The ROYAL MARSDEN

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Chief Investigator:	Dr Merina Ahmed

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

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Abbreviations

Abbreviation	Explanation
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
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
FEV1	forced expiratory volume in one second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Gy	Gray
HRQoL	Health related quality of life
irAE	immune-related adverse events
LR	Local relapse
LRR	Loco-regional relapse
NSCLC	Non-small-cell lung carcinoma
OS	Overall survival
PD-L1	Programmed death-ligand 1
QLQ	Quality of Life Questionnaire
QOL	quality of life
RR	Regional relapse
SAP	Statistical Analysis Plan
SBRT	Stereotactic body radiation therapy
SD	standard deviation

Version history

Version	Date	Comments
1.0	21.01.2026	First version of the final statistical report.
1.1	25.02.2026 (Added by LS)	Table 2a added (Radiotherapy Planning) to section 3.4 as per CI request.

1 Background

1.1 Study Synopsis

Study title	Stereotactic body radiotherapy (SBRT) with immunotherapy in early stage non-small cell lung cancer: tolerability and lung effects
Short study title	STILE
CCR Number	4644
Clinical Phase	1b/2
Target Disease	Non-small cell lung cancer (NSCLC)
Study Site(s)	Royal Marsden
Study Primary Objective	To assess the lung toxicity of nivolumab after SBRT for early stage NSCLC
Primary Endpoint	Rate of grade ≥ 3 pneumonitis with nivolumab after stereotactic body radiotherapy (SBRT) within 6 months of the final fraction of SBRT.
Study design	Single arm, multicentre, phase 1b/2 open label study
Treatment dose	240 mg q2w over 30 minutes for 13 cycles followed by 480mg q4w over 60 minutes for 7 cycles, until 20 cycles in total to complete
Route of Administration	Nivolumab will be administered intravenously
Number of patients	31

1.2 Study Objectives

1.2.1 Primary Objective

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

1.2.2 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)

1.2.3 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

1.3 Study Endpoints

1.3.1 Primary Endpoint

The rate of CTCAE version 4 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.

1.3.2 Secondary Endpoints

1. 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.
2. The proportion of patients receiving at least 1, 2, 3, 4, 5 and 6 doses within 16 weeks of commencing nivolumab after SBRT.
3. 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.

4. 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.
5. 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.
6. 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.

1.3.3 Exploratory Endpoints

1. 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.
2. LRR, DR, OS and DFS will be estimated by tumour PD-L1 status (expressers (≥1%) versus non-expressers (<1%)).
3. LRR, DR, OS and DFS will be estimated by squamous versus non-squamous histology.

Exploratory objective #4 as per section 1.2.3 (tumour biology and immune function) will not be evaluated as part of the final analysis and are therefore not covered in this report.

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

4. 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.

1.4 Sample Size

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 A: Upper bound of a one-sided 95% Confidence interval according to observed proportion of grade 3+ pneumonitis 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

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 29 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%.

2 Methods

2.1 Statistical Analysis

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). Additionally, relatedness to nivolumab, SBRT and immune checkpoint inhibitors (irAE) will be reported by grade. Toxicities will also be presented by CTCAE SOC and Term.

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, measured from first fraction of radiotherapy. 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.

The EORTC QLQ-C30 and QLQ-LC13 (HRQOL measures) will be scored according to published guidelines [1, 2]. Analyses will use all available results without imputation of missing outcomes (either per item or per scale) and will follow any relevant guidelines on how to handle missing data. Summary statistics (median score and interquartile range or frequency and percent) for each questionnaire will be presented 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.

2.2 Deviations from the SAP

- It was pre-specified that we would perform the survival (overall, disease-free and relapse rates) and QOL secondary analyses in the safety population as an additional sensitivity analysis. As there were so few events of deaths and relapse, and the change in population would only be excluding one additional patient, it was decided this was an unnecessary addition to the analysis.
- Exploratory endpoints #2 and #3 could not be evaluated as sub-group analyses for relapse and survival rates were not possible due to the low number of events.
- Rates of relapse split by local, loco-regional and distant rates was evaluated using raw numbers only. Kaplan Meir methods could not be used due to events of 2 or less within each group.
- Survival rates following 24 months could not be established as the maximum follow-up recorded was 27 months (i.e. mature data for 3/4/5 year rates was not available at time of analysis).

2.3 Data extraction

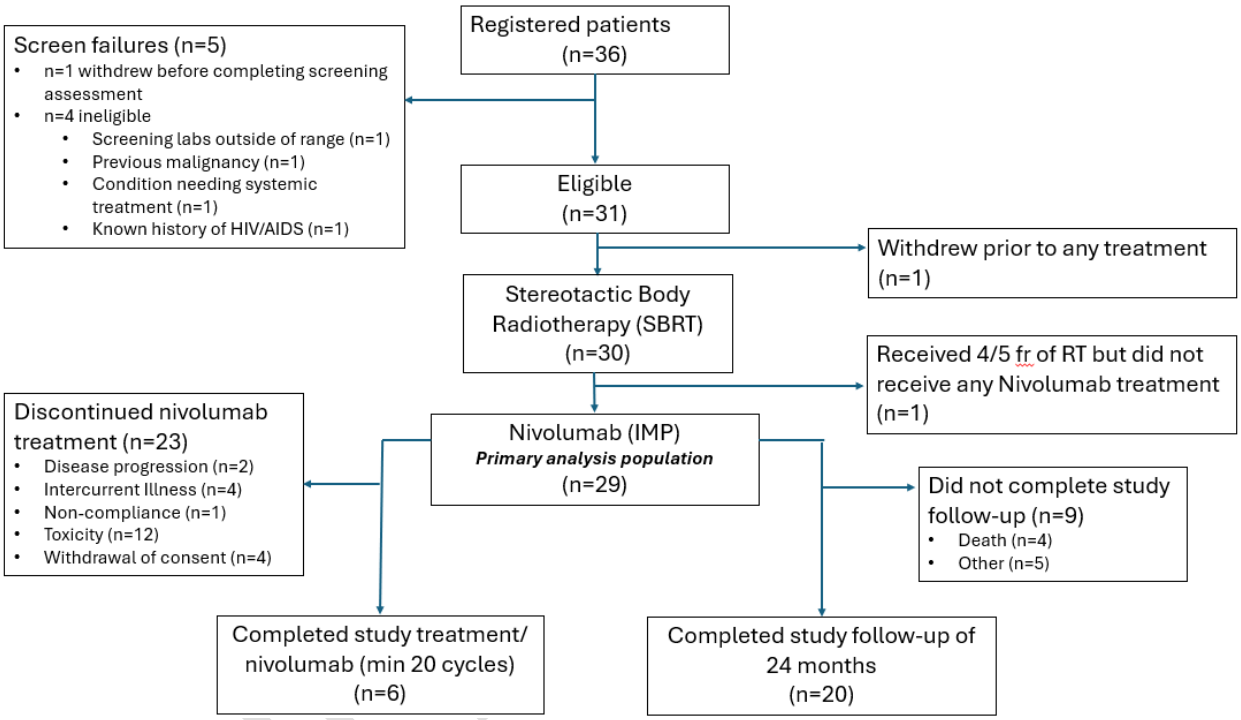
The final snapshot was taken from the MACRO database on 22/10/2025.

