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

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Protocol Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):
Dr Merina Ahmed

Statistician:

Signature: Date:

..../...../.....

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Table of Revisions Made to Protocol

Protocol v2.0			
Page/Section	**Previous Wording**	**New Wording**	**Rationale for Amendment**
Protocol Synopsis Study Design	N/A	SBRT will be delivered in either 3 or 5 fractions for peripheral disease or 8 fractions in central disease. A flat dose of 240 mg Q2W nivolumab infusion will begin after the final fraction of SBRT, within 24 hours and typically on the same day. Nivolumab will subsequently be given every 2 weeks at a flat dose of 240 mg for a further 13 cycles followed by Nivolumab 480mg Q4W for 7 cycles until 20 cycles in total are complete, unless any study drug discontinuation criteria are met. Treatment (20 cycles) will take a minimum of 1 year to complete but may exceed this timeframe if treatment delays are encountered. (Patients who have enrolled on Nivolumab Q2W 240mg regimen for 26 cycles and are beyond cycle 14 will receive 26 cycles Q2W in total to complete treatment) Assessment of toxicities will be performed at each clinic visit during treatment, at 30 days after the final nivolumab infusion or 14 days after decision to discontinue treatment (in the event of toxicities) and until 100 days after the final nivolumab infusion. Changes in spirometry values and PFTs will be assessed throughout the trial.	Summary of the amended dosing schedule
Study Population: Inclusion criteria & Section 5.1.2 Target Population	~~Peripheral lesions i.e. outside a 2cm radius of main airways and proximal bronchial tree. This is defined as 2cm from the bifurcation of the second order bronchus e.g. where the right upper lobe bronchus splits~~	-Up to five PS2 patients can be enrolled and followed up for 3 months following their final radiotherapy fraction at which stage an IDMC meeting is required to assess further PS2 patient enrolment. -Single or synchronous (up to 2) primary NSCLC lesions tumour stage T1-3 (≤5cm) N0 M0 (UICC v.8) as determined by the	Additional Inclusion Criteria: 1. Includes synchronous and metachronous lesions 2. Includes 'central/ termed NSCLC

		local MDT based on minimum investigations of CT chest/abdomen within 8 weeks and FDG-PET performed within 6 weeks of 1st fraction of SBRT -For synchronous tumours one lesion must have a histological diagnosis of NSCLC. For other lesions, Radiological diagnosis of NSCLC as determined by lung MDT -Metachronous (single) primary NSCLC lesions, tumour stage T1-3 (($\leq$5cm) N0 M0 (UICC v.8) presenting after previous treatment of T1-3($\leq$5cm) N0 M0 (UICC v.8) with surgery or SBRT are eligible for inclusion. Lung constraints must be able to feasibly achieved (according to dose constraints in 7.1.2). -Up to 5 patients with multi-focal primary NSCLC (up to 2 lesions) can be enrolled and followed up for 3 months following the final radiotherapy fraction at which stage an IDMC meeting is required to assess further multifocal disease recruitment -Tumour stage T1-3 termed as 'central' disease within 2cm of main airways and proximal bronchial tree, but not abutting these structures (ultra-central), are suitable for entry. Up to 5 patients with 'central' primary NSCLC can be enrolled and followed up for 3 months following their final radiotherapy fraction at which stage an IDMC meeting is required to assess further 'central' primary NSCLC recruitment	3. TNM staging system has changed to UICC v8 from UICC v7.
Study Population: Exclusion Criteria & Section 5.2.2. Medical History and Concurrent Diseases		Subjects with previous malignancies (except non-melanoma skin cancers, early stage NSCLC treated with surgery OR previous stereotactic body radiotherapy outside of the planned stereotactic treatment field, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma or breast) are	Addition to excluded previous malignancies.

		excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period	
1.1.2. Stereotactic Body Radiation Therapy (SBRT)	-	SBRT to primary NSCLC within 2cm of the central airways (designated 'central' tumours) has reported higher grade ≥3 toxicity rates than peripheral tumours. Grade 3 toxicities have been reported to range from 3-46%.[12,13] Concerns are primarily regarding proximity to mediastinal structures including proximal airways but also heart, pericardium and large blood vessels where hypofractionated radiation doses may lead to severe toxicity which may lead to life-threatening consequences.[14] Chadhuri et al reported retrospective data on patients with peripheral, central and ultra-central lung tumours and did not find significantly different grade ≥2 treatment related toxicities (0%).[15] However, a structured literature review in 2013 found treatment-related mortality to be 2.3% in patients with SBRT to central lung tumours. A retrospective review of 107 patients, 61 central and 46 ultra-central, defined as where the ITV directly abutted the proximal bronchial tree reported grade 5 toxicity rates of 3.5% with central tumours and 2.2% with ultra-central tumours, consistent with other published literature.[12] Dose fractionation regimes vary widely however with up to 20Gy per fraction in some studies. There are no published prospective trials with clear standardised techniques in centrally located NSCLC tumours. Previous trials have adopted a conservative 8 fraction regime in respect to tumours within 2cm of the proximal bronchial tree but not abutting the structure. The UK SABR consortium has adopted this same approach and central lung SBRT is now routine	Justification for amended radiotherapy schedule.

Section1.1.3 Role of Adjuvant systemic therapy		practice. The approach to these ultra-central tumours is unclear is still being assessed.[16] Multiple primary NSCLC, either synchronous or metachronous, is a well-described presentation in up to 10% of lung cancer patients.[18] Multiple case series have reported low rates of grade 3 toxicity in patients treated with synchronous SBRT treatment fields.[18,19] However relatively little data exists in the literature for toxicity. Retrospective analysis suggests improved outcomes for patients with metachronous primary disease over synchronous primary disease.[19] SBRT to multiple tumours at different time points is a safe and well tolerated treatment and will become more widespread as lung cancer screening programmes are implemented. The UK SABR Consortium has offered guidance on treating multiple lung lesions, in which standard lung dose constraints are applied, with SBRT. This guidance also extends to patients with early stage lung cancers for whom surgery is not feasible due to poor lung function.[16] The TNM (UICC v8) staging system classifies synchronous lung tumours arising in the same lobe as T3 and synchronous ipsilateral lesions in different lobes as T4. In addition M1a describes patients with synchronous bilateral lesions. These patients would be eligible for combined radical radiotherapy and systemic therapy. SBRT to patients with synchronous and metachronous lesions show excellent local control rates and 2 year survival rates and presents a potential paradigm shift in the treatment of these specific presentations of T3 and T4 tumours.[18] Synchronous and metachronous primary NSCLC patients remain a potential population in whom	

		adjuvant systemic therapy may benefit.	
1.2.2 Dosing Schedule Rationale	-	Nivolumab will be administered intravenously at a flat dose of 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 (1 year of treatment if no delays are encountered). (Patients who were eligible and began treatment as per STILE protocol V1.1 (STILE_CCR4644_Protocol_v1 1_22Aug2017) and are currently on treatment cycle 14 or later will continue on Nivolumab 240mg Q2W to complete a total of 26 cycles). Recently the Federal Drug administration and European Medicines Agency have licensed the use of Nivolumab 480mg Q4W administration. A recent analysis evaluated PK exposure and clinical safety of nivolumab 480 mg Q4W compared with 240 mg Q2W and 3 mg/kg Q2W dosing schedules used quantitative clinical pharmacology approaches and pooled safety data from four phase III clinical trials (CheckMate 066, 025, 057, and 017). A flat dose of 240 mg Q2W was previously approved by the FDA based on modeled comparisons of exposure, and bridging of efficacy and safety data demonstrating comparability with 3 mg/kg Q2W. More recently, a less frequent flat dose of 480 mg Q4W was approved as an additional option for several monotherapy indications, including NSCLC, based on a similar modeling approach together with clinical safety data. Patients who transition from 240mg to 480mg Nivolumab experienced 14.8% of treatment related side effects, although this is considered to be comparable with what would be expected for patients who continued with	-Rationale for amendment to dosing schedule

		the Q2W dosing schedule.[53] Checkmate 384 has reported similar findings offering support for the use of nivolumab Q4W dosing as a more convenient option for patients with similar efficacy and safety [54]	
Section 4.1 Study Plan	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. The study will recruit 31 patients. We anticipate it will take approximately ~~18~~ months to recruit 31 patients	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. The study will recruit 31 patients. We anticipate it will take approximately 36 months to recruit 31 patients. Similarly, after 5 patients with multi-focal primary NSCLC (up to 2 lesions) are enrolled and followed up for 3 months the IDMC wil meet to assess whether further multifocal disease patients can be safely recruited. Patients may continue to enroll while awaiting the outcome of these IDMC meetings. A further IDMC review is required after enrolment of 5 'central' primary NSCLC have been enrolled and followed up for 3 months following the final fraction of radiotherapy.	Additional IDMC requirements according to amended inclusion criteria
Section 4.2.1 SBRT		Radiotherapy planning and delivery will be carried out as detailed in section 7.1. Patients will receive a total of 54 Gy if delivered in 3 fractions, 55 Gy if delivered in 5 fractions or 60Gy if delivered in 8 fractions.	Amendment to radiotherapy schedule
Section 4.2.2 Investigational Medicinal product	All subjects will receive nivolumab at 240 mg ~~–~~as in IV infusion ~~over 30 minutes every 2 weeks~~ to complete ~~1 year total~~ nivolumab treatment.	All subjects will receive nivolumab at 240 mg q2w for 13 cycles followed by 480mg q4w for 7 cycles as an IV infusion to complete 20 doses to complete (a total of 1 year treatment if no delays encountered). (Patients who were eligible and began treatment as per STILE protocol V1.1 (STILE_CCR4644_Protocol_v1 1_22Aug2017) and are currently on treatment cycle 14 or later will continue on Nivolumab 240mg Q2W to complete a total	Clarification regarding amended dosing schedule

		of 26 cycles. Patients enrolled within the trial who have not yet received cycle 14 can be considered for Nivolumab 480mg Q4W for a further 7 cycles from cycle 14)	
Section 4.3 Study Schema	-	-See amended Schema, Protocol v2.0.	Figure 1 amended to reflect the changes to treatment schedule
Section 4.5	-	Treatment may continue beyond a year if there is a need to delay treatment.	Clarification regarding timeframe for treatment with Nivolumab.
Section 4.7.1 Safety Follow up & 6.9 Safety Follow-up Visit		All subjects will be followed up at a minimum of 30 days after completion of their last dose of nivolumab or 14 days +/- 3 days after the decision to discontinue treatment (if beyond 30 days since their last dose of nivolumab). All subjects will be assessed for toxicity a minimum of 30 days (+/- 7 days) after their final dose of nivolumab or 14 days (+/-7 days) after the decision to discontinue IMP (if this decision has been taken greater than 30 days since their last dose of Nivolumab).	Amended due to timeframe of 12 weeks IMP delay due to toxicity etc changing to discontinuation within those 12 weeks. These patients may therefore fail the 30 safety review if decision to 'discontinue' IMP is made after that 30 day period (a protocol violation). Addition of 14 day review after last IMP dose if beyond timeframe 30 days since last IMP allows for this eventuality.
Section 4.8 Independent Data Monitoring Committee (IDMC)		4.8.1 The IDMC will meet when the first 5 patients have reached 3 months follow up from their final fraction of radiotherapy or have withdrawn consent to follow-up. 4.8.2 Once 5 patients with multifocal disease have been recruited and achieved 3 months of follow-up: the IDMC will review safety of the first 5 patients enrolled with multifocal disease when they have reached 3 months of follow-up or have withdrawn consent to follow-up. And, separately, once 5 patients with central disease have enrolled an IDMC review will occur once they have reached 3 months of follow-up or have withdrawn consent to follow-up. Patients that have enrolled but did not	Additional IDMC requirements according to amended inclusion criteria

		receive IMP will be replaced. Further patients with multifocal disease will *not* be able to enroll unless recommendation is given by the IDMC. In the event that 5 'central disease' or, separately, 5 multifocal disease patients have not enrolled by the point that a further 15 patients have enrolled since the previous IDMC meeting, 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. Patients may continue to enroll while awaiting the outcome of this IDMC meeting.	
Section 6.3 Histological Confirmation	-	All patients with synchronous primary lung cancers (up to 2) must have one lesion with a documented, biopsy proven, histological diagnosis of NSCLC. For other lesions radiological diagnosis of NSCLC as determined by lung MDT Metachronous lesions must be biopsy proven for trial entry.	
Section 6.6.1	-	PD-L1 assessment can happen at any timepoint during the patients inclusion within the trial but must be requested prior to completion of patient participation.	
Section 6.6.12 Bedside Spirometry	-	Spirometry will be performed on the day of the final fraction of SBRT, every 6 weeks (+/- 7 days) until cycle 14 and then every 8 weeks thereafter, while receiving nivolumab.	Clarification regarding frequency of bedside spirometry assessments
Section 6.7.2		Subjects will be assessed with chest radiographs (CXR) for evidence of pneumonitis as laid out in the schedule of events. A CXR will be performed during screening, at 4 weeks and 8 weeks (+/- 7 days) from the final fraction of SBRT, at the 9 month (+/- 14 days) follow-up review, 15 month follow-up review and at the safety follow-up visit (30 days (+/- 7 days) post the final dose of nivolumab). The CXRs should follow calendar time	Additional time-point for imaging review at 15 month follow-up

		points rather than cycle numbers of nivolumab. If the Investigator or qualified designee identifies features suggestive of pneumonitis/relapse on the CXR then a contrast chest CT should be performed, as clinically indicated.	
Section 6.8 Research Tissue and Blood Samples	Subsequent samples will be taken on day 1 of cycles 1~~, 3 and 5~~ of nivolumab.	This sample can be taken any time from day -28 to until day 1 of radiotherapy treatment but must occur before any treatment is delivered. Subsequent samples will be taken on day 1 of cycles 1of nivolumab Two further samples will be taken at time points of weeks 4, 8.	Clarification that baseline research blood sample can be taken on day 1 of treatment as long as it is taken before any treatment is administered. If patients experience delay of IMP we are taking blood samples at different time points. Taking it a week 4 and 8 ensures all research blood are taken at the same timepoints. The variable can be how much IMP they will have had at the timepoints.
Section 6.10 Follow up Phase Visits	All subjects will be assessed for evidence of relapse and secondary endpoints at 3 monthly (+/- 14 days) intervals from the final fraction of radiotherapy for the~~ first year.~~	All subjects will be assessed for evidence of relapse and secondary endpoints at 3 monthly (+/- 14 days) intervals from the final fraction of radiotherapy for the 18 months then at a six month interval at the last follow-up visit at 24 months.	
Section 6.11	See Schedule of Events Protocol v1.1 (dated 22 August 2017)	See Schedule of Events Protocol v2.0 for updated Schedule	Schedule of events updated in order to support text.
Section 7.1.2. Delineation and treatment planning	**Proximal Bronchial Tree plus 2 cm** ~~As part of adhering to the incligibility requirements for not enrolling patients with tumours in the zone of the proximal bronchial~~	**Proximal Bronchial Tree** To adhere to eligibility requirements, GTV abutting this structure or PTV encompassing a bronchus should not receive SBRT within this trial.	

