdrawn consent to follow-up. Patients that have enrolled but did not receive IMP will be replaced. Further patients with ECOG PS2 will not be able to enrol unless recommendation is given by the IDMC. In the event that 5 PS2 patients have not enrolled by the point that the 15th patient, that has received a minimum of 1 dose of IMP has reached 3 months follow up, then there will be a further mandated IDMC meeting to assess safety data from the study.

The IDMC performed a further mandated safety review in Dec 2021 when 20 eligible patients were recruited to the study, but only 4 patients were ECOG PS2 (of which 3 have received Nivolumab treatment after SBRT). No safety conerns were reported and study recruitment could continue. Members agreed that the final safety review committee meeting would take place after completion of recritment as they had already reviewed 4 out of 5 central disease patients (the next safety review milestone). This has been scheduled for June 2024.

3.6 Timing of Final Analysis

Final analysis will take place once all patients have completed treatment (due June 2025). Primary, secondary and exploratory endpoints will be evaluated at this point with the data that is available.

3.7 Timing of outcome assessment

The schedule of study procedures is given in Protocol along with the expected visit dates and visit windows. The start time for each calculation is the participants' registration date for the assessments.

4. Statistical Principles

4.1 Confidence Intervals and P values

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level. Primary endpoint will be presented as a one-sided 95% CI. All other confidence intervals presented will be 95% and two-sided.

4.2 Adherence and protocol deviations

Adherence to the protocol will be defined as receiving at least one dose of nivolumab treatment after the final fraction of SBRT.
Any protocol deviations and violations will be reported as recorded on the relevant CRF.

4.3 Analysis populations

	At least one dose of Nivolumab following final fraction of SBRT (evaluable)	At least one dose of Nivolumab and one fraction of SBRT	At least one fraction of SBRT	No treatment
Primary	X			
Safety		X		
Tolerability		X		
Relapse		X (sensitivity)	X	
Survival		X (sensitivity)	X	
QOL		X (sensitivity)	X	

All patients who received at least one dose of nivolumab treatment after the final fraction of SBRT will be included for analysis.

All eligible patients who received at least one dose of nivolumab treatment after the final fraction of SBRT will be included for the primary analysis.

All eligible patients who received at least one dose of nivolumab treatment and at least one fraction of SBRT will be included for the secondary endpoints analysis of safety and tolerability of nivolumab after SBRT, and for toxicity assessment of exploratory endpoints.

All eligible patients who received at least one fraction of SBRT will be included for all other secondary endpoints and exploratory endpoints related to survival, relapse rates and HRQoL.

A detailed Statistical Analysis Plan (SAP) will be drafted and agreed prior to any analysis being undertaken. Analyses relating to the primary endpoint (pneumonitis events) and other toxicity will include patients receiving at least 1 dose of nivolumab. Survival endpoints and relapse rates will include all patients regardless of their drug exposure. A sensitivity analysis will be conducted however for these endpoints for the subset of patients that have received at least 1 dose of nivolumab.