3 Results

3.1 Accrual

Thirty-six patients were registered into the study from the Royal Marsden site between February 2018 and January 2024. However, only 31 were eligible and of which 29 started study treatment. The flow of patients through the study is shown in Figure 1.

Figure 1: Flow diagram of patients through the STILE study



3.2 Analysis Population

Evaluable population: The primary analysis population consists of all eligible patients who received at least one dose of Nivolumab following the final fraction of SBRT, which will include **29/31 eligible patients.**

Safety population: 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, which will include **29/31 eligible patients.**

Efficacy population: 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, which will include **30/31 eligible patients.**

3.3 Demographics

Demographics for the 31 eligible patients recruited into the STILE study are summarised in Table 1, which includes their cancer history and diagnosis.

Table 1: Demographics for all registered and eligible patients recruited into the STILE study (n=31 patients)

(N=31)		
	N	**%**
Age at registration (years)		
n	31	
Median	73.0	
IQR	64.0 - 76.0	
Range	53.0 - 87.0	
Gender		
Female	18	58
Male	13	42
Race		
African/Caribbean	2	6
Asian	1	3
Caucasian (White)	28	90
Smoking status		
Current Smoker	4	13
Ex-smoker	25	81
Never Smoker	2	6
ECOG Performance Status		
ECOG 0	7	23
ECOG 1	18	58
ECOG 2	6	19
Type of NSCLC [n=30]		
Adenocarcinoma	24	80
NOS	1	3
Squamous	5	17
T Stage at diagnosis [n=30]		
T1A	5	17
T1B	10	33
T1C	4	13
T2A	8	27
T2B	2	7

(N=31)		
	N	**%**
T3	1	3
N Stage at diagnosis [n=30]		
N0	30	100
M Stage at diagnosis [n=30]		
M0	30	100
Stage at diagnosis [n=30]		
IA	16	53
IB	11	37
IIA	2	7
IIB	1	3
Single or synchronous disease [n=30]		
Single	27	90
Synchronous	3	10
If synchronous, number of lesions [n=3]		
2	3	100
a. Site of disease [n=30]		
LLL	4	13
LUL	8	27
Lingular	1	3
RLL	7	23
RML	1	3
RUL	9	30
b. Site of disease [n=30]		
Central	4	13
Peripheral	26	87
Patient had previously treated NSCLC [n=30]		
No	22	73
Yes	8	27
Number of previously treated primary NSCLC [N=8]		
1	6	75
2	2	25

3.4 Study Treatment

Participants are treated with both SBRT and nivolumab during the study and a summary of treatment taken for those who started the treatment are reported in Tables 2a, 2b and 3.

3.4.1 Radiotherapy

Table 2a: Radiotherapy Planning (n=30 patients)

	N	n (%)
Lesion to be Irradiated, n(%)	30	
Left lower lobe		3 (10)
Left upper lobe		9 (30)
Lingula		1 (3)
Right lower lobe		5 (17)
Right middle lobe		1 (3)
Right upper lobe		11 (37)
	N	**Median (IQR) Range**
Brachial Plexus, D max (0.5 cc)	17	0.6 (0.3 – 4.1) 0 – 27.0
Heart, D max (0.5 cc)	30	12.5 (2.3 – 18.6) 0 -49.6
Trachea, D max (0.5 cc)	30	18.0 (10.9 – 23.2) 1.1 – 44.0
Lung, GTV (volume 20 Gy)	30	4.2 (2.8 – 5.4) 1.5 – 19.3
Chest wall, D max (0.5 cc)	29	57.1 (38.2 – 65.0) 25.1 – 74.5
Great vessels, D max (0.5 cc)	23	15.1 (10.5 – 27.6) 0.8 – 52.5
Oesophagus, D max (0.5 cc)	30	13.5 (9.7 – 18.3) 4.0 – 28.8
Skin, D max (0.5 cc)	30	17.2 (15.3 – 21.8) 8.5 – 39.5
Spinal cord, D max (0.1 cc)	30	13.5 (10.5 – 15.2) 5.3 – 24.1

Table 2b: Summary of SBRT treatment (n=30 patients)

		N (%)
Planned dose given	Yes	29 (97)
Dose given for those who had planned dose [N=29]	50 GY 5Fr	1 (3)
	54GY 3Fr	3 (10)
	55GY 5Fr	20 (69)
	60Gy 8Fr	5 (17)

Type Of SBRT	LINAC	29 (100)
Prescription Isodose	Median (IQR) Range	74 (72 – 79) 25 – 95
Dose given for those who did not have planned dose [N=1]	4 out of 5 fractions given (GY not specified)	

3.4.2 Nivolumab

Table 3: Summary of nivolumab treatment (n=29 patients, n=320 cycles)

		N (%)
N=29 patients		
Number of cycles completed on study	1	3 (10)
	2	2 (7)
	3	1 (3)
	5	1 (3)
	6	1 (3)
	7	1 (3)
	8	3 (10)
	10	1 (3)
	11	1 (3)
	12	2 (7)
	13	3 (10)
	15	2 (7)
	16	2 (7)
	20	5 (17)
	22	1 (3)
	Median (IQR)	12 (6 – 16)
Discontinued treatment early (before 20 cycles)	Yes	23 (79)
Reason for finishing treatment [n=23]	Disease Progression	2 (9)
	Intercurrent Illness	4 (17)
	Non-compliance	1 (4)
	Toxicity	12 (52)
	Withdrawal of consent	4 (17)
N=320 cycles		
Any dose delays?	Yes	61 (19)
Days delayed [N=61]	Median (IQR)	7 (6 – 14)

		N (%)
	Range	1 – 48
Reason for delay	Toxicity Other	10 (16) 51 (84)
Planned dose given	Yes	319 (99)

3.5 Primary endpoint

Using the 29 patients in the evaluable population, there were **no observed grade 3+ pneumonitis events** within 6 months of the final fraction of RT treatment. Therefore, as the observed rate was <10% and the upper limit of the CI excludes a rate of 20%, this treatment is deemed acceptable.