	~~tree~~, it is convenient to define an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this artificial structure, the patient should not receive SBRT in this trial. (See Appendix 4).	**Proximal Bronchial Tree plus 2cm** Patients whose GTV falls within this structure should receive treatment over 8 fractions **To classify a lesion as peripheral, central or ultracentral see definitions in Appendix 4.**	
Section 7.1.2. Tumour Location/OAR doses		-See amended table Protocol v2.0 Where patients are having more than one lung lesion treated with SABR, it is recommended that these should be treated on alternate days and with the same dose/ fractionation (usually the most conservative schedule). The use of alternate day treatments reduces the dose per fraction to the whole lung, and is recommended in an effort to limit the risk of severe pneumonitis and fibrosis. Both sites may be treated on the same day is if the tumours can be encompassed in a single field, for small metastases in otherwise fit patients, or when the combined percentage of lung volume receiving a dose of 20 Gy or higher (V20 Gy) is below the tolerance for a single lesion. There are few published data on normal tissue tolerances for multiple lesions and ideally the standard thoracic constraints should be met. However, the OAR constraint that will probably be exceeded is the V20 Gy. In the case of treating two lung lesions, the following V20 Gy lung constraints should be followed: • Optimal <12.5% • Acceptable in all cases <15% • Acceptable in selected cases with good lung function <20% Where the lung function parameters of forced expiratory volume in 1 second (FEV1) and transfer factor (DLCO) are below 40% of predicted, it is strongly recommended that the V20 Gy	

		should be kept below 12.5% (optimal) or 15% (mandatory).[16]	
Section 7.1.2. Fractionation	The conservative dose fractionation is recommended when any part of the PTV is in contact with the chest wall.	Central disease dose fractionation: 7.5Gy x 8 fractions The conservative peripheral lesion dose fractionation (55Gy in 5 fractions) is recommended when any part of the PTV is in contact with the chest wall. The central disease dose fractionation is recommended when any part of the GTV is within the artificial structure 'proximal bronchial tree plus 2cm' but not abutting the structure 'proximal bronchial tree'. (See appendix 4)	
Section 7.2.5. Dose Calculations and Administration	Nivolumab will be given every 14 days at a flat dose of 240 mg for 13 cycles followed by 480mg every 28 days for 7 cycles (20 cycles in total), to be administered ~~as a 30 minute IV infusion.~~	Nivolumab will be given every 14 days at a flat dose of 240 mg intravenously over 30 minutes for 13 cycles. This will be followed by 480mg intravenously over 60 minutes every 28 days for 7 cycles (20 cycles in total).	Clarification that Nivolumab 480mg dose will be given over 60 minutes.
Section 8.22. Management of Immunotherapy related colitis	*Not Applicable*	Patients with symptoms of grade 3 colitis must have a confirmed histological inflammation via flexible sigmoidoscopy or colonoscopy. These patients should be management according to guidelines provided in appendix 8. Patients should be managed locally by appropriately trained specialists. Patients whose symptoms are refractory to infliximab should be considered for Vedoluzimab dosing (appendix 8). This is a non-funded drug and individual cases must be referred to Bristol-Meyer Squibb for consideration of funding.	-Additional clarification regarding the management of colitis.
Section 9.2.2. Secondary Endpoints	-	We do not anticipate that the new treatment schedule of this amendment will alter the toxicity profile of nivolumab or the survival rates, however, a further sensitivity analyses may take place to exclude any patients that have received the q2W treatment schedule throughout the treatment period. This	Additional sensitivity analysis to take into account the amended treatment schedule.

		analysis will be applied only to endpoints assessed beyond 6 months (after C13 of treatment).	
Section 11.3.4. Independent Data Monitoring Committee (IDMC)	-	Responsibilities of the IDMC are as follows: Review safety data and make recommendations regarding escalation to enrolment of patients with multifocal and central primary NSCLC treated with SBRT and IMP	Additional responsibility of IDMC added in view of amended inclusion criteria
Special Situations-GI Adverse Event Management	*Not Applicable*	*-See additional table in Appendix 8 of Protocol v2.0.*	
Appendix 1 *Highly effective methods of contraception*	*Highly effective methods of contraception* ~~*Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena© by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug*~~ ~~*Non-hormonal IUDs, such as ParaGard©*~~ ~~*Tubal ligation*~~ ~~*Vasectomy*~~ ~~*Complete abstinence NOTE: Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs provided that this is in line with the subject's usual and preferred lifestyle. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests on a*~~	For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include: _ combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1: o oral o intravaginal o transdermal _ progestogen-only hormonal contraception associated with inhibition of ovulation 1: o oral o injectable o implantable 2 _ intrauterine device (IUD) 2 _ intrauterine hormone-releasing system (IUS) 2 The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.	Guidance on contraceptive use updated according to current guidelines

	~~*6 weekly basis. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence*~~		
Appendix 1 *Less effective methods of contraception*	~~Diaphragm with spermicide~~ ~~Cervical cap with spermicide~~ ~~Vaginal sponge~~ ~~Male condoms with spermicide~~ ~~Male condom without spermicide~~ ~~Progestin only pills by WOCBP subject or male subject's WOCBP partner~~ ~~Female condom~~ ~~NOTE: A male and female condom must not be used together.~~	Acceptable birth control methods that result in a failure rate of more than 1% per year include: _ progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action _ male or female condom with or without spermicide 5 _ cap, diaphragm or sponge with spermicide 5 5 A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods	Guidance on contraceptive use updated according to current guidelines
Appendix 8	See specific toxicity management algorithms in Protocol v1.1 (dated 22 August 2017)	See updated toxicity management algorithms in Protocol v2.0 for updated guidance - Management of toxicities should follow Royal Marsden guidelines below.	Toxicity management guidance updated according to latest guidance available at RMH.
Protocol v3.0			
Page/Section	**Previous Wording**	**New Wording**	**Rationale for Amendment**
KEY TRIAL CONTACTS AND PROTOCOL CONTRIBUTORS	~~David Walder~~ ~~david.walder~~ ~~Ria Kalaitzaki~~ ~~Ria.kalaitzaki~~ ~~Andrea Pejenaute~~ ~~Andrea.pejenaute~~	Simon Page Simon.page Ranga Gunapala Ranga.gunapala Marta Vergnano Marta.vergnano	Update to study contact information
Protocol Synopsis Study Population: Inclusion criteria & Section 5.1.2 Target Population	- Single or synchronous ~~(up to 2)~~ primary NSCLC lesions tumour stage T1-3 (≤5cm) N0 M0 (UICC v.8) as determined by the local MDT based on minimum investigations of CT chest/abdomen within 8 weeks and FDG-PET		Additional Inclusion Criteria: - Include more than 2 primary lesions - further IDMCs removed as these patients will be reviewed at the regular IDMCs.

	performed within 6 weeks of 1st fraction of SBRT. ~~- Up to 5 patients with multi-focal primary NSCLC (up to 2 lesions) can be enrolled and followed up for 3 months following their final fraction of radiotherapy at which stage an IDMC meeting is required to assess further multifocal disease recruitment~~		
Protocol Synopsis Study Population: Exclusion criteria	- Subjects with previous malignancies (except non-melanoma skin cancers, early stage NSCLC treated with surgery OR previous stereotactic body radiotherapy~~ outside of the planned stereotactic treatment field,~~ and the following in situ cancers:	- Subjects with previous malignancies (except non-melanoma skin cancers, early stage NSCLC treated with surgery OR previous stereotactic body radiotherapy, and the following in situ cancers:	Exclusion criteria have been further clarified.
Section 1.2.2 Dosing Schedule Rationale	Nivolumab will be administered intravenously at a flat dose of 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 (1 year of treatment if no delays are encountered).	Nivolumab will be administered intravenously at a flat dose of 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 (a minimum of 1 year of treatment if no delays are encountered).	Dosing Schedule Rationale has been further clarified.
Section 4.1 Study Plan	~~We anticipate it will take approximately 36 months to recruit 31 patients.~~ ~~Similarly, after 5 patients with multi-focal primary NSCLC (up to 2 lesions) are enrolled and followed up for 3 months the IDMC wil meet to assess whwether further multifocal disease patients can be safely recruited.~~		Timeline of anticipated recruitment as well as further IDMCs have been removed in light of amendments to inclusion criteria.
Section 4.8 Independent Data Monitoring Committee (IDMC)	~~Once 5 patients with multifocal disease have been recruited and achieved 3 months of follow-up: the IDMC will review safety of the first 5 patients enrolled with multifocal disease when they have reached 3 months of follow-up or have withdrawn consent~~	Once 5 patients…	Further IDMCs have been removed in light of amendments to inclusion criteria.

	~~to follow-up. And, separately~~ once 5 patients…		
Section 5.1.2 Target Population	• For other lesion~~-~~ ~~R~~adiological diagnosis of NSCLC as determined by lung MDT.	For the other lesion a radiological diagnosis of NSCLC as determined by lung MDT is sufficient.	
Section 5.2.1 Tumour Characteristics		•'Ultra-central' tumours, i.e. those adjacent to the hilar structures, with the gross tumour volume directly abutting a main bronchus	Exclusion criteria have been further clarified
Section 6.3 Histological Confirmation	All patients with synchronous primary lung cancers ~~(up to 2)~~ must have one lesion with a documented, biopsy proven, histological diagnosis of NSCLC.		Inclusion criteria have been amended.
Section 6.6.1 PD-L1 Assessment	PD-L1 assessment can happen at any timepoint during the patients inclusion within the trial but must be requested prior to completion of patient ~~participation~~.	PD-L1 assessment can happen at any timepoint during the patients inclusion within the trial but histological sample must be requested to be sent to the Royal Marsden Hospital prior to completion of patient screening.	Timing of histological sample for PD-L1 assessment has been clarified.
Section 6.10 Follow up Phase Visits	• Imaging should follow the Follow-up visit schedule. CXRs will not be performed when a CT has been performed (or is scheduled) within ~~7~~ days unless clinically indicated	• Imaging should follow the Follow-up visit schedule. CXRs will not be performed when a CT has been performed (or is scheduled) within 21 days unless clinically indicated	Schedule of follow-up CXRs has been clarified.
Section 6.11 Schedule of Events	See Schedule of Events and Notes/Key in Protocol v2.0 (dated 19 December 2019)	See Schedule of Events and Notes/Key in Protocol v3.0 for updated Schedule	Schedule of events updated to clarify and support text.
Section 7.1.2 Delineation and treatment planning	The constraints recommended are based on ~~those that have been safely used to treat > 500 patients at the VU centre in Amsterdam and subsequently implemented for the ROSEL study~~. ~~As defined above, the GTV must be outside the defined 2cm margin around the proximal airways.~~	The constraints recommended are based on the UK SABR consortium guidance. Peripheral and centrally located tumours can be treated in this study. Ultra-central disease is however excluded. Please refer to eligibility criteria.	Reference guidance for treatment planning and tumour location/OAR doses have been amended.
Section 8.8 Management of Immune-mediated Adverse events	~~Evaluation and management guidelines for the following groups of Aes were developed to assist Investigators and~~	Local guidelines should be followed for the management of immune-mediated toxicities.	Toxicity management guidelines from RMH have been removed, as local guidance will be followed.

	~~can be found in Appendix 9:~~ ~~• Pulmonary toxicity~~ ~~• Gastrointestinal toxicity (diarrhoea or colitis)~~ ~~• Endocrinopathies~~ ~~• Hepatotoxicity (including asymptomatic LFT elevations)~~ ~~• Renal toxicity~~ ~~• Skin toxicity~~ ~~• Neurological toxicity~~		
Section 8.21 Management of Nivolumab Related Infusion Reactions	~~T~~reatment recommendations ~~are provided below and may be modified based on~~ local treatment standards and guidelines as appropriate~~:~~ ~~For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)~~ ~~Remain at bedside and monitor subject until recovery from symptoms.~~ ~~The following prophylactic premedications are recommended for future infusions:~~ ~~diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.~~ ~~For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).~~	For treatment recommendations, please refer to local treatment standards and guidelines as appropriate.	Guidelines on the management of Nivolumab related infusion reactions have been removed, as local guidance will be followed.

	~~Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used. For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e. not rapidly responsive to~~		

	~~symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g. renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated). Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine, or corticosteroids).~~		
Section 8.22 Management of Immunotherapy related colitis	These patients should be ~~management~~ according to guidelines ~~provided in appendix 8~~.	These patients should be managed according to local guidelines.	Toxicity management guidelines from RMH have been removed, as local guidance will be followed.

Appendix 1	In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level ~~less~~ than 40 mIU/mL.	In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level greater than 40 mIU/mL.	FSH levels for menopause definition have been amended.
Appendix 8	~~• Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.~~ •Management of toxicities should follow ~~Royal Marsden~~ guidelines ~~below~~. See specific toxicity management algorithms Protocol v2.0 (dated 19 December 2019)	Management of toxicities should follow local guidelines.	Toxicity management algorithms from RMH have been removed, as local guidance will be followed.
Protocol v4.0			
Page/Section	**Previous Wording**	**New Wording**	**Rationale for Amendment**
Protocol Synopsis: - Study Objectives: Primary Objective; - Study Population: Inclusion criteria; Section 1.3. Research Hypotheses Section 2.1. Primary Objective Section 4.1. Study Plan Section 5.1.2 Target Population	T1-3 (≤~~5~~cm) N0 M0	T1-3 (≤6cm) N0 M0	Size of tumour lesion has been increased to 6cm in line with data from international SBRT trials (SPACE and SUNSET). The main benefit is that as tumour size increases, we know that local control, progression-free survival and overall survival rates start to decrease. Hence larger tumours i.e. 4-6cm are more likely to benefit from maintenance immune therapy than the small tumours we treat with SBR.
Protocol Synopsis: -Exclusion criteria Section 5.2.2 Medical History and Concurrent Diseases	Previous conventional radiotherapy to the chest or mediastinum. Patients who have had previous breast radiotherapy may be eligible at the discretion of the Chief Investigator.	Previous conventional radical radiotherapy to the chest or mediastinum. Patients who have had previous breast radiotherapy may be eligible at the discretion of the Chief Investigator. Patients who have previously received palliative	Lower dose palliative dose conventional radiotherapy is not considered to present significant long term lung effects in comparison to conventional radical doses used in NSCLC for

		dose radiotherapy to the chest may be considered if it is felt SBRT can be safely delivered. These cases must be discussed with the Chief Investigator	example. An immunogenic response with historical low dose to lung is not expected and is unlikely to elicit immune toxicity. Standard radiotherapy planning lung constraints will be required to be met across combined SBRT and palliative treatments.
Section 4.7.3. Follow-Up Phase		In the event of local or national restrictions, such as those seen in a pandemic, some flexibility should be expected. Telephone consultations can be conducted via telephone clinics in patients who have discontinued Nivolumab. Physical assessments and investigations will be carried out as is deemed clinically applicable and necessary to ensure safety of patients both from the risk of infections and from a Nivolumab perspective.	The possibility of telephone consultations during follow-up phase has been introduced to account for the impact of a pandemic on the study.
Section 6.6.11. Pulmonary Function Tests (PFTs)		In the event of a pandemic, full lung function test results obtained within 6 months of first fraction of SBRT can be accepted.	Flexibility has been allowed to account for the impact of a pandemic on the study.
Section 6.11 Schedule of Events	See Schedule of Events plus Notes/Key inProtocol v3.0 (dated 15 May 2020)	See Schedule of Events plus Notes/Key in Protocol v4.0 (dated 15 January 2021)	Notes/Key of Schedule of Events updated to clarify and support text. Removal of trial assessments at SBRT day/ fraction 1. Patients would not usually be reviewed at this timepoint as standard of care and no study procedures would have occurred between screening and commencing SBRT.
8.1. Adverse Event Definition		Please note, only clinically significant abnormal laboratory values will be recorded as adverse events.	Clarifications on which type of abnormal laboratory values are considered adverse events and therefore recorded as such.
Protocol v5.0			
Page/Section	**Previous Wording**	**New Wording**	**Rationale for Amendment**
KEY TRIAL CONTACTS AND PROTOCOL CONTRIBUTORS	Simon Page Sarah Webb Ranga Gunapala	Agnieszka Niebrzydowska Laura Satchwell	Update to study contact information