5. Trial Population

5.1 Screening Data

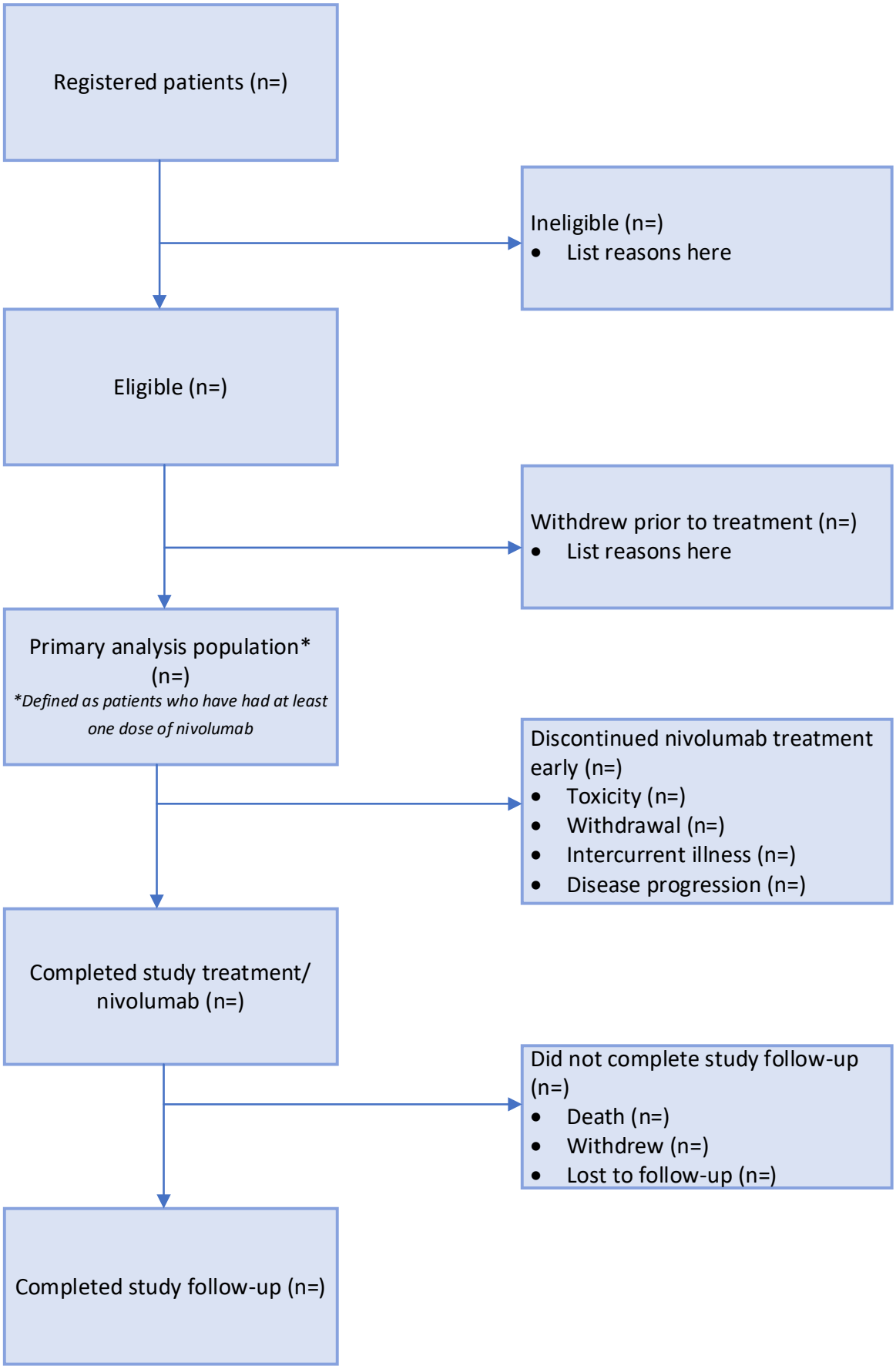
No screening data has been collected for this study.

5.2 Eligibility

The number of ineligible patients incorrectly registered, if any, will be reported, with reasons for ineligibility (criteria they failed).

5.3 Recruitment

A CONSORT flow diagram (see template below) will be used to summarise the number of people: registered, eligible/ ineligible, received treatment, discontinued treatment, withdrawal/lost to follow-up will be used to report patients' participation on the study.


Registered patients (n=)
Ineligible (n=)
• List reasons here
Eligible (n=)
Withdrew prior to treatment (n=)
• List reasons here
Primary analysis population* (n=)
*Defined as patients who have had at least one dose of nivolumab
Discontinued nivolumab treatment early (n=)
• Toxicity (n=)
• Withdrawal (n=)
• Intercurrent illness (n=)
• Disease progression (n=)
Completed study treatment/ nivolumab (n=)
Did not complete study follow-up (n=)
• Death (n=)
• Withdrew (n=)
• Lost to follow-up (n=)
Completed study follow-up (n=)

5.4 Withdrawal/ Follow up – level of withdrawal

The level of consent withdrawal will be tabulated. The timing of withdrawals and lost to follow up will be presented in the CONSORT as well in a table, with numbers and reasons for withdrawal and/or exclusion from analysis given at each stage (SBRT start/ end, nivolumab start, X months after nivolumab start etc.). The numbers (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial will be summarised.

5.5 Baseline patient characteristics

Baseline characteristics will be summarised descriptively for all enrolled patients. Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, SD and range if data are normal and median, IQR and range if data are skewed. Minimum and maximum values will also be presented for continuous data. Tests of statistical significance will not be undertaken for baseline characteristics.

6. Analysis

6.1 Outcome definitions

Primary Endpoint is rate of grade ≥ 3 pneumonitis with nivolumab after stereotactic body radiotherapy (SBRT) within 6 months of the final fraction of SBRT. For the purposes of this study 6 months is defined as 26 weeks. A rate that exceeds 20% will be deemed unacceptable and will lead to a rejection of the null hypothesis.

Secondary Endpoints

- Frequency of treatment related adverse events of all grades and grade ≥ 3 as per CTCAE version 4. Rates of toxicity will be summarised as worse toxicity grade during treatment.
- The proportion of patients receiving at least 1, 2, 3, 4, 5 and 6 doses within 16 weeks of commencing nivolumab after SBRT
- Local, loco-regional and distant rates of relapse at 3, 6, 12 and 24 months*. Local relapse (LR) will be defined as relapse within the planned treatment volume and involved lobe. Regional relapse (RR) will be defined as relapse within the regional lymph node stations. Loco-regional relapse (LRR) will be defined as any recurrence that is either LR, regional relapse or both local and regional. Distant relapse (DR) will be defined as any recurrence outside of LRR.
- Overall survival rate (OS) of the 31 patients at 6, 12 and 24 months*. OS will be measured from the date of first radiotherapy fraction to date of death from any cause. Patients without an event will be censored at date of last follow up.