There were 22 pneumonitis events from the 29 evaluable patients in total, 14 were before the 6 month cut off (grades 1-2 only) and 8 were following the 6 month cut off (including two grade 3 events). All pneumonitis events are summarised in Table 4.

Table 4: Summary of all reported pneumonitis events using CTCAE V4.0 for all patients in the evaluable population (n=29 patients)

	<6 months of the final fraction of RT treatment				>6 months of the final fraction of RT treatment				All events			
	Grade 1	**Grade 2**	**Grade 3**	**Total events**	**Grade 1**	**Grade 2**	**Grade 3**	**Total events**	**Grade 1**	**Grade 2**	**Grade 3**	**Total events**
All pneumonitis events	9 (64)	5 (36)	0 (0)	14	5 (63)	1 (12)	2 (25)	8	14 (64)	6 (27)	2 (9)	22
All pneumonitis events for nivolumab-related events	4 (50)	4 (50)	0 (0)	8	5 (63)	1 (12)	2 (25)	8	9 (56)	5 (31)	2 (13)	16
All pneumonitis events for SBRT-related events	7 (64)	4 (36)	0 (0)	11	4 (67)	1 (17)	1 (17)	6	11 (65)	5 (29)	1 (6)	17
All pneumonitis events for immune-related events	3 (43)	4 (57)	0 (0)	7	4 (57)	1 (14)	2 (29)	7	7 (50)	5 (36)	2 (14)	14
Worst grade by patient	**4 (50)**	**4 (50)**	**0 (0)**	**8 pts**	**4 (57)**	**1 (14)**	**2 (29)**	**7 pts**	**5 (42)**	**5 (42)**	**2 (17)**	**12 pts**

3.6 Secondary endpoints

3.6.1 Toxicities

The toxicity endpoints were evaluated using the 29 patients in the safety population. All reported adverse events are summarised in Table 5. Tabulation of grade by SOC and Term on the patient level using worst reported grade is presented in Tables 6 and 7.

Table 5: Summary of all reported adverse events using CTCAE v4.0 for all patients in the safety population (n=29 patients)

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
All toxicity types for all events (n=442)	286 (65)	121 (27)	34 (8)	1 (1)
All toxicity types for nivolumab-related events (n=235)	145 (62)	67 (28)	22 (9)	1 (1)
All toxicity types for SBRT-related events (n=92)	60 (65)	24 (26)	8 (9)	0 (0)
All toxicity types for immune-related events (n=74)	36 (49)	24 (32)	14 (19)	0 (0)

Table 6: Summary of worst grade reported adverse events using CTCAE v4.0 for all patients in the safety population (n=29 patients) by SOC

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
All toxicity types by patient using worst grade (n=29)	1 (3)	11 (38)	16 (55)	1 (3)
By CTCAE SOC				
02-Cardiac disorders	0	0	1	0
05-Endocrine disorders	0	1	1	0
07-Gastrointestinal disorders	0	1	2	0
08-General disorders and administration site conditions	0	1	0	0
11-Infections and infestations	0	1	3	0
12-Injury, poisoning and procedural complications	0	2	0	0
13-Investigations	0	0	1	0
14-Metabolism and nutrition disorders	0	0	3	1
17-Nervous system disorders	0	0	1	0
20-Renal and urinary disorders	0	0	1	0

22-Respiratory, thoracic and mediastinal disorders	0	1	1	0
23-Skin and subcutaneous tissue disorders	1	3	2	0
26-Vascular disorders	0	1	0	0

Table 7: Summary of worst grade reported adverse events using CTCAE v4.0 for all patients in the safety population (n=29 patients) by Term

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
All toxicity types by patient using worst grade (n=29)	1 (3)	11 (38)	16 (55)	1 (3)
By CTCAE Term				
02-Myocardial infarction	0	0	1	0
05-Arenal insufficiency	0	0	1	0
05-Hypothyroidism	0	1	0	0
07-Colitis	0	0	1	0
07-Diarrhea	0	0	1	0
07-Dyspepsia	0	1	0	0
08-Infusion related reaction	0	1	0	0
11-Lung infection	0	1	1	0
11-Skin infection	0	0	1	0
12-Venous injury	0	1	0	0
13- Serum amylase increased	0	0	1	0
14-Hypoglycemia	0	0	1	0
14-Hypokalemia	0	0	2	0
14-Hyponatremia	0	0	0	1
17-Stroke	0	0	1	0
20-Urinary retention	0	0	1	0
22- Cough	0	1	0	0
22- Pneumonitis	0	0	1	0
23-Pruritus	0	2	0	0
23-Rash acneiform	0	0	1	0
23-Rash maculo-papular	0	0	1	0
99-Other	1	3	1	0

3.6.2 Tolerability

The tolerability endpoints were evaluated using the 29 patients in the safety population. The proportion of patients receiving 1,2,3,4,5 and 6 doses within 16 weeks of commencing treatment are reported with a 95% exact confidence interval.

Table 8: Proportion of patients receiving at least 1, 2, 3, 4, 5 and 6 doses within 16 weeks of commencing adjuvant nivolumab after SBRT (n=29 patients)

Number of doses	Proportion	95% CI
1	29/29 = 1.00	0.88 - 1*
2	26/29 = 0.90	0.73 - 0.98
3	24/29 = 0.83	0.64 - 0.94
4	23/29 = 0.79	0.60 - 0.92
5	23/29 = 0.79	0.60 - 0.92
6	22/29 = 0.76	0.56 - 0.90

*One-sided 97.5% CI

The median number of doses received was 12 (IQR 6 - 16) as per Table 3.

3.6.3 Relapse

All rates of relapse (local, loco-regional and distant rates) were evaluated using the 30 patients in the efficacy population and presented as a proportion with a 95% exact binomial confidence interval. Time to event analysis was not performed within these endpoints as the number of events were too low.

Table 9: Proportion of patients experiencing relapse by type (n=30 patients)

Type of relapse	Number of events	Proportion	95% CI	Median time to relapse (months)
Local	1	1/30 = 0.03	0.001 - 0.17	19
Loco-regional	1	1/30 = 0.03	0.001 - 0.17	9
Distant	2	2/30 = 0.07	0.01 - 0.22	8
Any relapse	4	4/30 = 0.13	0.04 - 0.31	11

3.6.4 Overall survival

Overall survival was evaluated using the 30 patients in the efficacy population. There were 6 deaths during the study. Causes are tabulated in Table 10.