Protocol Synopsis – Study Objectives - Secondary Objectives	To assess the overall survival rate at 6, 12 and 24 months To assess the disease free survival (DFS) rate at 6, 12 and 24 months	To assess the overall survival rate at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data available) To assess the disease free survival (DFS) rate at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data available)	The addition of 'up to 5 years' for survival endpoints where data is available.
Protocol Synopsis – Secondary Endpoints	Overall survival (OS) rate of the 31 patients at 6, 12 and 24 months Disease Free Survival (DFS) rate of the 31 patients at 6, 12 and 24 months	Overall survival (OS) rate of the 31 patients at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data mature and available) Disease Free Survival (DFS) rate of the 31 patients at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data mature and available)	The addition of 'up to 5 years' for survival endpoints where data is available.
2. Study Objectives 2.2 Secondary Objectives	To assess the overall survival rates at 6, 12 and 24 months To assess the disease free survival (DFS) rates at 6, 12 and 24 months	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) 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)	The addition of 'up to 5 years' for survival endpoints where data is available.
3. Evaluation of outcome 3.2 Secondary Endpoints	Overall survival rate (OS) of the 31 patients at 6, 12 and 24 months Disease Free Survival (DFS) rate of the 31 patients at 6, 12 and 24 months	Overall survival rate (OS) of the 31 patients at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data mature and available) Disease Free Survival (DFS) rate of the 31 patients at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data mature and available)	The addition of 'up to 5 years' for survival endpoints where data is available.
4.7.3 Follow-Up Phase		Survival data and disease status will be available on patient medical notes after 24 months to be collected under unscheduled visits.	The addition of 'up to 5 years' for survival endpoints where data is available.
6.10 Follow up Phase Visits		Survival data and disease status will be available on patient medical notes after 24 months to be collected under unscheduled visits.	The addition of 'up to 5 years' for survival endpoints where data is available.

9.2.2 Secondary Endpoints OS rate of the 31 patients at 6, 12 and 24 months DFS rate of the 31 patients at 6, 12 and 24 months		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.	The addition of 'up to 5 years' for survival endpoints where data is available.
9.4 Timing of Analysis	A subsequent analysis will address the secondary endpoints once the data are mature enough i.e. follow up data of 24 months.	A subsequent analysis will address the secondary endpoints once the data are mature enough i.e. follow up data of 24 months (and beyond up to 5 years if available).	The addition of 'up to 5 years' for survival endpoints where data is available.
4.2 Treatment Schedule 4.2.1 Stereotactic Body Radiotherapy		The time period within which all SBRT fractions should be delivered is as follows: * 3 fractions – 2 weeks * 5 fractions – 2 weeks * 8 fractions – 3 weeks.	The addition of clarification on SBRT time period.
Protocol v6.0			
Page/Section	**Previous Wording**	**New Wording**	**Rationale for Amendment**
6.10 Follow up Phase Visits		This will also be collected for patients who completed the study before the up to 5 years data collection was implemented. These patients will be reconsented to the study at their next clinic visit; survival data and disease status will be collected from their medical notes.	The addition of survival data and disease status for up to 5 years where data is available for patients who completed the study.

Protocol Synopsis

Study Title	Stereotactic body radiotherapy with immunotherapy in early stage non small-cell lung cancer: tolerability and lung effects (STILE)
Study Design	This is a single arm, multi-centre, phase Ib/II open label study of nivolumab with stereotactic body radiotherapy (SBRT) for early stage non-small cell lung cancer. SBRT will be delivered in either 3 or 5 fractions for peripheral disease or 8 fractions in central disease. A flat dose of 240 mg Q2W nivolumab infusion will begin after the final fraction of SBRT, within 24 hours and typically on the same day. Nivolumab will subsequently be given every 2 weeks at a flat dose of 240 mg for a further 13 cycles followed by Nivolumab 480mg Q4W for 7 cycles until 20 cycles in total are complete, unless any study drug discontinuation criteria are met. Treatment (20 cycles) will take a minimum of 1 year to complete but may exceed this timeframe if treatment delays are encountered. (Patients who have enrolled on Nivolumab Q2W 240mg regimen for 26 cycles and are beyond cycle 14 will receive 26 cycles Q2W in total to complete treatment) Assessment of toxicities will be performed at each clinic visit during treatment, at 30 days after the final nivolumab infusion or 14 days after decision to discontinue treatment (in the event of toxicities) and until 100 days after the final nivolumab infusion. Changes in spirometry values and PFTs will be assessed throughout the trial. Relapse rates will be assessed with staging CT scans at 3, 6, 12, 18 and 24 months post SBRT. An exploratory assessment will be made of the effect pre-treatment pulmonary function tests (PFTs) have on outcome measures.
Study Objectives	**Primary Objective:** • To assess the lung toxicity of nivolumab after stereotactic body radiotherapy (SBRT) for early stage NSCLC (T1-3 (≤6cm) N0 M0) **Secondary Objectives:** • To assess the overall safety of nivolumab after SBRT • To assess the tolerability of nivolumab after SBRT • To assess local, local-regional and distant disease relapse rates

- To assess the overall survival rate at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data available)

- To assess the disease free survival (DFS) rate at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data available)
- To measure health related quality of life (HRQoL)

Exploratory Objectives:

- To describe the relationship between lung function and the tolerability of adjuvant nivolumab following SBRT
- To assess relapse rates and survival rates in relation to tumour PD-L1 status
- To assess relapse rates and survival rates in relation to squamous versus non-squamous histology
- To assess tumour biology and immune function changes with treatment

Study Population

31 patients with pathologically proven NSCLC deemed amenable for radical treatment with SBRT

Inclusion Criteria

- Signed written informed consent
- ECOG Performance status (PS) 0-2
- Minimum of first 5 patients to be PS 0-1
- PS 2 patients to be enrolled only following recommendation by the Independent Data Monitoring Committee (IDMC) **(COMPLETED 2/10/2018)**
- Up to five PS2 patients can be enrolled and followed up for 3 months following the final fraction of radiotherapy at which stage an IDMC meeting is required to assess further PS2 patient enrolment.
- Patients with histological diagnosis of NSCLC, all histological sub-types are eligible
- Not suitable for surgery because of medical co-morbidity, lesion is technically inoperable or patient declines surgery after surgical assessment (or option of assessment)
- Single or synchronous primary NSCLC lesions tumour stage T1-3 (≤6cm) N0 M0 (UICC v.8) as determined by the local MDT based on minimum investigations of CT chest/abdomen within 8 weeks

and FDG-PET performed within 6 weeks of 1st fraction of SBRT. Where the radiological nodal status is equivocal then only eligible if possible nodal disease is subsequently confirmed as histologically negative with mediastinoscopy or endoscopic bronchial or oesophageal ultra-sound biopsy as necessary

- For synchronous tumours one lesion must have a histological diagnosis of NSCLC. For other lesions radiological diagnosis of NSCLC as determined by lung MDT.
- Metachronous (single) primary NSCLC lesions, tumour stage T1-3 (≤6cm) N0 M0 (UICC v.8) presenting after previous treatment of T1-3 (≤6cm) N0 M0 (UICC v.8) with surgery or SBRT are eligible for inclusion. Lung constraints must be able to feasibly achieved (according to dose constraints in 7.1.2).
- Tumour stage T1-3 termed as 'central' disease within 2cm of main airways and proximal bronchial tree, but not abutting these structures (ultra-central), are suitable for entry. Up to 5 patients with 'central' primary NSCLC can be enrolled and followed up for 3 months following their final fraction of radiotherapy at which stage an IDMC meeting is required to assess further 'central' primary NSCLC recruitment.

- Screening laboratory values must meet the following criteria prior to commencement of treatment:

  i) WBCs ≥ 2000/µL

  ii) Neutrophils ≥1500/µL

  iii) Platelets ≥ 100 X10^3/µL

  iv) Haemoglobin ≥ 9.0 g/dL

  v) Serum creatinine of ≤ 1.5 X ULN or creatinine clearance (CrCl)/glomerular filtration rate (GFR) > 40 mL/minute

  (using Cockcroft/Gault formula or as assessed by local practice)

  (1). Female CrCl= [(140- age in years) X weight in kg X 0.85) ÷ (72 X serum creatinine in mg/ dL)]

  (2). Male CrCl= [(140- age in years) X weight in kg X 1.00) ÷ (72 X serum creatinine in mg/ dL)]

  vi) AST ≤ 3 X ULN

  vii) ALT ≤ 3 X ULN

viii) Total bilirubin ≤ 1.5 X ULN (except subjects with Gilbert Syndrome, who must have total bilirubin < 50 µmol/L)

- No prior or foreseen neo-adjuvant or adjuvant chemotherapy is allowed
- Males and Females ≥18 years of age
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) in the screening period and within 24 hours prior to the start of study drug.
- Women must not be breastfeeding

Exclusion Criteria

- Any tumour that is not clinically definable on the treatment planning CT scan e.g. surrounded by consolidation or atelectasis
- Subjects with active or known autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of the first dose of study drug administration. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease
- Subjects with previous malignancies (except non-melanoma skin cancers, early stage NSCLC treated with surgery OR previous stereotactic body radiotherapy, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period
- Patient with known interstitial lung disease or active, non-infectious pneumonitis
- Previous conventional radical radiotherapy to the chest or mediastinum. Patients who have had

previous breast radiotherapy may be eligible at the discretion of the Chief Investigator. Patients who have previously received palliative dose radiotherapy to the chest may be considered if it is felt SBRT can be safely delivered. These cases must be discussed with the Chief Investigator

- Any serious or uncontrolled medical disorder or active infection that, in the opinion of the Investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive protocol therapy
- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug
- Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment
- Subjects who received prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or who have previously taken part in a randomized BMS clinical trial of nivolumab or ipilimumab
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBVs Ag) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic
- Patients with a positive HCV antibody but no detection of HCV RNA are eligible
- Patients who have received a live vaccine within 30 days prior to the first dose of trial treatment

- History of allergy to study drug components

Primary Endpoint

- Rate of grade ≥ 3 pneumonitis with adjuvant nivolumab after stereotactic body radiotherapy (SBRT) within 6 months of the final fraction of SBRT. 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 v. 4
- 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
- Overall survival (OS) rate of the 31 patients at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data mature and available)
- Disease Free Survival (DFS) rate of the 31 patients at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data mature and available)
- Estimation of the health related quality of life (HRQoL) score at each time point of analysis

Exploratory Endpoints

- Assessment of rates of toxicity within percentage of predicted FEV1 bands
- Assessment of rates of toxicity within percentage of predicted DLCO bands
- OS and DFS rates in PD-L1 expressers (≥ 1%) and non-expressers (< 1%)
- OS and DFS rates in squamous and non-squamous subgroups
- Analysis of research blood and biopsy samples

List of Abbreviations

ABC	Active Breathing Control
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
APC	Antigen Presenting Cell
AST	Aspartate Transaminase
ATP	Adenosine Triphosphate
BMS	Bristol-Myers Squibb
BUN	Blood Urea Nitrogen
CALGB	Cancer and Leukaemia Group B
CBCT	Cone Beam Computed Tomography
CD	Cluster of Differentiation
CI	Confidence Interval
CrCl	Creatinine Clearance
CRF	Case Report Form
CSS	Cancer Specific Survival
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour deoxyribonucleic acid
CTLA-4	Cytotoxic T-lymphocyte-associated-protein-4
CTV	Clinical Target Volume
CXR	Chest Radiograph
DC	Dendritic Cells
DFS	Disease Free Survival
DILI	Drug Induced Liver Injury
DLCO	Diffusing Capacity of the lung for Carbon Monoxide
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
DR	Distant Relapse
DVH	Dose-Volume Histogram
ECOG	Eastern Cooperative Oncology Group
EPL	Extended Path Length
ESR	Expedited Safety Report
EU	European Union
FDG-PET	Fludeoxyglucose-Positron Emission Tomography
FEV1	Forced Expiratory Volume in 1 second
FFPE	Formalin-fixed, paraffin embedded
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GTV	Gross Tumour Volume
Gy	Gray (unit)
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
irAE	Immune Related Adverse Event
ITV	Internal Target Volume
IUD	Intrauterine Device
LACE	Lung Adjuvant Cisplatin Evaluation

LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LINAC	Linear particle accelerator
LR	Local Relapse
LRR	Loco-regional Relapse
MDT	Multidisciplinary Team
MHC	Major Histocompatibility Complex
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NCI	National Cancer Institute
NHS	National Health Service
NK	Natural Killer cells
NSCLC	Non-Small Cell Lung Cancer
OAR	Organs at risk
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD-1	Programmed Death-1
PD-2	Programmed Death-2
PD-L1	Programmed Death-Ligand 1
PEFR	Peak Expiratory Flow Rate
PFTs	Pulmonary Function Tests
PIS	Patient Information Sheet
PK	Pharmacokinetics
PPK	Population Pharmacokinetics
PS	Performance Status
PTV	Planning Target Volume
q2w	Every 2 weeks
q4w	Every 4 weeks
RCC	Renal Cell Carcinoma
REC	Research Ethics Committee
RM-CTU	Royal Marsden Clinical Trial Unit
RNA	Ribonucleic acid
RR	Regional Relapse
RSI	Reference Safety Information
SAE	Serious Adverse Event
sAg	Surface antigen
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBRT	Stereotactic Body Radiotherapy
SFU	Safety Follow-Up Visit
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Event
Tregs	T regulatory cells
TSH	Thyroid Stimulating Hormone
UICC	Union for International Cancer Control
ULN	Upper Limit of Normal
USMs	Urgent Safety Measures
WBC	White Blood Cell
WOCBP	Women of childbearing potential

1. BACKGROUND & RATIONALE

1.1. *Background*

1.1.1. Early Stage Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC), which includes adenocarcinoma, squamous cell carcinoma and large cell carcinoma accounts for approximately 80-85% of all lung cancers. Only approximately 20% of these cases are diagnosed at an early stage.[1] Age and performance status are the two most important prognostic factors in early stage NSCLC.