- Disease Free Survival (DFS) rate of the 31 patients at 6, 12 and 24 months*. DFS will be measured from the date of first radiotherapy fraction to date of relapse (radiological or clinical evidence) or death from any cause. Patients without an event (neither relapsed nor died in that interval) will be censored at last follow up date.
- Estimation of the health-related quality of life (HRQoL) score at each time point of analysis (screening, then at 3, 6, 9, 12, 18, 24 months post-SBRT). QOL questionnaires will be scored according to the EORTC Quality of Life Questionnaire (QLQ-C30) version 3 and lung module (QLQ-LC13) scoring manual. These will be measured as the mean change from baseline (pre-treatment) to each assessment time point in the functional scales (physical, role, emotional, cognitive, social) and in the global health and shortness of breath sub-scales.

*In addition to reporting up to two year survival rates, we will also report survival rates for any mature data available at this time, numbers permitting, which for some patients may be up to five years.

Exploratory Endpoints

- Lung function at baseline will be quantified using the FEV1 (forced expiratory volume in 1 second) and DLCO (diffusing/transfer factor of the lung for carbon monoxide) which will be analysed against the tolerability of nivolumab after SBRT, measured by rates of pneumonitis, to establish any relationship. Lung function measured at other study timepoints may be evaluated as part of future analyses.
- LRR, DR, OS and DFS will be estimated by tumour PD-L1 status (expressers (≥1%) versus non-expressers (<1%))
- LRR, DR, OS and DFS will be estimated by squamous versus non-squamous histology

Exploratory objective #4 as per section 2 (tumour biology and immune function) will not be evaluated as part of the final analysis and are therefore not covered in this Statistical Analysis Plan.

The following endpoint has been added prior to analysis but after protocol-development:

- LRR, DR, OS and DFS will be estimated by the baseline neutrophils/lymphocytes (109/L) ratio, which will be dichotomised using the median as a cut-off.

6.2 Analysis Methods

Primary analysis

Primary outcome of rate of grade ≥ 3 pneumonitis events observed within the 6 month period from the final fraction of radiotherapy will be calculated as percentage along with a one-sided 95% CI using the exact method.

Secondary analyses

The overall safety and tolerability of treatment will be assessed (for the entire duration of the treatment) by grading and recording of toxicities. All toxicities (including pneumonitis events) will be graded using CTCAE v4.0 and the proportion of grades 1-4 will be tabulated, both by number of events and patients (using worst grade).

Toxicities will also be presented by CTCAE SOC and Term. Other safety data will include reported adverse events, abnormal laboratory, spirometry values and irAE.

The proportion of patients receiving at least 1, 2, 3, 4, 5 and 6 doses within 16 weeks of commencing adjuvant nivolumab after SBRT will be calculated. The proportions will be presented along with 95% exact CIs. The median number of doses received will be presented along with its interquartile range (IQR).

All rates of relapse (local, loco-regional and distant rates), along with disease-free and overall survival, will be estimated using Kaplan-Meier methods. Rates at 6, 12 and 24 months (+ any mature data available at 36, 48 and 60 months) will be calculated along with their 95% exact CIs.

All questionnaires for (HRQoL) will be scored and a total will be produced. Analyses will use all available results without imputation of missing outcomes (either per item or per scale) and will follow any relevant guidelines. Summary statistics (median score and interquartile range or frequency and percent) for each questionnaire will be recorded overall and according to subscale and no hypothesis testing will take place.

Exploratory analyses

Rates of pneumonitis within 6 months of final fraction of SBRT (using worst grade as per CTCAE v4.0) will be tabulated against lung function at baseline using the percentage of predicted FEV1 bands, as per the GOLD criteria (≥80% ; ≥50 - <80% ; ≥30 - <50% ; <30%), and DCLO bands as follows: (≥80% ; ≥60 - <80% ; ≥40 - <60% ; <40%). A chi-squared test (Fishers exact test in the event of cell counts <5) will be used to statistically establish any relationship.

If numbers are sufficient, relapse and survival rates (LRR, DR, DFS and OS) will be described according to PD-L1 expression for expressers (≥1%) and non-expressers (<1%) (BMS assay), by squamous and non-squamous histology, and by neutrophils/lymphocytes ratio at baseline (split into two groups by the median cut-off). Any survival differences between groups will be assessed using median survival with 95% confidence interval and a log-rank test.

7. Statistical Packages

The analysis will be carried out using Stata version 18 or higher.

8. References

Please look at list of references in the protocol.

9. Data Management & Central Statistical Monitoring Plan

The SAP should be drafted and executed in line with the STILE Central Statistical Monitoring and Data Management Plans.

STILE: Stereotactic body radiotherapy with immunotherapy in early stage non-small cell lung cancer: tolerability and lung effects

Trial Statistician

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10/09/2025

Laura Satchwell — Date

Peer Reviewer

11/09/2025

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STILE: Stereotactic body radiotherapy with immunotherapy in early stage non-small cell lung cancer: tolerability and lung effects

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16/09/25

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