Table 10: Summary of deaths during the study (n=30 patients)

Cause of death	Frequency (%)
Pneumonia	1 (17)
Lower respiratory tract infection & Covid-19	1 (17)
Metastatic Lung Cancer	1 (17)
Myocardial Infarction	1 (17)
Sepsis	1 (17)
Unknown	1 (17)
Total	6 (100)

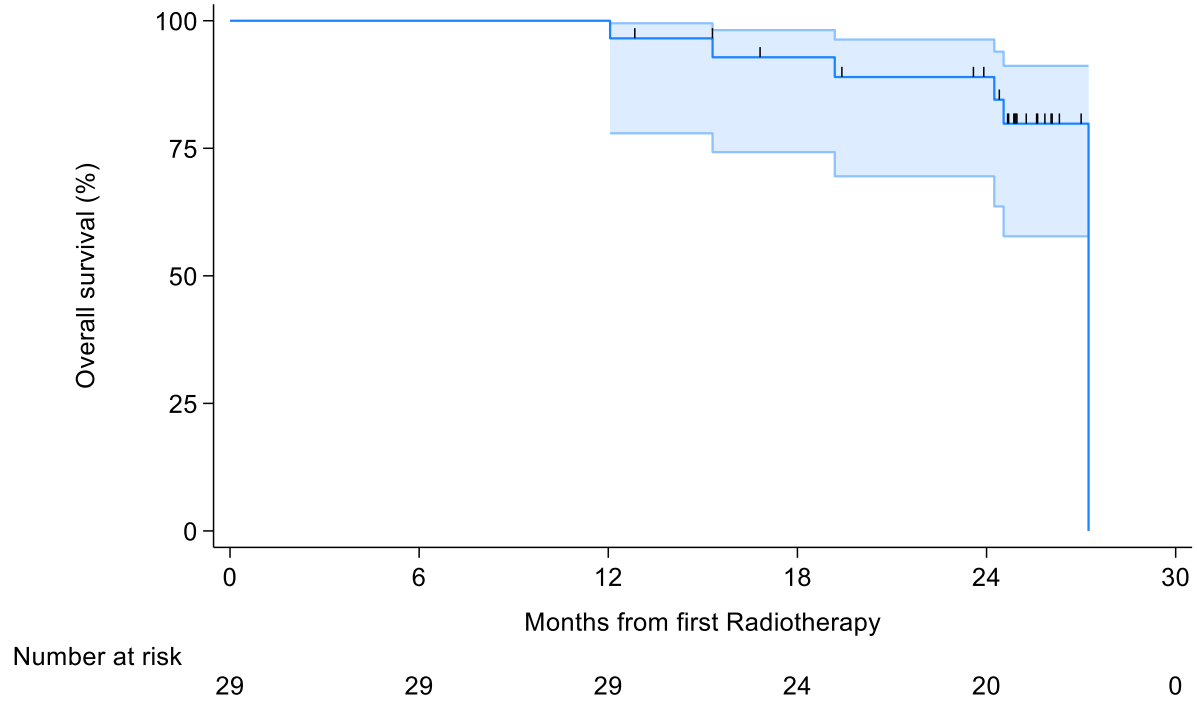
Twenty-nine patients were included in the overall survival analysis, 1 patient out of the 30 eligible for this analysis could not be included as they withdrew during RT treatment and no RT start date was recorded.

Table 11: Overall survival rates at 12 and 24 months (n=29 patients)

Efficacy population	N at risk	N events	1 year OS (95% CI)	2 year OS (95% CI)
All patients	29	6	100% (n/c)	89% (70%-96%)

The Kaplan-Meier analysis is presented in Figure 2. Censoring of participants are marked on the graph (last follow-up). There was no follow-up after 28 months.

Figure 2: Overall survival (with 95% CI)



Median overall survival could not be estimated.

3.6.5 Disease-free survival

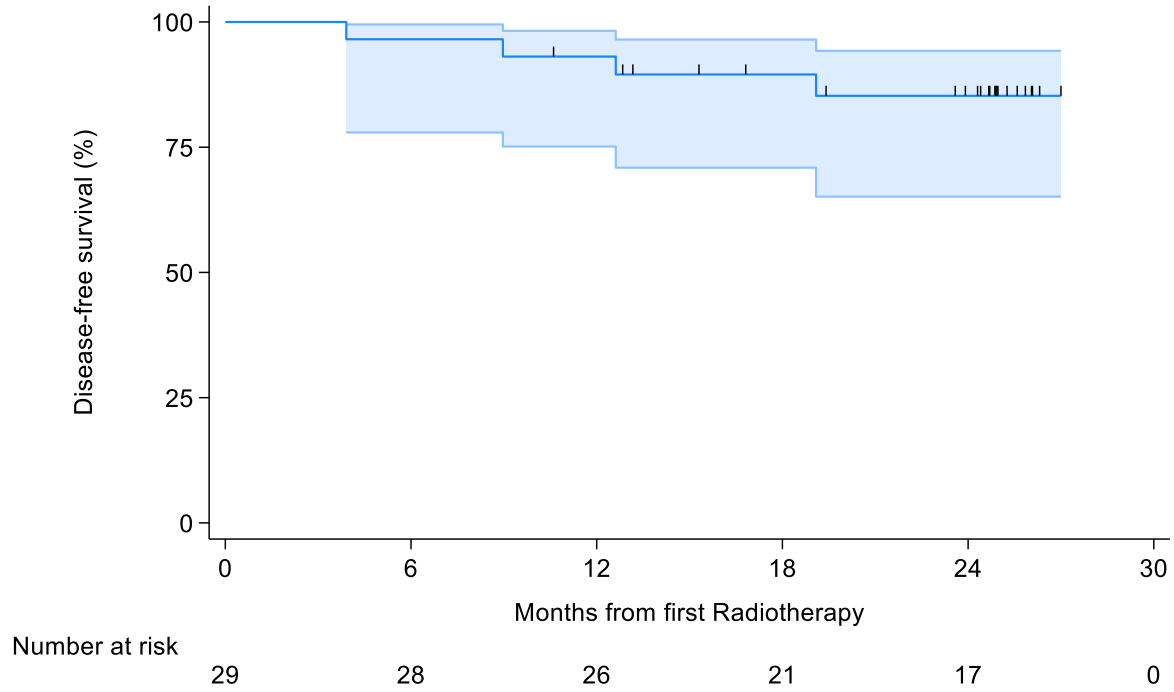
Disease-free survival was evaluated using the 30 patients in the efficacy population. Twenty-nine patients were included in the disease-free survival analysis, 1 patient out of the 30 eligible for this analysis could not be included as they withdrew during RT treatment and no RT start date was recorded.