The use of low dose CT screening programs can improve patient survival, as evidenced by the National Lung Screening Trial, by increasing the diagnosis of early stage NSCLC.[2] The incidence and prevalence of lung cancer in the elderly population has been steadily increasing, however the optimal treatment option for these patients remains in question.

Although gold standard treatment for stage I to IIIA disease remains to be lobectomy with mediastinal lymph node dissection or sampling, around 20% of such patients do not receive definitive surgery.[3] A minimally invasive thoracoscopic operation is an alternative approach to open lobectomy with less perisurgical morbidity.[4] Sublobar resections, wedge resections and segmental resections are frequently used where there is necessity to preserve healthy lung tissue and in patients with poor cardiorespiratory reserve, however these more limited procedures correspond with higher rates of local and distant recurrence.[5] Historically, patients deemed unsuitable to undergo a definitive operation or those who declined it were offered external beam radiotherapy, which offered inferior 5 year local control rates of between 40 and 70%.[6,7]

1.1.2. Stereotactic Body Radiation Therapy (SBRT)

More recently, stereotactic body radiotherapy (SBRT) that delivers focused, hypofractionated high dose radiotherapy has become the treatment of choice for inoperable early stage NSCLC where there is no evidence of nodal involvement. SBRT achieves superior tumour cell death to

conventional radiotherapy by delivering higher biologic-equivalent doses. SBRT can be delivered in up to 8 fractions with doses of between 6 and 20 gray (Gy) per fraction.

For inoperable patients, SBRT offers much improved local control compared to standard radiotherapy with rates of 85% to 100% across prospective and retrospective studies. Overall survival rates of between 40% and 80% at 3 years have been achieved with SBRT for patients with inoperable tumours.[8] Phase III trials comparing surgery with SBRT have proved difficult to recruit to. Despite this, a systemic review has shown equivalent local control and overall survival at one year between surgery and SBRT for stage I NSCLC.[9] A subsequent meta-analysis in 2014 showed unadjusted overall survival rate to be higher for the surgically resected patients at 1, 3 and 5 years (92.5%, 77.9% and 66.1%) compared to SBRT (83.4%, 56.6% and 41.2%). However, when adjusted for age and patient eligibility for surgery there was no significant difference in overall survival between the treatments.[10]

A recent retrospective study has compared SBRT with thoracoscopic sublobar lung resection in an elderly population with a propensity matched comparative analysis.[11] Overall survival (OS) and cancer specific survival (CSS) were longer in patients undergoing sublobar lung resections compared to SBRT (OS HR: 2.11 95% CI 1.67 to 2.68 p<0.001 CSS HR: 1.47 95% CI 0.95 to 2.28 p 0.08). The matched cohort accounted for variables including age, sex, race, tumour size, stage, histology and co-morbidities. Overall survival but not cancer specific survival was significantly longer with surgery when the tumour was less than 2cm diameter (OS HR: 1.80 (1.33 to 2.43) p<0.001 CSS HR: 1.32 (0.77 to 2.26) p 0.32). However, for all tumours less than 5cm even in the matched cohort both OS and CSS were significantly longer in patients undergoing surgery rather than SBRT (OS HR: 1.92 (1.62 to 2.26) p<0.001 CSS HR: 2.10 (1.52 to 2.89) p<0.001). The estimated cancer specific survival at 3 years was 80.0% for SBRT and 90.3% for thoracoscopic resection.[11]

Despite the advantages in morbidity with the use of SBRT over surgery, longer-term outcomes are likely to be less good. This is particularly important for younger patients considering SBRT over surgery. One significant limitation of SBRT is the lack of pathological nodal staging, which has the capacity to upstage surgically resected tumours that may benefit from adjuvant chemotherapy.
SBRT to primary NSCLC within 2cm of the central airways (designated 'central' tumours) has reported higher grade ≥3 toxicity rates than peripheral tumours. Grade 3 toxicities have been

reported to range from 3-46%.[12,13] Concerns are primarily regarding proximity to mediastinal structures including proximal airways but also heart, pericardium and large blood vessels where hypofractionated radiation doses may lead to severe toxicity which may lead to life-threatening consequences.[14] Chadhuri et al reported retrospective data on patients with peripheral, central and ultra-central lung tumours and did not find significantly different grade ≥2 treatment related toxicities (0%).[15] However, a structured literature review in 2013 found treatment-related mortality to be 2.3% in patients with SBRT to central lung tumours. A retrospective review of 107 patients, 61 central and 46 ultra-central, defined as where the ITV directly abutted the proximal bronchial tree reported grade 5 toxicity rates of 3.5% with central tumours and 2.2% with ultra-central tumours, consistent with other published literature.[12] Tekatli et al reported on outcomes of patients receiving SBRT to ultra-central located NSCLC. Ultra-central disease was defined non-small cell lung cancers with planning target volumes overalapping the trachea or main bronchi. This series also reported grade 5 toxicity in 10 patients (21%) with 7 (15%) due to fatal pulmonary haemorrhage. [16]

Dose fractionation regimes vary widely however with up to 20Gy per fraction in some studies. There are no published prospective trials with clear standardised techniques in centrally located NSCLC tumours. Previous trials have adopted a conservative 8 fraction regime in respect to tumours within 2cm of the proximal bronchial tree but not abutting the structure. The UK SABR consortium has adopted this same approach and central lung SBRT is now routine practice. The approach to these ultra-central tumours is unclear is still being assessed.[17]

SBRT is a well-tolerated procedure with rates of pneumonitis consistently less than 10%. In a large multi-centre study of 483 patients, the rate of pneumonitis at grade 2 or above was only 7% and there was no correlation between pre-treatment pulmonary function tests (PFTs) and rates of pneumonitis. [18]

Multiple primary NSCLC, either synchronous or metachronous, is a well-described presentation in up to 10% of lung cancer patients.[19] Multiple case series have reported low rates of grade 3 toxicity in patients treated with synchronous SBRT treatment fields.[19,20] However relatively little data exists in the literature for toxicity. Retrospective analysis suggests improved outcomes for patients with metachronous primary disease over synchronous primary disease.[20] SBRT to multiple tumours at different time points is a safe and well tolerated treatment and will become more widespread as lung cancer screening programmes are implemented. The UK SABR Consortium has offered guidance on treating multiple lung lesions, in which standard lung dose

constraints are applied, with SBRT. This guidance also extends to patients with early stage lung cancers for whom surgery is not feasible due to poor lung function.[17]

1.1.3. Role of Adjuvant Systemic Therapy

Adjuvant chemotherapy is currently offered as standard treatment for patients with completely resected stage II or III NSCLC. The Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative group published a meta-analysis of five adjuvant cisplatin-based trials that demonstrated a 5.3% improvement in survival at 5 years with adjuvant chemotherapy. The evidence for stage IB disease was not significant and there was a tendency towards harm for adjuvant chemotherapy in stage IA disease.[13] The prospective CALGB study suggested that patients with stage IB disease whose tumours were ≥ 4cm diameter benefited from adjuvant chemotherapy also.[14] Adjuvant chemotherapy is currently offered to stage II and stage III disease and to stage IB disease with T ≥ 4cm. Although SBRT is able to treat lesions up to a maximum diameter of 5cm, currently there is no recommended adjuvant treatment for patients post SBRT.

The TNM (UICC V8) staging system classifies synchronous lung tumours arising in the same lobe as T3 and synchronous ipsilateral lesions in different lobes as T4. In addition M1a describes patients with synchronous bilateral lesions. These patients would be eligible for combined radical radiotherapy and systemic therapy. SBRT to patients with synchronous and metachronous lesions show excellent local control rates and 2 year survival rates and presents a potential paradigm shift in the treatment of these specific presentations of T3 and T4 tumours.[19] Synchronous and metachronous primary NSCLC patients remain a potential population in whom adjuvant systemic therapy may benefit.

1.1.4. Immune Regulation and Anti-PD1 in NSCLC

Cancer is an inflammatory disease in which the innate and adaptive immune systems play a central role in the regulation of cancer growth. Escape from immune destruction is a key feature that allows cancer cells to survive and proliferate. In order to do this, tumour cells acquire the ability to promote immunosuppressive mechanisms to avoid recognition and destruction.

Immunotherapy attempts to disinhibit the immune system by modulating regulatory checkpoints[23].

The programmed death-1 (PD-1) receptor is expressed on several immune cells including CD4 and CD8 lymphocytes, B lymphocytes, natural killer (NK) cells and T regulatory cells (Tregs)[24]. One of the ligands for PD-1, PD-L1 is expressed on T and B lymphocytes, dendritic cells and macrophages[25]. PD-L1 interaction with PD-1 on T cells leads to downregulation of T cell effector function. PD-L1 is upregulated in a range of solid tumours including in around 25-60% of NSCLC[26]. Overexpression of PD-L1 in resected NSCLC is associated with poorer outcomes. A second ligand, PD-L2 is expressed less extensively and predominantly limited to macrophages and dendritic cells[28]. The increased interaction between PD-1 and its ligands leads to a downregulation of T cell activation, proliferation and therefore reduced T-cell mediated anti-tumour response.

Nivolumab is a genetically engineered, fully human immunoglobulin G4 (IgG4) monoclonal antibody that is specific for human PD-1[29,30]. Nivolumab binds to PD-1 with high affinity and therefore blocks interaction with its ligands PD-L1 and PD-L2 and hence has the potential to activate T cell anti-tumour responses[31]. PD-L1 expression on tumour cells has been postulated as a biomarker for predicting response to PD-1/PD-L1 inhibition[32].

There is substantial data on the efficacy and safety of monotherapy with nivolumab in advanced NSCLC from Phase 1 (CA209-003)[33], 2 (CA209063/CheckMate 063)[34] and 3 (CA209017[35], CA209057[32]) studies. CA209003 showed an objective response rate (ORR) of 24.3% with 3mg/kg nivolumab and 20.3% with 10mg/kg administered every 2 weeks (q2w). The estimated median duration of response for NSCLC patients was 74 weeks with 3mg/kg nivolumab and 83.1 weeks with 10mg/kg[33].

Nivolumab was FDA approved in 2015 to treat metastatic squamous NSCLC based on the results of the data from the phase II study, CheckMate 063 and the phase III study CheckMate 017[34,35]. CheckMate 017 randomly assigned 272 squamous cell NSCLC patients to receive nivolumab at a dose of 3mg/kg every two weeks or docetaxel (75mg/kg) every 3 weeks. The objective response rate was significantly higher in the nivolumab arm (20% vs. 9% p=0.008). Although the median progression free survival (PFS) improvement was only modest (3.5 months v 2.8 months), those

patients that did respond tended to have a prolonged response and hence PFS rate at 1 year was 21% in the nivolumab group compared to only 6% in the docetaxel group. The median OS was 9.2 months with nivolumab versus 6 months with docetaxel. The overall survival (OS) rate at 1- and 2- years was 42% and 23% respectively in the nivolumab arm and 24% and 8% respectively in the docetaxel arm.[28,29] A retrospective analysis of PD-L1 expression on pre-treatment biopsy samples failed to stratify for response or prognosis[35].

CheckMate 057 study randomised 582 patients with non-squamous NSCLC population post platinum doublet chemotherapy to nivolumab (3mg/kg q2w) or docetaxel[32]. The confirmed objective response rate was 19% with nivolumab and 12% with docetaxel (p=0.02). Median PFS did not favour nivolumab although PFS rate at 1 year was higher with nivolumab (19 % vs. 8%), which again points to the enduring response of responders. Median OS was 12.2 months versus 9.5 months with nivolumab and docetaxel respectively; the 1- and 2- year OS rates were 51% and 29%, respectively for nivolumab, and 29% and 16%, respectively, for docetaxel[36]. In contrast to the squamous patients, higher levels of PD-L1 were associated with a greater magnitude of benefit in this patient population[32,36].

In September 2016, the FDA licence for nivolumab was changed to a flat dose of 240mg. [30]Flat dosing offers several advantages over body weight normalized dosing, including reduced potential for dosing errors and shortened dosage preparation time.

The nivolumab dose of 240 mg q2w was selected based on clinical data and modeling and simulation approaches using population pharmacokinetics (PPK) and exposure-response analyses of data from studies in multiple tumour types (melanoma, NSCLC and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used. PPK analyses have shown that the pharmacokinetics (PK) of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than the proportional increase in weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK.

In a dataset of 1544 patients with melanoma, NSCLC and RCC, the median weight was 77 kg (35 kg - 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg subject, nivolumab 240 mg q2w was selected for further studies. To predict relevant summary exposures of nivolumab 240 mg q2w, the PPK model was used to simulate virtual trials, each consisting of two arms, nivolumab 3 mg/kg q2w and 240 mg q2w. In the simulations, the simulated patient populations consisted of subjects randomly sampled from aforementioned pooled database of cancer patients. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg q2w are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg q2w.

In early stage disease (Stage IB – IIIA), the on-going ANVIL trial is a phase 3 open label randomised study of nivolumab versus observation post adjuvant chemotherapy after surgery (NCT02595944; CA209427). In this study nivolumab is administered at 240mg q2w for up to 1 year. As reliable biomarkers have not been established in the adjuvant setting this trial is recruiting regardless of PD-L1 status but will perform planned subgroup analysis in various PD-L1 patterns.

Nivolumab has a more tolerable safety profile compared to chemotherapy. Pooled analyses from CheckMates 017[35] and 057[15] with a minimum of 2 years follow-up, showed that treatment-related adverse events (AEs) were reported in fewer nivolumab-treated patients versus docetaxel-treated patients (any grade: 68% vs. 88%; grade 3–4: 10% vs. 55%) and less frequently led to discontinuation (any grade: 6% vs. 13%; grade 3–4: 4% vs. 7%)[36].

Most treatment-related select AEs, that is AEs with a potential immunologic cause that may require management through immune-modulating medications such as corticosteroids, were uncommon, and they rarely led to discontinuation [36]. Serious adverse events were also less frequent with nivolumab compared to docetaxel (7% vs. 20% of patients had events of any grade, and 5% vs. 18% had events of grade 3 or 4)[15].

1.1.5. Combining Anti-PD-1 with Radiotherapy

The development and progression of cancer is a result of the balance between tumour cells and the immune system. The innate immune system senses tissue changes during neoplastic transformation, which leads to cytotoxic cell death by macrophages. The cytotoxic action leads to release of tumour-associated antigens which are loaded into the major histocompatibility complex on dendritic cells and recognised by CD4 and CD8 T cells. [38] The activation of tumour-specific T cells leads to the elimination of further tumour cells. [38] However, where elimination is incomplete surviving tumour cells generate mutations due to genetic instability and escape destruction. Eventual resistance to immune rejection ultimately leads to tumour progression that becomes a clinically detectable mass. Despite the loss of control over cell proliferation the immune system continues to play a role in slowing tumour progression and in doing so generates further neoantigens that can be recognised by T cells. 40

Cell death has recently been established as an efficient process to transfer tumour antigens to dendritic cells. Dendritic cells (DC) process the antigens into peptides that are loaded into the major histocompatibility complex (MHC) class 1 and 2 molecules and these are subsequently recognised by CD8 and CD4 T cells. [3]8 Three key molecular signals have recently been established that are necessary to achieve an immunological cell death. [41] The currently known steps are cell surface translocation of calreticulin, extracellular release of high-mobility group protein B1 and release of ATP. [42-45]

Ionising radiation leads to the release of proinflammatory cytokines including interleukin 1β, tumour necrosis α and type 1 and 2 interferons. [37] Exposure to ionizing radiation results in a high rate of tumour cell destruction and subsequent release of tumour neoantigens which prime the adaptive immune system for immunological cell death and hence holds the potential to act as an in situ vaccine. Also, tumour cells that receive sublethal doses of radiation undergo phenotypic changes such as increased expression of MHC class 1 molecules that enhances their susceptibility to immunological cell death. [4]6

Radiotherapy, by causing release of tumour neoantigens and pro-inflammatory sequelae could potentially engage both the innate and adaptive arms of the immune system. The generation of tumour-specific T cells would provide immune memory which may explain radiotherapy's ability to improve final outcomes for irradiated patients. [47]

The rationale for combining radiotherapy with immunotherapy is based on this concept that the radiotherapy can be immune priming. There is preclinical evidence to support this as administration of the DC growth factor, Flt3-ligand to mice following radiotherapy led to the induction of antitumour T cells that were able to inhibit metastases in a lung carcinoma model. The effect of combination therapy was greater than with either therapy alone. [48]

In another preclinical study, the use of checkpoint inhibition with an antibody that targets the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) was not effective as a single agent in the relatively poorly immunogenic tumours that mimic the clinical setting. However, when combined with radiotherapy, anti-CTLA-4 could inhibit early lung metastases and elicit response in bulky tumours outside of the irradiated field in mice models of mammary and colorectal cancer.[42,43]

Similarly, in a mice model of glioblastoma multiforme SBRT when combined with blockade of PD-1 produced a pronounced treatment effect. Median survival for the combination therapy was 53 days, compared to 25 days in the control group and 27 days and 28 days for anti-PD-1 therapy or SBRT, respectively. Immunological data from cadaveric samples at 21 days showed increased tumour infiltration by cytotoxic T cells and decreased regulatory T cells in the combination treatment group compared to either single modality arm[51].

The optimal radiation regime to convert tumour to an in situ vaccine is not known. In a syngeneic mouse model of cancer the combination of anti-CTLA-4 with a single dose of 20 Gy had little effect but complete regression in the majority of irradiated tumours and abscopal effects were seen when a hypofractionated regimen of 8 Gy in three fractions was used. [50]

The addition of immunotherapy to radiotherapy may overcome the dominant immunosuppressive pathways driven by tumour cells. This may lead to enhanced immunogenic cell death of tumour cells both locally and at distant micrometastatic sites that otherwise may emerge from dormancy later in the host's life as relapsed disease.

1.2. *Study and Treatment Rationale*

1.2.1. Study Rationale

Currently, no adjuvant systemic treatment post SBRT is offered to patients regardless of size or stage of the tumour in NSCLC. Recently a feasibility study assessing ability to deliver platinum doublet chemotherapy post SBRT was closed early due to poor recruitment. One explanation for this is the inherent frailty of most patients that undergo SBRT rather than surgical resection and the expectation that the toxicity of chemotherapy would outweigh any potential benefit. In this more elderly, frailer population overall survival and cancer-specific survival appear inferior to wedge resection. This is in part likely due to the lack of pathological nodal staging in the majority of patients undergoing SBRT. 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. If tolerated, then a subsequent phase III placebo controlled trial could investigate the effect on outcomes of combining nivolumab with SBRT for early stage NSCLC.

The primary endpoint is rate of grade 3 pneumonitis within 6 months of the final fraction of SBRT. There is already a large evidence base regarding the safety of nivolumab in NSCLC.[32-36] The overall incidence of grade 3-4 immune-mediated pneumonitis observed with nivolumab in clinical trials is low,[35,52] Immune-related adverse events can occur at any time during treatment and for several months after the final dose. However, the median time to the appearance of pneumonitis is 3.5 months (range 0.0-19.6).[45,52] SBRT can cause an early acute radiation pneumonitis which generally occurs within the first 6 months. Clinical symptoms of acute radiation-induced lung injury develop at approximately 3 to 6 months after treatment.[53] In this study we are 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.

1.2.2. Dosing Schedule Rationale

Nivolumab will be administered intravenously at a flat dose of 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 (a minimum of 1 year of treatment if no delays are encountered).

(Patients who were eligible and began treatment as per STILE protocol V1.1 (STILE_CCR4644_Protocol_v1 1_22Aug2017) and are currently on treatment cycle 14 or later will continue on Nivolumab 240mg Q2W to complete a total of 26 cycles).

There is no consensus agreement as to the optimal duration of treatment for immunotherapy in the adjuvant setting. The on-going registrational study ANVIL, CA209427 which compares nivolumab versus observation post surgery and adjuvant chemotherapy in early stage NSCLC, is investigating nivolumab treatment for 1 year.

In phase 1 studies, the spectrum, frequency, and severity of nivolumab-related AEs were generally similar across all dose levels tested, although the 10mg/kg dose level had numerically higher Grades 3-4 drug-related serious adverse events (SAEs) and AEs leading to discontinuation. Based upon the totality of the safety, efficacy, and exposure-response data, a dose of 3 mg/kg every 2 weeks was selected as the dose anticipated to achieve an appropriate balance of efficacy and risk. Subsequent review of the pharmacokinetics and dose/exposure-responses analyses has confirmed the comparability of a flat dose of 240 mg every two weeks with 3 mg/kg every two weeks.

Recently the Federal Drug administration and European Medicines Agency have licensed the use of Nivolumab 480mg Q4W administration. A recent analysis evaluated PK exposure and clinical safety of nivolumab 480 mg Q4W compared with 240 mg Q2W and 3 mg/kg Q2W dosing schedules used quantitative clinical pharmacology approaches and pooled safety data from four phase III clinical trials (CheckMate 066, 025, 057, and 017). A flat dose of 240 mg Q2W was previously approved by the FDA based on modeled comparisons of exposure, and bridging of efficacy and safety data demonstrating comparability with 3 mg/kg Q2W. More recently, a less frequent flat dose of 480 mg Q4W was approved as an additional option for several monotherapy indications, including NSCLC, based on a similar modeling approach together with clinical safety data. Patients who transition from 240mg to 480mg Nivolumab experienced 14.8% of treatment related side effects, although this is considered to be comparable with what would be expected

for patients who continued with the Q2W dosing schedule.[54] Checkmate 384 has reported similar findings offering support for the use of nivolumab Q4W dosing as a more convenient option for patients with similar efficacy and safety [55]

Although there is scientific rationale for commencing nivolumab prior to the first fraction of SBRT, there is the potential for treatment related toxicity to delay or even contraindicate SBRT. On this basis, the first dose of nivolumab will be administered within 24 hours after the final fraction of SBRT (typically on the same day) to maximize the synergistic relationship between radiotherapy and immunotherapy but without risking the patient from completing their potentially curative treatment.

Treatment related toxicity can be seen at all time points for patients receiving immunotherapy. Median onset of immune related adverse events with nivolumab is between 6 to 14 weeks from first dose.45 In the pooled analysis from second line treatment of nivolumab in advanced NSCLC the median onset of immune related adverse events was between 4.9 and 30.3 weeks.29

1.2.3. Rationale for Assessments of Lung Function

Current guidelines for SBRT do not specify exclusion pulmonary function criteria. Severely reduced FEV1 and DLCO (<40% predicted) are common reasons for medical inoperability leading to the choice of SBRT. In a large prospective study of patients undergoing SBRT, poor baseline PFT was not predictive of toxicity including pneumonitis. At the 2 year follow up, the mean decline in percentage of predicted forced expiratory volume in one second (FEV1) and diffusion capacity of carbon monoxide (DLCO) were only 5.8% and 6.3% respectively.[47] Focal SBRT is a well-tolerated procedure and acute complications are generally transient. Symptomatic radiation pneumonitis has been reported at rates of 4-25% of patients.[48]

Pneumonitis with nivolumab may be of particular concern for patients with poor lung reserve. Drug induced pneumonitis is reported at 6% in lung cancer patients receiving nivolumab and at 2% with grade 3-4 toxicity.49 Of note, such rates are similar or lower to other drugs used in NSCLC including docetaxel for which no PFT restrictions occur. In this study, frequent assessment of spirometry values may help to predict patients that are developing subclinical pneumonitis and prompt for early intervention.

1.3. *Research Hypotheses*

- Nivolumab following SBRT for stage I-II NSCLC (T3 (≤6cm) N0 M0 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%

2. STUDY OBJECTIVES

2.1. *Primary Objective:*

- To assess the lung toxicity of nivolumab after stereotactic body radiotherapy (SBRT) for early stage NSCLC (T1-3 (≤6cm) N0 M0).

2.2. *Secondary Objectives:*

- To assess the overall safety of nivolumab after SBRT
- To assess the tolerability of nivolumab after SBRT
- To assess local, local-regional and distant disease relapse rates
- 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)
- 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)
- To measure health related quality of life (HRQoL)

2.3. *Exploratory Objectives:*

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

3. *EVALUATION OF OUTCOME*

3.1. *Primary Endpoint*

- Rate of grade ≥ 3 pneumonitis with nivolumab after stereotactic body radiotherapy (SBRT) within 6 months of the final fraction of SBRT. A rate that exceeds 20% will be deemed unacceptable and will lead to a rejection of the null hypothesis. Further details are provided in the sample size justification (Section 9.1).

3.2. *Secondary Endpoints*

- Frequency of treatment related adverse events of all grades and grade ≥ 3 as per CTCAE v. 4
- 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
- Overall survival rate (OS) of the 31 patients at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data mature and available)
- Disease Free Survival (DFS) rate of the 31 patients at 6, 12 and 24 months (and up to 5 years at 36, 48 and 60 months if data mature and available)
- Estimation of the health related quality of life (HRQoL) score at each time point of analysis

3.3. *Exploratory Endpoints*

- Assessment of rates of toxicity within percentage of predicted FEV1 bands
- Assessment of rates of toxicity within percentage of predicted DLCO bands
- OS and DFS rates in PD-L1 expressers (≥ 1%) and non-expressers (< 1%)
- OS and DFS rates in squamous and non-squamous subgroups
- Analysis of research blood and biopsy samples

4. STUDY DESIGN

4.1. *Study Plan*

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. The study will recruit 31 patients

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 .

Subjects will receive nivolumab as per the treatment schedule (Section 4.2) unless any withdrawal criteria (Section 4.5) are met. The first nivolumab infusion will be given after the final fraction of SBRT, within 24 hours and generally on the same day. Clinical follow up and investigations are as detailed in the schedule of assessment (Section 6.11).

The first 5 patients to enroll must have Eastern Co-operative Oncology Group (ECOG) performance status < 2 at the time of first dose of investigational medical product (IMP). An Independent Data Monitoring Committee (IDMC) will meet when the first 5 patients have reached 3 months follow up from their final fraction of radiotherapy or have withdrawn consent to follow-up. Patients that have enrolled but did not receive IMP will be replaced. The IDMC, if satisfied with the safety data from the initial 5 patients, may recommend escalation to include recruitment of patients with ECOG performance status of 2. Further patients of PS <2 may enroll while awaiting the outcome of the IDMC meeting.

The IDMC will perform a further safety review when the first 5 patients enrolled with ECOG performance status 2 have reached 3 months follow up from their final fraction of radiotherapy or have withdrawn consent to follow-up. Patients that have enrolled but did not receive IMP will be replaced. Further patients with ECOG performance statsus 2 will *not* be able to enroll unless recommendation is given by the IDMC. In the event that 5 PS2 patients have not enrolled by the point that the 15th recruited patient has reached 3 months follow up, then there will be a further mandated IDMC meeting to assess safety data from the study. Patients may continue to enroll

while awaiting the outcome of these IDMC meetings. A further IDMC review is required after enrolment of 5 'central' primary NSCLC have been enrolled and followed up for 3 months following their final fraction of radiotherapy.

4.2. *Treatment Schedule*

4.2.1. Stereotactic Body Radiotherapy

Radiotherapy planning and delivery will be carried out as detailed in section 7.1. Patients will receive a total of 54 Gy if delivered in 3 fractions, 55 Gy if delivered in 5 fractions or 60Gy if delivered in 8 fractions.

The time period within which all SBRT fractions should be delivered is as follows:

- 3 fractions – 2 weeks
- 5 fractions – 2 weeks
- 8 fractions – 3 weeks.

4.2.2. Investigational Medicinal Product (IMP)

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 (See Section 4.5).

(Patients who were eligible and began treatment as per STILE protocol V1.1 (STILE_CCR4644_Protocol_v1 1_22Aug2017) and are currently on treatment cycle 14 or later will continue on Nivolumab 240mg Q2W to complete a total of 26 cycles. Patients enrolled within the trial who have not yet received cycle 14 can be considered for Nivolumab 480mg Q4W for a further 7 cycles from cycle 14)

No dose reductions of nivolumab are allowed.

All subjects will receive the first infusion of nivolumab within 24 hours of completing their final SBRT fraction regardless of whether they are receiving 3, 5 or 8 fractions. The infusion of nivolumab will be after the final fraction of radiotherapy.

4.3. *Study Schema*

Figure 1: Overall trial schema

4.4. *Study Withdrawal Criteria*

Subjects may withdraw consent at any time, for any reason or discontinue treatment. In this study, a subject may discontinue from study treatment but continue in trial follow up, provided they have not withdrawn consent. If a patient discontinues treatment for any reason then he/she will not be allowed to begin treatment within the trial again. This is distinct from treatment delays as required due to adverse events. A subject that has discontinued study treatment should be encouraged to continue to be monitored within the trial.

If a patient withdraws consent for further follow up clarification should be sought to as to whether they no longer wish to attend trial specific follow up visits or wish to stop

contributing further data to the study. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent (e.g. death records). The investigator must document this agreement regarding withdrawal of full consent as well as discuss appropriate procedures for withdrawal from the study. If the patient withdraws from the study before their tissue has been analysed, and requests that their tissue is not used in the study, this will be transferred to an appropriate biobank or destroyed as per the patient's wishes.

In addition, a patient may be withdrawn from the study by the investigator if enrollment into the study is inappropriate, the trial plan is violated or for administrative reasons and/or other safety reasons.

4.5. *Study Drug Discontinuation Criteria*

Criteria for discontinuation of treatment are as follows:

- The subject or legal representative (e.g. power of attorney for welfare) withdraws consent
- Disease relapse as determined by agreement of the local MDT
- Inter-current illness (including second malignancy) that, in the opinion of the Investigator warrants the patient's withdrawal from study treatment
- The subject has a positive pregnancy test or is pregnant
- Unacceptable adverse events (see section 4.6)
- The subject completes the proposed treatment course of Nivolumab.