Table 12: Disease-free survival rates at 6, 12 and 24 months (n=29 patients)

Efficacy population	N at risk	N events	6 month DFS (95% CI)	1 year DFS (95% CI)	2 year DFS (95% CI)
All patients	29	4	97% (78% - 99%)	93% (75% - 98%)	85% (65% - 94%)

The Kaplan-Meier analysis is presented in Figure 3. Censoring of participants are marked on the graph (last follow-up). There was no follow-up after 28 months.

Figure 3: Disease-free survival (with 95% CI)



Median disease-free survival could not be estimated.

3.6.6 Quality of life

Quality of life was evaluated using the 30 patients in the efficacy population. Both the EORTC QLQ-C30 and QLQ-LC13 was collected at repeated timepoints and subscale totals are summarised in Tables 13 and 14, along with graphical representations.

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item (Fatigue - Financial difficulties) represents a high level of symptomatology / problems.

The lung cancer module incorporates one multi-item scale to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis, which follow the same scoring principles, a higher score represents a high level of symptomatology/problems.

EORTC QLQ-C30 version 3

Table 13: Summary of EORTC QLQ-C30 by subscale (n=30 patients)

	Screening		3m PSBRT		6m PSBRT		9m PSBRT		12m PSBRT		15m PSBRT		18m PSBRT		24m PSBRT	
	N	**Med [Range]**	**N**	**Med [Range]**	**N**	**Med [Range]**	**N**	**Med [Range]**	**N**	**Med [Range]**	**N**	**Med [Range]**	**N**	**Med [Range]**	**N**	**Med [Range]**
Global health status	30	67 [33-100]	26	67 [25-100]	26	63 [0-100]	25	67 [0-100]	24	67 [17-100]	15	67 [25-100]	20	58 [17-100]	17	67 [17-100]
Physical functioning	30	80 [53-100]	26	80 [40-100]	27	73 [13-100]	25	67 [13-100]	24	70 [13-100]	15	53 [27-100]	20	80 [7-100]	17	73 [13-100]
Role functioning	30	83 [0-100]	26	83 [33-100]	27	67 [0-100]	25	83 [17-100]	24	67 [0-100]	15	67 [0-100]	20	67 [0-100]	17	50 [0-100]
Emotional functioning	30	92 [33-100]	26	92 [25-100]	26	83 [0-100]	25	83 [42-100]	24	75 [0-100]	15	75 [0-100]	20	75 [17-100]	17	75 [8-100]
Cognitive functioning	30	83 [50-100]	26	92 [33-100]	26	83 [0-100]	25	83 [33-100]	24	83 [17-100]	15	83 [0-100]	20	75 [17-100]	17	67 [17-100]
Social functioning	30	92 [33-100]	26	83 [0-100]	26	75 [33-100]	25	83 [17-100]	24	67 [0-100]	15	83 [0-100]	20	67 [17-100]	17	67 [0-100]
Fatigue	30	22 [0-56]	26	22 [0-78]	27	33 [0-100]	25	22 [0-89]	24	33 [0-100]	15	33 [0-100]	20	33 [0-67]	17	44 [0-78]
Nausea and vomiting	30	0 [0-17]	26	0 [0-33]	27	0 [0-67]	25	0 [0-17]	24	0 [0-50]	15	0 [0-50]	20	0 [0-33]	17	0 [0-33]
Pain	30	0 [0-67]	26	0 [0-83]	27	0 [0-100]	25	17 [0-100]	24	33 [0-100]	15	0 [0-100]	20	17 [0-83]	17	0 [0-100]
Dyspnea	30	33 [0-100]	26	33 [0-33]	27	33 [0-100]	25	33 [0-100]	24	33 [0-100]	15	33 [0-100]	20	33 [0-100]	16	33 [0-100]
Insomnia	30	0 [0-100]	26	0 [0-100]	27	33 [0-100]	24	33 [0-100]	24	33 [0-100]	14	33 [0-100]	20	17 [0-67]	17	33 [0-100]
Appetite Loss	30	0 [0-67]	26	0 [0-67]	27	33 [0-100]	25	0 [0-100]	24	0 [0-100]	15	33 [0-100]	20	0 [0-67]	17	0 [0-67]
Constipation	30	0 [0-67]	26	0 [0-100]	27	0 [0-100]	25	0 [0-33]	24	0 [0-67]	15	0 [0-100]	20	0 [0-100]	17	0 [0-67]
Diarrhea	30	0 [0-33]	26	0 [0-67]	26	0 [0-100]	25	0 [0-67]	24	0 [0-67]	15	0 [0-100]	20	0 [0-67]	17	0 [0-100]
Financial difficulties	30	0 [0-67]	26	0 [0-100]	26	0 [0-100]	25	0 [00-100]	24	0 [0-100]	15	0 [0-100]	20	0 [0-100]	17	0 [0-67]

Figure 4: Longitudinal plot presenting the median (IQR) of the QLQ-C30 Global Health Status subscale over time since screening

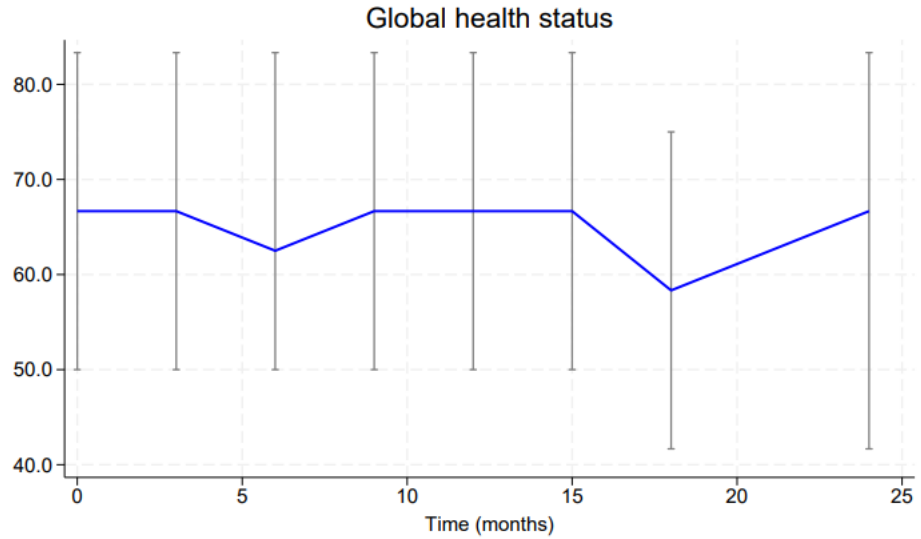


Figure 5: Longitudinal plot presenting the median (IQR) of the QLQ-C30 Functional subscales over time since screening