4.6. *Adverse events leading to discontinuation of study treatment*

Assessment of toxicities will commence from day of consent (baseline) up to and including 100 days from the last dose of nivolumab or longer if clinically relevant. The National Cancer Institute (NCI) common toxicity criteria (CTCAE version 4.0) will be used to grade all toxicities related to drug and SBRT. Adverse events considered probably or definitely related to the combination of SBRT and nivolumab that should lead to study drug discontinuation are as follows:

- Grade 3 bronchopulmonary haemorrhage
- Grade ≥ 2 pulmonary fistula
- Grade ≥ 2 oesophageal perforation

- Grade ≥ 3 febrile neutropaenia
- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypophysitis, adrenal insufficiency, hypersensitivity reaction or infusion reaction
- Any other Grade 3 non-skin, drug-related adverse event lasting > 7 days with the exception below:
    - **Exception:** Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding
- Grade 3 drug related serum creatinine elevation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT > 5 x ULN
    - Total bilirubin > 3 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 3 immune-mediated adverse reaction that recurs
- Symptoms or signs of Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
- Any other life-threatening immune-mediated adverse reaction
- Any Grade 4 drug-related adverse event or laboratory abnormality, with the following exceptions, which do not require discontinuation:
    - **Exception:** Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset

- **Exception:** Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- **Exception:** Grade 4 lymphopaenia or leucopaenia

- Any dosing interruption lasting > 12 weeks with the following exceptions:
  - Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g. elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should restart nivolumab within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

4.7. *Follow-Up*

4.7.1. Safety Follow-Up

All subjects will be followed up at a minimum of 30 days after completion of their last dose of nivolumab or 14 days +/- 3 days after the decision to discontinue treatment (if beyond 30 days since their last dose of nivolumab). In the event that the patient has relapsed or is diagnosed with a second malignancy then this visit will be prior to the initiation of any new anti-cancer treatment.

4.7.2. Follow-Up Post Discontinuation of Treatment

Subjects that have discontinued treatment for any reason other than withdrawal of consent will be followed up as per the follow-up phase protocol (See Section 4.7.3).

4.7.3. Follow-Up Phase

Subjects will be assessed every 3 months from the final fraction of radiotherapy in the first 18 months and then at a six month interval to 24 months to determine disease status. Survival data and disease status will be available on patient medical notes after 24 months to be collected under unscheduled visits. For patients that are still receiving nivolumab, this review will be combined with the appropriate treatment visit. AEs that occur within 100 days of the last dose of nivolumab will be recorded in the case report form (CRF). After this time, any unresolved adverse events should be followed up as clinically indicated. Where clinically indicated, AEs that occur after 100

days from the last dose of nivolumab may be recorded in the CRF. Patients that have relapsed or who have discontinued nivolumab for any reason will continue to be followed up as per the schedule, provided consent has not been withdrawn, to allow documentation of secondary endpoints. In the event of local or national restrictions, such as those seen in a pandemic, some flexibility should be expected. Telephone consultations can be conducted via telephone clinics in patients who have discontinued Nivolumab. Physical assessments and investigations will be carried out as is deemed clinically applicable and necessary to ensure safety of patients both from the risk of infections and from a Nivolumab perspective.

4.7.4. Study Termination

The end date of the study is deemed to be the date of last data capture. The study will terminate when the last patient has completed their final follow up. Criteria for early termination of the trial are as follows:

- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to patients
- At the recommendation of the Independent Data Monitoring Committee (IDMC)
- Quality or quantity of data recording is inaccurate
- Poor adherence to protocol and regulatory requirements
- Plans to modify or discontinue the study drug

4.8. *Independent Data Monitoring Committee (IDMC)*

The Independent Data Monitoring Committee (IDMC) will be set-up to monitor the safety data from the trial and to authorize the escalation to recruitment of patients with ECOG PS 2. As a minimum the IDMC will include one consultant medical oncologist, one consultant clinical oncologist and a senior statistician.

The IDMC will meet when the first 5 patients have reached 3 months follow up from their final fraction of radiotherapy or have withdrawn consent to follow-up. Patients that have enrolled but did not receive IMP will be replaced. The IDMC, if satisfied with the safety data from the initial 5 patients, may recommend escalation to include recruitment of patients with ECOG performance status of 2. Further patients of PS <2 may enroll while awaiting the outcome of the IDMC decision.

The IDMC will perform a further safety review when the first 5 patients enrolled with ECOG performance status 2 have reached 3 months follow up from their final fraction of radiotherapy or have withdrawn consent to follow-up. Patients that have enrolled but did not receive IMP will be replaced. Further patients with ECOG performance status 2 will *not* be able to enroll 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. Patients may continue to enroll while awaiting the outcome of this IDMC meeting.

Once 5 patients with central disease have enrolled an IDMC review will occur once they have reached 3 months of follow-up or have withdrawn consent to follow-up. Patients that have enrolled but did not receive IMP will be replaced.

In the event that 5 'central disease' patients have not enrolled by the point that a further 15 patients have enrolled since the previous IDMC meeting, 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. Patients may continue to enroll while awaiting the outcome of this IDMC meeting.

In addition, specific radiotherapy associated toxicities, which if seen at any point in the trial should lead to a suspension of recruitment until review by the IDMC. Patients already enrolled will be permitted to continue on trial treatment pending the IDMC review. The specific toxicities are as follows:

- Grade 3 bronchopulmonary haemorrhage
- Grade 2 pulmonary fistula
- Grade 2 oesophageal perforation

At the discretion of the IDMC, further safety review points may be scheduled. The terms of the IDMC will be defined in a charter.

5. STUDY POPULATION

5.1. *Inclusion Criteria*

5.1.1. Signed Written Informed Consent

- Subjects must have signed and dated a Research Ethics Committee (REC) approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care
- Subjects must be willing and able to comply with scheduled visits, treatment schedule, and laboratory tests

5.1.2. Target Population

- ECOG Performance status (PS) 0-2
    - Minimum of first 5 patients to be PS 0-1
    - PS 2 patients to be enrolled only following recommendation by the Independent Data Monitoring Committee (IDMC) **(COMPLETED 2/10/2018)**
    - Up to five PS2 patients can be enrolled and followed up for 3 months following their final fraction of radiotherapy at which stage an IDMC meeting is required to assess further PS2 patient enrolment.

- Patients with histological diagnosis of NSCLC, all histological sub-types are eligible
- Not suitable for surgery because of medical co-morbidity, lesion is technically inoperable or patient declines surgery after surgical assessment (or option of assessment).
- Single or synchronous /metachronous primary NSCLC lesions, tumour stage T1-3 (≤6cm), N0 M0 (UICC v.8) as determined by the local MDT based on minimum investigations of CT chest/abdomen within 8 weeks and FDG-PET within 6 weeks of 1st fraction of SBRT. Where the radiological nodal status is equivocal then only eligible if possible nodal disease is subsequently confirmed as pathologically negative with mediastinoscopy or endoscopic bronchial or oesophageal ultra-sound biopsy as necessary.

  In light of the COVID-19 pandemic, a CT chest alone without an abdominal component within 8 weeks of first SBRT fraction is sufficient as long as PET-CT

imaging within 6 weeks has been completed. This imaging amendment will be reviewed at the next IDMC meeting after 15 patients have been enrolled, received at least 1 dose of IMP and completed 3 months of follow-up when an assessment of the pandemic restrictions can be made.

- For synchronous tumours one lesion must have a histological diagnosis of NSCLC. For the other lesion a radiological diagnosis of NSCLC as determined by lung MDT is sufficient. (Upon diagnosis of metachronous primary NSCLC these lesions require biopsy for trial entry)
- Metachronous (single) primary NSCLC lesions, tumour stage T1-3 (≤6cm) N0 M0 (UICC v.8) presenting after previous treatment of T1-3(≤6cm) N0 M0 (UICC v.8) with surgery or SBRT are eligible for inclusion. Lung constraints must be able to feasibly achieved (according to dose constraints in 7.1.2
- Tumour stage T1-3 termed as 'central' disease within 2cm of main airways and proximal bronchial tree, but not abutting these structures (ultra-central), are suitable for entry. Up to 5 patients with 'central' primary NSCLC (up to 2 lesions) can be enrolled and followed up for 3 months following their final fraction of radiotherapy at which stage an IDMC meeting is required to assess further 'central' primary NSCLC recruitment
- Screening laboratory values must meet the following criteria prior to commencement of treatment:

  i) WBCs ≥ 2000/μL

  ii) Neutrophils ≥1500/μL

  iii) Platelets ≥ 100 $X10^3$/μL

  iv) Haemoglobin ≥ 9.0 g/dL

  v) Serum creatinine of ≤ 1.5 X ULN or creatinine clearance (CrCl)/glomerular filtration rate (GFR) > 40 mL/minute

  (using Cockcroft/Gault formula or as assessed by local practice)

  (1). Female CrCl= [(140- age in years) X weight in kg X 0.85) ÷ (72 X serum creatinine in mg/ dL)]

  (2). Male CrCl= [(140- age in years) X weight in kg X 1.00) ÷ (72 X serum creatinine in mg/ dL)]

  vi) AST ≤ 3 X ULN

vii) ALT ≤ 3 X ULN

viii) Total bilirubin ≤ 1.5 X ULN (except subjects with Gilbert Syndrome, who must have total bilirubin < 50 µmol/L)

- No prior adjuvant or foreseen neo-adjuvant or adjuvant chemotherapy is allowed

5.1.3. Age and Reproductive Status

- Males and Females ≥ 18 years of age
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) in the screening period and within 24 hours prior to the start of study drug.
- Women must not be breastfeeding during the study treatment and for a period up to 23 weeks post treatment completion (See Appendix 1)
- WOCBP must agree to follow instructions for method(s) of contraception during the study treatment and for a total of 23 weeks post treatment completion (See Appendix 1)
- Males who are sexually active with WOCBP must agree to follow instructions for method(s) for contraception for a total of 31 weeks post treatment completion (See Appendix 1)

5.2. *Exclusion Criteria*

5.2.1. Tumour Characteristics

- Any tumour that is not clinically definable on the treatment planning CT scan e.g. surrounded by consolidation or atelectasis
- 'Ultra-central' tumours, i.e. those adjacent to the hilar structures, with the gross tumour volume directly abutting a main bronchus

5.2.2. Medical History and Concurrent Diseases

- Subjects with active, known autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.

- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of the first dose of study drug administration. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease
- Subjects with previous malignancies (except non-melanoma skin cancers, early stage NSCLC treated with SBRT or surgery and current lesion not considered to be relapsed NSCLC, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period
- Patient with known interstitial lung disease or active, non-infectious pneumonitis
- Previous conventional radical radiotherapy to the chest or mediastinum. Patients who have had previous breast radiotherapy may be eligible at the discretion of the Chief Investigator. Patients who have previously received palliative dose radiotherapy to the chest may be considered if it is felt SBRT can be safely delivered. These cases must be discussed with the Chief Investigator
- Any serious or uncontrolled medical disorder or active infection that, in the opinion of the Investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive protocol therapy
- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE v.4.0) or baseline before administration of study drug
- Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment
- Subjects who received prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or who have previously taken part in a randomized BMS clinical trial for nivolumab or ipilimumab
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

- Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBVsAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection
    - Patients with a positive HCV antibody but no detection of HCV RNA indicating no current infection are eligible
- Patients who have received a live vaccine within 30 days prior to the first dose of trial treatment
- History of allergy to study drug components

5.2.3. Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption); adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted. A brief (< 3 weeks) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen, exacerbation of chronic obstructive pulmonary disease) is permitted.

Subjects may continue to receive hormone replacement therapy if initiated prior to first dose of study therapy.

Concomitant medications are recorded at screening/baseline and throughout the treatment phase of the study in the appropriate section of the case report form (CRF). All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

6. STUDY PROCEDURES

The study procedures are outlined as below and summarised in the schedule of events (See Section 6.10)

6.1. *Informed consent procedure*

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each patient prior to participation in the study, following adequate explanation of the aims, methods, anticipated benefits and potential hazards. The Investigator or designee will explain that potential patients are under no obligation to enter the study and that they can withdraw at any time, without having to give a reason.

Potential patients will be identified during routine clinical practice and will be approached by a member of the research team. If they are interested in the study, they will be offered a copy of the current patient information sheet (PIS) detailing the study and have the study explained to them by a member of the research team who has received training on the study and signed the delegation register. They will have the opportunity to ask questions. All patients wishing to enter into the study will be asked to sign and date a consent form which will be countersigned and dated by a researcher.

Consent procedures will conform to Good Clinical Practice (GCP), national and local regulations. No study procedures will be conducted prior to taking consent from the patient. The investigational site must retain the original signed consent and provide a copy to the patient

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

6.2. *Inclusion/Exclusion Criteria*

All inclusion and exclusion criteria must be met during the screening period to ensure the patient is eligible for the trial.

6.3. *Histological Confirmation*

All patients must have a documented histological diagnosis of non-small cell lung cancer (NSCLC). All histological sub-types of NSCLC are eligible. Diagnoses made from only cytology samples are not eligible.

All patients with synchronous primary lung cancers must have one lesion with a documented, biopsy proven, histological diagnosis of NSCLC. For the other lesions a radiological diagnosis of

NSCLC is required as determined by lung MDT. Metachronous lesions must be biopsy proven for trial entry.

6.4. *Clinical & Demographic Data Collection*

Demographic data to be collected will include subject date of birth, sex and ethnicity. A full medical history by the Investigator or qualified designee will be obtained to include all previous and current medical conditions. Smoking status to include - years smoked and total pack years to be documented by the Investigator or qualified designee.

6.5. *Prior and Concomitant Medications*

The Investigator or qualified designee will review all current mediation in use by the subject. This will include over-the-counter and alternative/herbal medications taken by the subject within 28 days of entry into the trial.

All drugs started after entry into the trial will be recorded by the Investigator or qualified designee in the concomitant medication section of the CRF at all scheduled or unscheduled clinical reviews. Scheduled reviews will occur regularly while receiving nivolumab and 30 days post the final treatment in the safety follow-up visit (SFU). Patients will subsequently be followed up as per the follow up phase (See 4.7.3). During the follow-up period all significant medications should be documented. Significant medications include but are not limited to, treatments for study related adverse events and all subsequent anti-cancer therapies.

6.6. *Clinical Assessments*

6.6.1. PD-L1 Assessment

All subjects must have a histologically proven diagnosis of NSCLC and will be naïve to treatment. Available tissue will be assessed for PD-L1 characterisation by a local laboratory using the Dako PD-L1 IHC 28-8 pharmaDx assay (See Appendix 5). As this trial is assessing the safety and tolerability of delivering adjuvant nivolumab to this patient group, the trial is unselected for PD-L1 status.

PD-L1 assessment can happen at any timepoint during the patients inclusion within the trial but histological sample must be requested to be sent to the Royal Marsden Hospital prior to completion of patient screening.

6.6.2. Full and Directed Physical Exam

The Investigator or qualified designee will perform a complete physical exam during the screening period to include an assessment of lymph node status, cardiovascular, respiratory, abdominal, neurological, skin and any other system deemed significant.