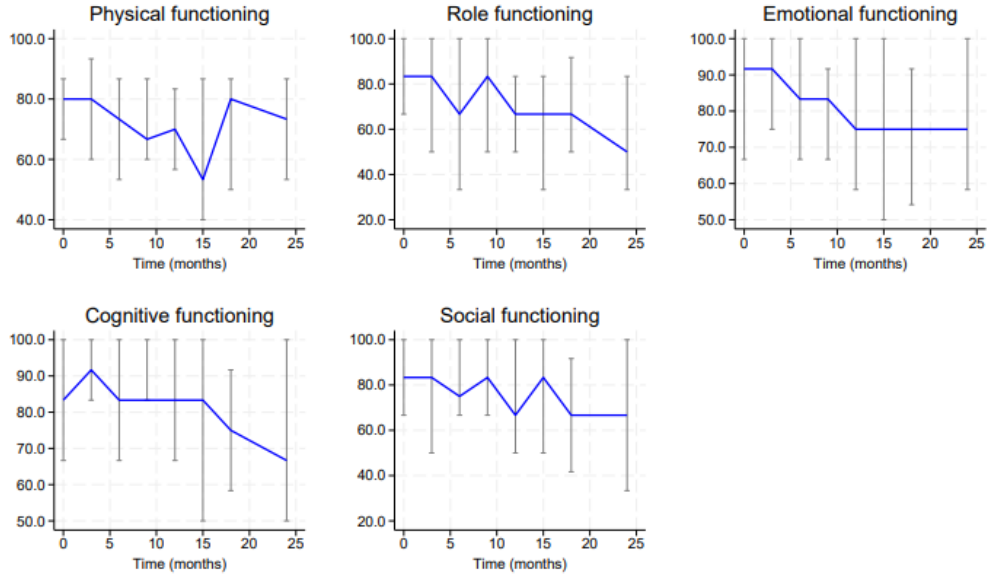
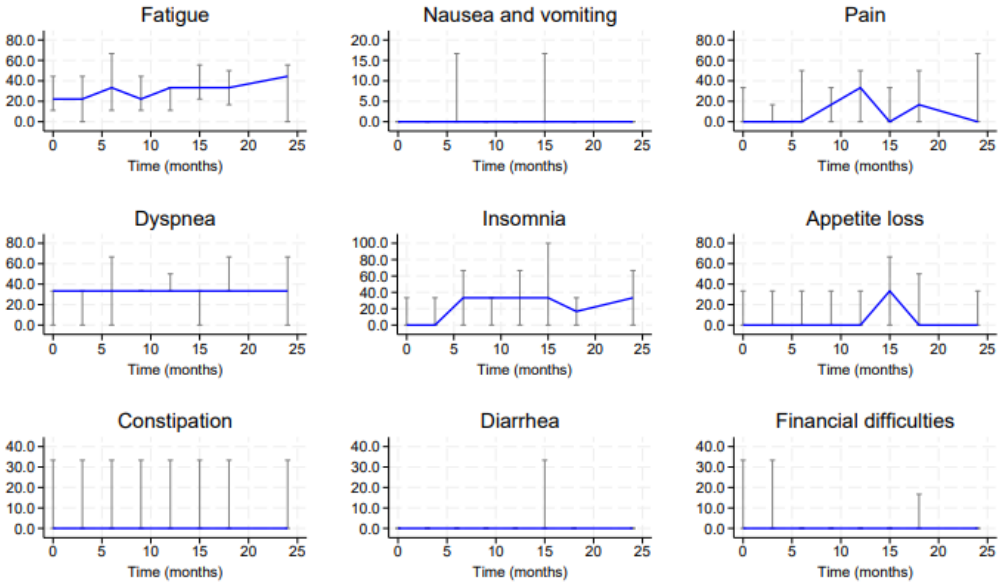


Figure 6: Longitudinal plot presenting the median (IQR) of the QLQ-C30 Symptom subscales over time since screening

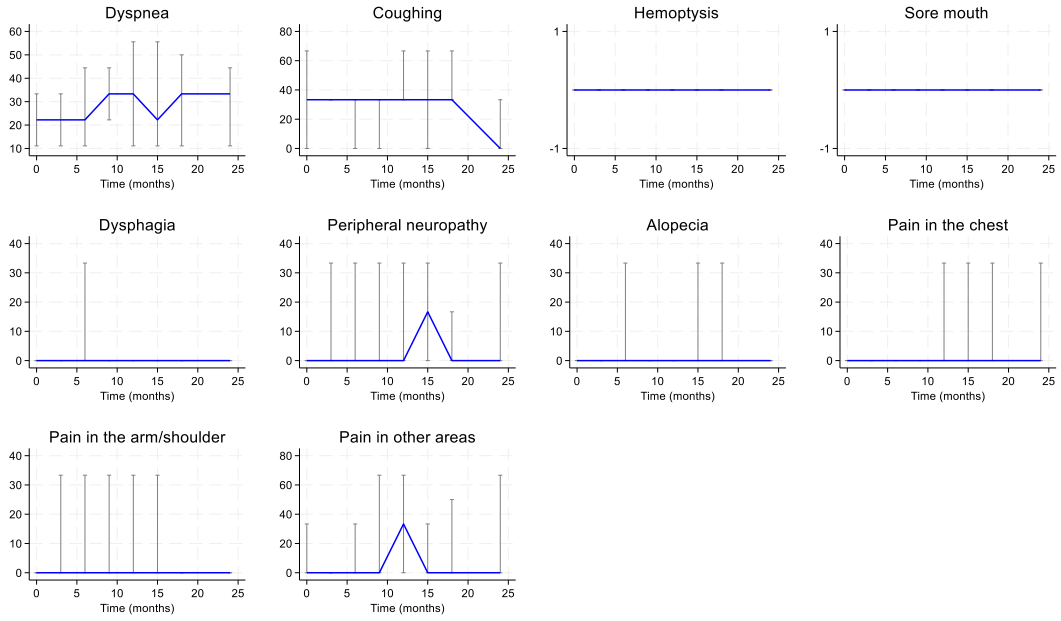


EORTC QLQ-LC13 (Lung cancer module)

Table 14: Summary of EORTC QLQ-LC13 by subscale (n=30 patients)