As laid out in the schedule of events a directed physical examination will be performed at all clinical reviews as indicated by patient symptoms. A respiratory examination will be performed by the Investigator or qualified designee as a minimum, where directed physical examination is indicated.

6.6.3. Symptoms and Adverse Event Monitoring

The Investigator or qualified designee will assess all symptoms during the screening period. AEs will be assessed by the Investigator or qualified designee as laid out in the schedule of events or as clinically indicated. All AEs will be graded as per NCI CTCAE v4.0 (See Appendix 6). All toxicities will be characterised regarding seriousness, causality, toxicity grading and action to be taken with regard to trial treatments. All treatment related adverse events will be assessed for categorisation as potential immune related adverse events (irAE). AEs will be recorded from time of consent to trial until 100 days post the final infusion of nivolumab.

6.6.4. Eastern Co-operative Oncology Group (ECOG) Performance Status

The Investigator or qualified designee will assess ECOG status (See Appendix 7) at screening and at each clinical review as laid out in the schedule of events.

6.6.5. Medical Research Council (MRC) Dyspnoea Scale

The Investigator or qualified designee will assess the subject's dyspnoea as per the MRC scale (See Appendix 3) at screening and at each clinical review as laid out in the schedule of events.

6.6.6. Vital Signs & Weight

The Investigator or qualified designee will take vital signs that include blood pressure, pulse, oxygen saturations, respiratory rate, temperature and weight during screening and at each clinical review as laid out in the schedule of events. Height will be recorded during the screening period.

6.6.7. Laboratory Tests

All laboratory tests will be performed at screening and at set time points as laid out in the schedule of events. The local study site laboratory using standard methods will perform the tests. All laboratory testing should be performed within 72 hours prior to each dose to include FBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase. Thyroid function testing with TSH (with free T4 and free T3 as necessary) should be performed at a minimum of every 6 weeks (+- 7 days) for subjects receiving nivolumab as laid out in the schedule of events.

6.6.8. Hepatitis Screen

Blood will be tested during the screening period for assessment of hepatitis B surface antigen (HBV sAg) and hepatitis C antibody (HCV Ab). In the event of a positive test for HCV Ab the sample should be sent for HCV RNA PCR for characterisation of possible active infection.

6.6.9. Pregnancy Tests

For WOCBP a serum or urine pregnancy testing is required during screening, within 24 hours of first dose of nivolumab and then as a minimum every 6 weeks (+/- 7 days) while receiving nivolumab. After discontinuation from nivolumab these should be repeated at approximately 30 days and 70 days.

6.6.10. Health Related Quality Of Life (HRQoL) Assessments

The questionnaires to be completed are (see Appendix 10):

- EORTC QLQ-C30
- EORTC QLQ-LC13 (Lung Module)
- Patient generated subjective global assessment questionnaires – Box 4 only

HRQoL is defined as the functional effect of a medical condition and/or its consequent treatment upon a patient. The purpose of HRQoL measurement is to quantify the degree to which the medical condition or its treatment impacts the individual's life in a valid and reproducible way.

HRQoL questionnaires will be completed in order to establish how patients are coping with trial treatment. Patients will be asked to complete questionnaires during the screening period, and then as laid out in the schedule of events. The assessments are to be performed, in screening, every 3 months (+/- 14 days) in the first year after SBRT and twice in the second year. For patients still receiving nivolumab they will be taken at the appropriate clinic reviews but should follow calendar time points rather than cycle numbers of nivolumab.

HRQoL will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3 and the QLQ-LC13 lung cancer module to the QLQ-C30, which measures HRQoL relevant to specific symptoms common in lung cancer. These instruments are composed of multi-item and single-item scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QoL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The lung module comprises 13 questions assessing lung cancer-associated symptoms (cough, haemoptysis, dyspnoea and site specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication.

All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language/cultural groups. The lung cancer module is meant for use among a wide range of lung cancer patients varying in disease stage and treatment modality.

The delegated Research Nurse or qualified designee should spend time with the patient going through the questionnaires and answering any questions patients might have. Thereafter the patient should answer the questionnaires independently.

6.6.11. Pulmonary Function Tests (PFTs)

Full lung function tests will be performed within 16 weeks of first fraction of SBRT. The PFTs are to include FEV1, FVC and transfer factor (DLCO) as minimum criteria. They will be repeated as laid out in the schedule of events at 6 months, 12 months and 24 months from the final fraction of SBRT. The intervals should follow calendar time points rather than cycle numbers of nivolumab. All subsequent PFTs are to be performed within 14 days of the relevant review.

In light of the COVID-19 pandemic pulmonary function tests performed within 6 months of the first fraction of SBRT are acceptable. This amendment will be reviewed at the next IDMC meeting after 15 patients have been enrolled, received at least 1 dose of IMP and completed 3 months of follow-up when an assessment of the pandemic restrictions can be made.

6.6.12. Bedside Spirometry

The Investigator or qualified designee to perform bedside spirometry at clinical reviews as laid out in the schedule of events. Spirometry will be performed on the day of the final fraction of SBRT, every 6 weeks (+/- 7 days) until cycle 14 and then every 8 weeks thereafter, while receiving nivolumab. The intervals should follow calendar time points rather than cycle numbers of nivolumab. Bedside spirometry is to be recorded as the best of minimum 3 attempts unless clinical reason to not repeat testing. Minimum spirometry requirements are to include FEV1, FVC, PEFR and FEV1/FVC.

6.7. *Tumour Imaging and Assessment*

6.7.1. Baseline tumour measurement

Baseline CT scans of chest and abdomen are to be performed within 8 weeks of the first fraction of SBRT. An FDG-PET is to be performed and reviewed to confirm radiological staging criteria within 6 weeks of the first fraction of SBRT. Imaging performed prior to enrolment in the study will be acceptable if the above criteria are met.

In light of the COVID-19 pandemic pulmonary function tests performed within 6 months of the first fraction of SBRT are acceptable. This amendment will be reviewed at the next IDMC meeting after 15 patients have been enrolled, received at least 1 dose of IMP and completed 3 months of follow-up when an assessment of the pandemic restrictions can be made.

6.7.2. Monitoring Imaging

Subjects will be assessed with chest radiographs (CXR) for evidence of pneumonitis as laid out in the schedule of events. A CXR will be performed during screening, at 4 weeks and 8 weeks (+/- 7 days) from the final fraction of SBRT, at the 9 month (+/- 14 days) follow-up review, 15 month follow-up review and at the safety follow-up visit (30 days (+/- 7 days) post the final dose of nivolumab). The CXRs should follow calendar time points rather than cycle numbers of nivolumab. If the Investigator or qualified designee identifies features suggestive of pneumonitis/relapse on the CXR then a contrast chest CT should be performed, as clinically indicated.

6.7.3. Follow-up Imaging

Cross sectional imaging with CT chest and abdomen to be performed as laid out in the schedule of events. CTs will be performed at 3, 6, 12, 18 and 24 months (+/- 14 days) from the date of the final fraction of SBRT. The intervals should follow calendar time points rather than cycle numbers of nivolumab. The assessment of local, loco-regional or distant relapse is to be performed by the local radiologist/MDT.

In light of the COVID-19 pandemic CT scans can be performed within 30 days of the above timepoints. This imaging amendment will be reviewed at the next IDMC meeting after 15 patients have been enrolled, received at least 1 dose of IMP and completed 3 months of follow-up when an assessment of the pandemic restrictions can be made.

6.8. *Research Tissue and Blood Samples*

Residual tumour from the diagnostic biopsy may be analysed within this study. Research blood samples from this study may undergo proteomic, genomic and transcriptional analyses. Research blood samples will be taken as laid out in the schedule of events. A baseline sample will be taken during screening. This sample can be taken from day -28 until day of fraction 1 of radiotherapy treatment but must occur before any treatment is delivered. Subsequent samples will be taken on day 1 of cycle 1 of nivolumab. Two further samples will be taken at time points of weeks 4, 8. A further optional blood sample may be obtained at time of disease relapse. All samples will be tracked securely to maintain a full chain of custody from obtaining the sample to processing, shipment, analysis and destruction or long term storage in a biobank.

In cases of disease relapse and where a new biopsy has been performed on clinical grounds, the patient may optionally consent for the relapse biopsy to be characterised in a similar fashion to the original diagnostic biopsy. Multiple biopsies may facilitate an understanding of how gene expression develops over time and in response to immunotherapy treatment.

The specific volumes of blood to be taken at each time point, details of processing, sample shipment and analyses to be performed will be laid out in a separate laboratory manual.

Assays may include, but are not restricted to:

- **Characterisation of tumour and immune biology**

RNA and DNA extraction from formalin-fixed, paraffin embedded (FFPE) tumour tissue before exposure to therapy. The RNA can be analysed for immunological and other transcriptional profiles within different components of the tumour. Peripheral blood samples can be used for functional assays of the innate and adaptive immune systems with characterisation of the activation status of specific blood immune cell subsets.

- **Circulating Tumour DNA (ctDNA)**

Research blood samples may be analysed for ctDNA before and during treatment.

6.9. *Safety Follow-Up Visit (SFU)*

All subjects will be assessed for toxicity a minimum of 30 days (+/- 7 days) after their final dose of nivolumab or 14 days (+/-7 days) after the decision to discontinue IMP (if this decision has been taken greater than 30 days since their last dose of Nivolumab). This will be to assess adverse events and toxicities. Assessments are to be performed as laid out in the schedule of events.

6.10. *Follow up Phase Visits*

All subjects will be assessed for evidence of relapse and secondary endpoints at 3 monthly (+/- 14 days) intervals from the final fraction of radiotherapy for the 18 months then at a six month interval at the last follow-up visit at 24 months. Survival data and disease status will be available on patient medical notes after 24 months to be collected under unscheduled visits. This will also be collected for patients who completed the study before the up to 5 years data collection was

implemented. These patients will be reconsented to the study at their next clinic visit; survival data and disease status will be collected from their medical notes. Assessments of toxicity and respiratory function are to be performed as laid out in the schedule of events. For patients that have not discontinued nivolumab, if the date range allows for this visit to be combined with one of the cycle visits/SFU, the assessment schedule as per the cycle visit/SFU should be followed with the following exceptions:

- Pulmonary Function Tests should be performed in place of bedside spirometry at the 6 and 12 month follow up visit
- Imaging should follow the Follow-up visit schedule. CXRs will not be performed when a CT has been performed (or is scheduled) within 21 days unless clinically indicated
- Health Related Quality of Life Assessments to follow the Follow-up visit schedule

6.11. *Schedule of Events*

		1 / 2 weeks	W0	W1	W2	W3	W4	W6	W8	Every 2 weeks	Every 6 weeks	Every 4 weeks	Every 8 weeks		Follow Up Visits						
Trial Phase	**Screening**	**Radiotherapy Phase**			**Nivolumab Phase**									**Safety Follow-Up**	**Follow-Up Phase**						
Treatment Cycle		1st#	Final # C1, D1	C1,D8	C2,D 1	C2,D8	C3,D1	C4,D1	C5,D1	C6 to C13	C6 to C13	C14 D1 onwards	C14 D1 onwards	14 days post decision to stop IMP[2]	3m post SBR T	6m post SBR T	9m post SBR T	12m post SBR T	15m post SBR T	18m post SBR T	24m post SBR T
Scheduling	-28 to -1										+/- 7			+/- 7 days	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14
Informed Consent	**X**																				
Inclusion/Exclusion	**X**																				
Demographics & Past Medical History	**X**																				
Concomitant Medications	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**£**	**£**	**£**	**£**	**£**	**£**	**£**
Full physical exam	**X**																				
Directed physical exam			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**£**	**£**	**£**	**£**	**£**	**£**	**£**
Adverse Events	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	¥	¥	¥	¥	¥	¥	¥
ECOG PS	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
MRC Dyspnoea score	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital signs & Weight	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**£**	**£**	**£**	**£**	**£**	**£**	**£**
Height	**X**																				
Haem & Biochem[1]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**£**	**£**	**£**	**£**	**£**	**£**	**£**
Thyroid function tests	**X**							**X**			**X**	**X**		**X**	**£**	**£**	**£**	**£**	**£**	**£**	**£**
Hepatitis screen	**X**																				
Research bloods	**X**[3]		**X**				**X**		**X**												
Pregnancy test (WOCBP)	**X**		**X**					**X**			**X**	**X**		**X**	**£**	**£**	**£**	**£**	**£**	**£**	
HRQoL Assessments	**X**														**X**	**X**	**X**	**X**	**X**	**X**	**X**
Pulmonary Function Tests	**X**[a]															**X**		**X**			**X**
PD-L1 tumour request	**X**[0]																				

Bedside spirometry			**X**					**X**			**X**		**X**	**X**	**X**		**X**		**X**	**X**	
Radiotherapy Planning	**X**																				
SBRT		**X**	**X**																		
Nivolumab infusion			**X**		**X**		**X**	**X**	**X**	**X**		**X**									
Imaging	**CXR (CT & PET)***						**CXR**		**CXR**					**CXR**	**CT**	**CT**	**CXR**	**CT**	**CXR**	**CT**	**CT**

Notes/Key

1 = Must be obtained ≤ 72 hours from dose administration

2 = Or before initiation of any new anti-cancer therapy

3 = Research bloods may be taken on day of fraction 1 of RT **before** radiotherapy* = CT chest/abdomen within 8 weeks of first fraction of SBRT. FDG-PET within 6 weeks of SBRT (A CT chest alone within 8 weeks is sufficient during the pandemic restrictions as documented above)

= Fraction of radiotherapy

¥ = For 100 days (Adverse Events) after final dose of IMP

£ = If indicated

a= Full lung function tests will be performed within 16 weeks of first fraction of SBRT, or within 6 months during the COVID-19 pandemic restrictions as documented above

0 = Tumour samples requested in preparation for PD-L1 testing.

Pulmonary Function Tests only to correspond with 6, 12 and 24 month post SBRT follow-up

Pregnancy test to be performed within 24 hours of IMP for cycle 1 then minimum of every 6 weeks until cycle 14 then every 4 weeks while on treatment.

Research blood samples at screening, and weeks 0, 4 and 8 of nivolumab. An additional (optional) sample will be taken at time of relapse if the patient consents.

CXR to be performed during screening, at 4 weeks, 8 weeks, 9 and 15 months from final fraction of SBRT and at the safety follow-up visit

CT chest/abdomen at 3, 6, 12, 18 and 24 months from final fraction of SBRT

7. STUDY TREATMENTS

7.1. *Stereotactic Body Radiotherapy*

Radiotherapy delivery is permitted on a conventional LINAC or on a CyberKnife machine. Tomotherapy is not permitted for this study.

7.1.1. Pre-treatment image acquisition

Patient positioning

For conventional LINAC, patients are positioned supine in a comfortable and reproducible position with their arms above their heads, on a lung board or wing board, with knee rests if required. For patients with apical lung tumours, the alternative position of arms by sides with or without an immobilization mask can be considered.

Devices such as customised vacuum bags or thermoplastic moulds can be used to achieve patient comfort and stability. Custom devices can be used for immobilization and to facilitate abdominal compression. The immobilization device should allow for patient and tumour imaging as necessary using any required imaging techniques and not interfere with dose calculation or treatment delivery. In addition, analgesics +/- mild sedatives and oxygen can be considered to help the patient maintain the treatment position during each fraction.