	Screening		3m PSBRT		6m PSBRT		9m PSBRT		12m PSBRT		15m PSBRT		18m PSBRT		24m PSBRT	
	N	Med [range]	N	Med [range]	N	Med [range]	N	Med [range]	N	Med [range]	N	Med [range]	N	Med [range]	N	Med [range]
Dyspnea	30	22 [0 - 56]	26	22 [0 – 89]	27	22 [0 – 100]	25	33 [0 – 67]	23	33 [0 – 89]	15	22 [0 – 89]	20	33 [0 – 67]	16	33 [0 – 78]
Coughing	30	33 [0 - 67]	25	33 [0 – 100]	27	33 [0 – 100]	25	33 [0 – 100]	24	33 [0 – 100]	15	33 [0 – 67]	20	33 [0 – 100]	17	0 [0 – 100]
Haemoptysis	30	0 [0 - 100]	26	0 [0 – 33]	27	0 [0 – 33]	25	0 [0 – 0]	24	0 [0 – 33]	15	0 [0 – 0]	20	0 [0 – 0]	17	0 [0 – 33]
Sore mouth	30	0 [0 - 33]	26	0 [0 – 100]	27	0 [0 – 100]	25	0 [0 – 67]	24	0 [0 – 67]	15	0 [0 – 0]	20	0 [0 – 100]	17	0 [0 – 67]
Dysphagia	30	0 [0 - 33]	26	0 [0 – 67]	27	0 [0 – 100]	25	0 [0 – 67]	24	0 [0 – 67]	15	0 [0 – 67]	20	0 [0 – 33]	17	0 [0 – 67]
Peripheral neuropathy	30	0 [0 - 67]	26	0 [0 – 67]	27	0 [0 – 100]	25	0 [0 – 67]	24	0 [0 – 67]	14	17 [0 – 67]	20	0 [0 – 67]	16	0 [0 – 67]
Alopecia	30	0 [0 - 100]	26	0 [0 – 67]	27	0 [0 – 100]	25	0 [0 – 67]	24	0 [0 – 67]	15	0 [0 – 100]	20	0 [0 – 67]	17	0 [0 – 100]
Pain in the chest	30	0 [0 - 67]	26	0 [0 – 67]	27	0 [0 – 100]	25	0 [0 – 33]	23	0 [0 – 100]	15	0 [0 – 100]	20	0 [0 – 67]	17	0 [0 – 67]
Pain in the arm/shoulder	30	0 [0 - 100]	26	0 [0 – 67]	27	0 [0 – 33]	25	0 [0 – 100]	24	0 [0 – 100]	15	0 [0 – 67]	20	0 [0 – 67]	17	0 [0 – 100]
Pain in other areas	30	0 [0 – 100]	25	0 [0 – 100]	27	0 [0 – 100]	25	0 [0 – 100]	23	33 [0 – 100]	15	0 [0 – 67]	20	0 [0 – 100]	17	0 [0 – 100]

Figure 7: Longitudinal plot presenting the median (IQR) of the QLQ-L13 Subscales over time since screening



3.7 Exploratory Endpoints

3.7.1 Tolerability of nivolumab by lung function

The tolerability of nivolumab measured by pneumonitis events within 6 months of the final fraction of SBRT was evaluated against lung function at baseline measured by FEV1 and DCLO GOLD categories in 29 patients from the safety population. FEV1 measures airflow limitation, categorised as mild to very severe, and DCLO measures how well gases diffuse across the alveolar–capillary membrane, categorised as normal to severely reduced. Unfortunately, DCLO was only measured on 19 of the 29 patients.

Table 15: A cross-tabulation of pneumonitis events against FEV1 at screening for patients in the safety population (n=29 patients)

	Pneumonitis event <6m after SBRT		
FEV1 Category	**No**	**Yes**	**Total**
<30% (Very severe)	1 (5)	0 (0)	1 (3)
≥30 - <50% (Severe)	5 (24)	0 (0)	5 (17)
≥50 - <80% (Moderate)	7 (33)	6 (75)	13 (45)
≥80% (Mild)	8 (38)	2 (25)	10 (35)
Total	21 (100)	8 (100)	29 (100)

There is some preliminary evidence of an association; for those 8 patients who had a pneumonitis event prior to 6 months after the last fraction of SBRT, they all had moderate or mild airflow limitation according to the FEV1. However the fishers exact test (as there are cell counts <5) was non-significant (p=0.206).

Table 16: A cross-tabulation of pneumonitis events against DCLO at screening for patients in the safety population (n=19 patients)

	Pneumonitis event <6m after SBRT		
DCLO Category	**No**	**Yes**	**Total**
<40% (Severely reduced)	1 (7)	0 (0)	1 (5)
≥40 - <60% (Moderately reduced)	6 (240)	1 (25)	7 (37)
≥60 - <80% (Mildly reduced)	7 (47)	2 (50)	9 (47)
≥80% (Normal)	1 (7)	1 (25)	2 (11)
Total	15 (100)	4 (100)	19 (100)

A trend is not apparent (Fishers exact p=0.653); however there are only 4 patients who had a pneumonitis event and also had DLCO measured at screening, so the sample size is very low.

3.7.2 Subgroup analyses on relapse and survival rates

Subgroup analysis on the relapse and survival rates is not possible due to the low number of relapse and deaths reported during the study.

3.8 Serious Adverse Events

There were 30 serious adverse events from 18 patients reported during the study and are listed in full in Appendix 1.

Table 17: Summary of grade by CTCAE SOC for all reported serious adverse events (SAE) across all patients (n=31 patients)

	Grade 1	**Grade 2**	**Grade 3**
All toxicity types (n=30)	1 (3)	8 (27)	21 (70)
By CTCAE SOC			
01-Blood and lymphatic system disorders	0	0	1
02-Cardiac disorders	1	0	2
05-Endocrine disorders	0	0	1
07-Gastrointestinal disorders	0	0	5

08-General disorders and administration site conditions	0	1	0
11-Infections and infestations	0	3	7
12-Injury, poisoning and procedural complications	0	1	0
15-Musculoskeletal and connective tissue disorders	0	1	0
17-Nervous system disorders	0	1	1
20-Renal and urinary disorders	0	0	1
22-Respiratory, thoracic and mediastinal disorders	0	1	2
23-Skin and subcutaneous tissue disorders	0	0	1

3.9 Withdrawals

There were 2 withdrawals prior to treatment, however only 1 reason is known as tabulated in Table 18. Nine patients did not complete follow-up; no official withdrawal took place but we know 4 were due to death.

Table 18: Summary of withdrawals during the STILE study (n=31 patients)

Reason for withdrawal	Frequency
Prior to treatment	
Patient withdrawn from study due to deterioration in cardiac function before completing radiotherapy	1 (50)
Withdrawal of consent (no other reason recorded)	1 (50)
Total	2
Prior to follow-up completion at 24 months	
Death	4 (44)
Unknown	5 (66)
Total	9

3.10 Protocol Deviations and Violations

There were 288 reported protocol deviations from 32 patients, and these are listed in full in Appendix 2.

Table 19: Summary of protocol deviations by category across all patients (n=31 patients)

Deviation category	Frequency
PD1 - Failure to comply to the timeline defined in the visit schedule	75 (26)

PD2 - Dose interruptions / modifications not specified in the protocol	5 (2)
PD3 - Failure to adhere to the study protocol	204 (70)
PD4 - Failure to provide original signed consent forms	2 (1)
PD7/PV13 - Other	2 (1)
Total	288

4 References

1. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee MC, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw KCA, Sullivan M, Takeda F. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute.* 1993;85:365-376.
2. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual (3rd Edition).* Brussels: European Organisation for Research and Treatment of Cancer; 2001.

5 Appendix

Appendix 1: SAE listings

Description	SOC	Term	Start date	Outcome	End date	Related to IMP	Related to SBRT	Grade	Action	irAE
abdominal pain	07-Gastrointestinal disorders	07-Abdominal pain	09/10/2018	Resolved	15/10/2018	Probably	Unrelated	Grade 3	Treatment Stopped	Yes
colitis	07-Gastrointestinal disorders	07-Colitis	03/01/2019	Resolved	13/02/2019	Definitely	Unrelated	Grade 3	Treatment Stopped	Yes
Lung Infection	11-Infections and infestations	11-Lung infection	14/02/2019	Resolved	20/02/2019	Possibly	Possibly	Grade 2	Treatment Stopped	No
Generalised Muscle Weakness	15-Musculoskeletal and connective tissue disorders	99-Other	22/02/2019	Resolved	26/02/2019	Unrelated	Unrelated	Grade 2	Treatment Stopped	No
Colitis	07-Gastrointestinal disorders	07-Colitis	02/10/2018	Resolved	04/10/2018	Definitely	Unrelated	Grade 3	Treatment Stopped	Yes
Colitis	07-Gastrointestinal disorders	07-Colitis	05/10/2018	Resolved	06/10/2018	Definitely	Unrelated	Grade 3	Treatment Stopped	Yes
Headache	17-Nervous system disorders	17-Headache	18/05/2018	Resolved	22/05/2018	Possibly	Unlikely	Grade 2	None	No
Bronchial Infection	11-Infections and infestations	11-Bronchial infection	12/06/2018	Resolved	22/06/2018	Possibly	Possibly	Grade 3	Treatment Postponed	No
Pneumonitis	22-Respiratory, thoracic and	22-Pneumonitis	12/06/2018	Resolved	25/06/2018	Possibly	Probably	Grade 2	Treatment Postponed	Yes

	mediastinal disorders									
lung infection	11-Infections and infestations	11-Lung infection	12/02/2019	Resolved	15/02/2019	Unlikely	Unlikely	Grade 2	Treatment Interrupted	No
organising pneumonia	11-Infections and infestations	11-Lung infection	04/01/2019	Resolved	15/01/2019	Possibly	Unlikely	Grade 3	Treatment Postponed	No
pneumonitis	22-Respiratory, thoracic and mediastinal disorders	22-Pneumonitis	17/01/2019	Resolved with Sequelae	05/02/2019	Definitely	Possibly	Grade 3	Treatment Stopped	Yes
Lung Infection	11-Infections and infestations	11-Lung infection	22/03/2019	Resolved	23/03/2019	Unlikely	Unlikely	Grade 2	Treatment Stopped	No
Urinary tract infection	11-Infections and infestations	11-Urinary tract infection	23/09/2019	Resolved	25/09/2019	Unlikely	Possibly	Grade 3	None	No
Diarrhoea	07-Gastrointestinal disorders	07-Diarrhea	22/08/2019	Resolved	26/08/2019	Unlikely	Possibly	Grade 3	None	No
Skin rash	23-Skin and subcutaneous tissue disorders	23-Rash maculo-papular	13/11/2019	Resolved with Sequelae	03/12/2019	Possibly	Unrelated	Grade 3	Treatment Stopped	Yes
Lung infection	11-Infections and infestations	11-Lung infection	19/02/2020	Resolved	23/02/2020	Possibly	Possibly	Grade 3	Treatment Postponed	No
Lung Infection	11-Infections and infestations	11-Lung infection	18/05/2020	Resolved	21/05/2020	Possibly	Possibly	Grade 3	Treatment Stopped	No
Anaemia	01-Blood and lymphatic system disorders	01-Anemia	08/04/2021	Resolved	21/04/2021	Unlikely	Unrelated	Grade 3	None	No
Skin infection	11-Infections and infestations	11-Skin infection	05/03/2021	Resolved	10/03/2021	Unlikely	Unrelated	Grade 3	Treatment Stopped	No
Heart failure	02-Cardiac disorders	02-Heart failure	11/11/2020	Resolved	12/11/2020	Unrelated	Unrelated	Grade 3	-8	No
COVID-19	11-Infections and infestations	99-Other	26/12/2020	Resolved	31/12/2020	Unlikely	Unrelated	Grade 3	Treatment Postponed	No

Chest Pain	02-Cardiac disorders	02-Chest pain - cardiac	18/09/2021	Resolved	04/11/2021	Unlikely	Unrelated	Grade 1	None	No
Infusion related reaction - patient unresponsive	08-General disorders and administration site conditions	08-Infusion related reaction	07/07/2022	Resolved	08/07/2022	Definitely	Unrelated	Grade 2	Treatment Stopped	Yes
Adrenal Insufficiency	05-Endocrine disorders	05-Adrenal insufficiency	03/04/2023	Resolved with Sequelae	07/04/2023	Definitely	Unrelated	Grade 3	Treatment Stopped	Yes
Myocardial Infarction	02-Cardiac disorders	02-Myocardial infarction	13/06/2023	Resolved with Sequelae	16/06/2023	Unrelated	Unrelated	Grade 3	Treatment Postponed	No
Stroke	17-Nervous system disorders	17-Stroke	18/03/2023	Resolved	22/03/2023	Unrelated	Unrelated	Grade 3	Treatment Stopped	No
Urinary retention	20-Renal and urinary disorders	20-Urinary retention	21/11/2023	Resolved with Sequelae	23/11/2023	Unrelated	Unrelated	Grade 3	Treatment Postponed	No
Pneumonitis	22-Respiratory, thoracic and mediastinal disorders	22-Pneumonitis	11/05/2024	Resolved with Sequelae	14/05/2024	Possibly	Unrelated	Grade 3	None	Yes
Right breast implant rupture	12-Injury, poisoning and procedural complications	99-Other	15/03/2024	Resolved with Sequelae	29/07/2024	Possibly	Unrelated	Grade 2	Treatment Postponed	No