The accuracy for any immobilization device/s used for positioning patients for SBRT should ensure systematic setup errors are within 3-5mm.

Tumour motion

Once the patient has been appropriately positioned it is highly recommended that patient-specific tumour motion be incorporated into treatment either by using direct tumour tracking methods or by the use of 4DCT at the treatment simulation stage.

(a) Motion Restriction to reduce tumour motion (to <1cm), e.g. by using one of the following methods:

1. Abdominal compression.

2. Respiratory gating.

3. Coached respiration

4. Active Breathing Control (ABC) device for patients with sufficient respiratory reserve to be able to breath hold for >20 seconds.

(b) Accounting for motion in RT planning:

1. Provided that the dose conformity, dose spillage and organs at risk (OAR) constraints can be met the whole motion envelope may be included in the internal target volume (ITV) and the patient treated whilst breathing normally (usually applies to small mobile tumours).

2. Planning using the mid-ventilation or time-weighted average image from 4DCT and accept that the ITV and planning target volume (PTV) may not always include all tumour motion.

It is the responsibility of each radiotherapy department to assess the reproducibility of their chosen method of managing tumour motion prior to commencing SBRT treatments.

Pre-treatment imaging

Patients will undergo a treatment planning CT scan in the treatment position within the chosen immobilization device. The extent of the scan must be sufficient to include all potential organs at risk, especially when non-coplanar beams are used. As a guide, contiguous axial slices of ≤3mm will be obtained from the upper cervical spine to the lower edge of the liver, taking care to include all lung parenchyma on the planning scan. More than one planning CT scan may be required for target definition/motion assessment. The planning CT scan(s) must allow for simultaneous viewing of internal organ anatomy if a stereotactic frame is used for immobilization, which will be identical for the treatment-planning phase and for each radiation fraction.

7.1.2. Delineation and treatment planning

Tumour Delineation

Gross Tumour Volume (GTV) = The GTV is defined as the radiologically visible tumour in the lung, contoured using lung settings. Mediastinal windows may be suitable for defining tumours proximal to the chest wall. Where available, information from PET/CT will be incorporated into delineating the GTV.

No Clinical Target Volume (CTV) is required for stereotactic body radiotherapy.

Internal Target Volume (ITV) = tumour volume obtained using a 4DCT scan.

This is defined as tumour contoured using either the (i) maximum intensity projection scan, (ii) maximum inspiratory and expiratory scans or (iii) as contoured on all 10 phases of a 4DCT scan.

The margins from ITV to PTV will depend on the method of immobilization, the assessment of tumour motion and methods for on treatment set-up verification/repositioning. Each centre will need to confirm the adequacy of the PTV margins with their immobilization techniques. 3-5mm margins are typically chosen for 4DCT-based SABR planning.

Organs at Risks (OAR)

It is recommended that the following organs at risk are delineated on the CT planning dataset.

- **Spinal cord**

The spinal cord should be contoured on all slices based on the bony limits of the spinal canal.

- **Oesophagus**

The oesophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia.

- **Brachial Plexus**

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neural foramina on the involved side from around C5 to T2. However, for the purposes of this protocol only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries), and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the 2nd rib.

- **Heart**

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring is defined as the superior aspect of pulmonary artery (as seen in a coronal reconstruction of the CT scan) and extended inferiorly to the apex of the heart.

- **Trachea and proximal bronchial tree**

The trachea and bronchial tree can be contoured either as a single structure or as two separate structures using lung windows. For this purpose, the trachea can be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree. Differentiating these structures in this fashion will facilitate the eligibility requirement for excluding patients with tumours within 2cm of the proximal bronchial tree.

- **Proximal trachea**

Contours should begin 10cm superior to superior extent of PTV or 5cm superior to the carina (whichever is the more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

- **Proximal bronchial tree**

This will include the most inferior distal 2cm of trachea and the proximal airways on both sides. The following airways will be included: distal 2cm trachea, carina, right and left main stem bronchi, right and left upper lobe bronchi, the bronchus intermedius, right middle lobe bronchus, lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation. To adhere to eligibility requirements, GTV abutting this structure or PTV encompassing trachea or a main bronchus should not receive SBRT within this trial.

- **Whole lung**

Both lungs should be contoured as one structure using pulmonary windows. All inflated and collapsed lung should be included. However, GTV and trachea/ipsilateral bronchus as defined above should not be included.

- **Proximal bronchial tree plus 2cm**

It is convenient to define an artificial structure 2 cm larger in all directions from the proximal bronchial tree. Patients whose GTV falls within this structure should receive treatment over 8 fractions **To classify a lesion as peripheral, central or ultracentral see definitions in Appendix 4.**

Treatment Planning

The constraints recommended are based on the UK SABR consortium guidance.

Beam selection

To achieve adequate target coverage using SBRT whilst sparing critical structures, including the skin surface, typically at least seven beams are required, although rotational delivery solutions may also be appropriate. The beam configuration may be coplanar or non-coplanar, depending on the size and location of the lesion. The paradigm dictates that the high-dose region should be conformal to the PTV, the medium-dose region surrounding the PTV should be compact and the low-dose region is permitted to be relatively large by comparison to the other regions. All dose calculations should be performed using heterogeneity correction. Due to uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, individual centres should satisfy themselves of the veracity of their small-field dosimetry. Lower energy beams (e.g. 6MV) should be used due to the wide penumbra of high-energy beams, the small beam apertures used in SBRT and the problems associated with buildup. Analysis of the dose-volume histogram (DVH) for the PTV and critical normal structures forms the basis for selecting a particular treatment plan. It is therefore recommended that plans be calculated on a fine dose grid, with a separation no greater than 2.5mm, to ensure accurate calculations.

In addition, the dose to skin should be limited to minimise cutaneous and subcutaneous toxicity. This is assisted by ensuring that beam entry points do not overlap on the skin. Dose deposition in regions of skin folds should be assessed carefully.

Treatment Planning System

Inhomogeneity corrections have a large influence on the dose delivered to the PTV and OARs for SBRT of lung tumours. Type A algorithms, which use an extended path length (EPL) calculation to account for heterogeneity, result in a wide range of errors relative to the actual dose distribution. This includes overestimation of the isocentric prescription dose and target coverage. The target coverage errors vary significantly depending on the location of the lesion, so a simple rescaling of prescription dose, as used in the RTOG and ROSEL studies, does not provide a reliable correction. Therefore Type B or Monte Carlo algorithms that consider changes in lateral electron transport should be used.

Tumour Location/OAR doses

. Peripheral and centrally located tumours can be treated in this study. Ultra-central disease is however excluded. Please refer to eligibility criteria. Appropriate dose limits for OARs are given in table below.

Note: when non-coplanar treatment beams are used additional organs may be irradiated (e.g. liver, bowel) – allowances must be made for this. It is recommended the entire liver be scanned, especially for lower lobe lesions and where non-coplanar beams are to be used.

Description	**Constraint**	**3 Fractions**		**5 Fractions**		**8 Fractions**	
		Optimal	**Mandatory**	**Optimal**	**Mandatory**	**Optimal**	**Mandatory**
Brachial Plexus	DMax (0.5cc)	< 24Gy	< 26Gy	< 27Gy	< 29Gy	<27Gy	<38Gy
Heart	DMax (0.5cc)	< 24Gy	< 26Gy	< 27Gy	< 29Gy	<50Gy	<60Gy
Trachea and bronchus	DMax (0.5cc)	< 30Gy	< 32Gy	< 32Gy	< 35Gy	<32Gy	<44Gy
Normal Lungs* (Lungs-GTV)	V20Gy	-	< 10%	-	< 10%	-	<10%
	V12.5Gy	-	< 15%	-	< 15%	-	-
Chest Wall	DMax (0.5cc)	< 37Gy	-	< 39Gy	-	<39Gy	-
	D30cc	< 30Gy	-	< 32Gy	-	<35Gy	-
Great Vessels	DMax (0.5cc)	-	< 45Gy	-	< 53Gy	-	-
Normal Liver (Liver minus GTV	V10gy	-	-	< 70%	-		
	Mean Liver dose	-	-	<13Gy	<15.2Gy		
	D50%	<15Gy	-	-	-		
	Dose to ≥700cc	<15Gy	<19.2Gy	-	-		

Where patients are having more than one lung lesion treated with SABR, it is recommended that these should be treated on alternate days and with the same dose/ fractionation (usually the most conservative schedule). The use of alternate day treatments reduces the dose per fraction to the whole lung, and is recommended in an effort to limit the risk of severe pneumonitis and fibrosis. Both sites may be treated on the same day if the tumours can be encompassed in a single field, for small metastases in otherwise fit patients, or when the combined percentage of lung volume receiving a dose

of 20 Gy or higher (V20 Gy) is below the tolerance for a single lesion. There are few published data on normal tissue tolerances for multiple lesions and ideally the standard thoracic constraints should be met. However, the OAR constraint that will probably be exceeded is the V20 Gy. In the case of treating two lung lesions, the following V20 Gy lung constraints should be followed:

- Optimal <12.5%
- Acceptable in all cases <15%
- Acceptable in selected cases with good lung function <20%

Where the lung function parameters of forced expiratory volume in 1 second (FEV1) and transfer factor (DLCO) are below 40% of predicted, it is strongly recommended that the V20 Gy should be kept below 12.5% (optimal) or 15% (mandatory).[16]

Fractionation

Acceptable dose fractionation regimes are suggested below. Individual centres may choose to prescribe dose fractionation regimes other than those suggested, however they must ensure that the BED is less than the highest dose in these guidelines, and that the appropriate OAR tolerances are meet.

Standard Dose Fractionation: 18 Gy x 3 fractions (NB 20 Gyx3 not allowed)
Conservative Dose Fraction: 11 Gy x 5 fractions
Central disease dose fractionation: 7.5Gy x 8 fractions

The conservative peripheral lesion dose fractionation (55Gy in 5 fractions) is recommended when any part of the PTV is in contact with the chest wall.
The central disease dose fractionation is recommended when any part of the GTV is within the artificial structure ‘proximal bronchial tree plus 2cm’ but not abutting the structure ‘proximal bronchial tree’. (See appendix 4)

It is recommended that the inter-fraction interval be at least 40 hours, with a maximum interval of ideally 4 days between fractions. However, the inter-fractional interval can be reduced to 18 hours if required to allow concomitant administration of nivolumab.

If dose constraints are not being met two approaches are possible:

1) Reduced prescription dose: The prescribed dose can be reduced but to no less than 90% of the BED.
2) Inhomogeneous PTV dose: in case of overlap of the PTV with OAR, a dose of 11* 5 Gy to the ITV should be maintained and the dose within the PTV may be reduced until the planned dose to the OAR meets the acceptable variation criteria for the OAR (see RTQA trial specific guidelines). The dose in 95% of the PTV should still at least be 80%.

The very conservative fractionation schedules may rarely be used if the dose constraints cannot be met at 55 Gy or 50 Gy in 5 fractions. The conformity constraints are as per 5 fraction treatments.

Dose distribution requirements

Successful treatment planning can be achieved by a range of planning techniques but will require accomplishment of all of the following criteria:

1. The dose prescription will be chosen such that 95% of the target volume (PTV) receives at least the nominal fraction dose (e.g. 18 Gy per fraction = 54 Gy total), and 99% of the target volume (PTV) receives a minimum of 90% of the fraction dose (e.g. 16.2 Gy per fraction = 48.6 Gy total for the standard fractionation)
2. The dosemax within the PTV should preferably not be less than 110%Gy
(e.g. 59.4 Gy for standard fractionation) or exceed 140%Gy (e.g. 75.6Gy for standard fractionation). A minor deviation will be scored in cases where the dosemax lies between either 105-110% (e.g. 56.7-59.4 Gy) or 140-145% (e.g. 75.6-78.3 Gy).
3. Conformity of PTV coverage will be judged as given in the tables below, which incorporate constraints used in the ROSEL study.

Dose conformity requirements for type B models

Vol(100%)/Vol(PTV): ratio of prescription isodose (e.g. 54Gy or 55Gy) volume to the PTV
Vol(50%)/Vol(PTV): ratio of 50% prescription isodose (27Gy or 27.5Gy) volume to the PTV
Max dose >2cm: maximum dose at least 2cm from the PTV in any direction
V20: percentage of total lung volume – GTV receiving >20Gy

Radiotherapy plans are expected to comply with these conformity requirements. If however there are difficulties in achieving an OAR constraint then compliance with an OAR constraint takes precedence over conformity.

7.1.3. Dose conformity requirements

3 fractions	Vol (100%)/Vol (PTV)		Vol (50%)/Vol (PTV)		Max dose >2cm	
Vol PTV (cc)	Tolerance	Minor dev	Tolerance	Minor dev	Tolerance	Minor dev
<20	<1.25	1.25–1.40	<12	12–14	<35.1Gy	35.1–40.5Gy
20–40	<1.15	1.15–1.25	<9	9–11	<37.8Gy	37.8–43.2Gy
>40	<1.10	1.10–1.20	<6	6–8	<37.8Gy	37.8–43.2Gy
60–90	<1.10	1.10–1.20	<5	5–7	<37.8Gy	37.8–43.2Gy
>90	<1.10	1.10–1.20	<4.5	4.5–6.5	<37.8Gy	37.8–43.2Gy

5–8 fractions	Vol (100%)/Vol (PTV)		Vol (50%)/Vol (PTV)		Max dose >2cm	
Vol (PTV) (cc)	Tolerance	Minor dev	Tolerance	Minor dev	Tolerance	Minor dev
<20	<1.25	1.25–1.40	<12	12–14	<35.8Gy	35.8–41.3Gy
20–40	<1.15	1.15–1.25	<9	9–11	<38.5Gy	38.5–44.0Gy
>40	<1.10	1.10–1.20	<6	6–8	<38.5Gy	38.5–44.0Gy
60–90	<1.10	1.10–1.20	<5	5–7	<38.5Gy	38.5–44.0Gy
>90	<1.10	1.10–1.20	<4.5	4.5–6.5	<38.5Gy	38.5–44.0Gy

7.1.4. Treatment Verification and Delivery

Once the treatment plan has been generated, it is recommended that centres conduct a 'trial set up' session, prior to starting treatment in order to confirm that all the beams are deliverable, that the patient can maintain the treatment position, to verify the patient setup procedure and, if the technology is available, use respiratory-correlation to assess margin adequate.

Verification

- LINAC based: Cone beam CT (CBCT) and on-line correction prior to each fraction (Greyscale match is required). Manual adjustment with direct visualization of the tumour is performed.

The position of critical OAR are checked, especially the spinal cord and any changes in the patients internal anatomy. Repeat CBCT scans are considered after correction prior to treatment delivery and again after treatment delivery for additional verification

7.1.5. Toxicity Assessments

Assessments of SBRT adverse events will occur at each clinical review as laid out in the schedule of events. All toxicities will be graded for severity by CTCAE v4.0. Expected toxicities from SBRT are listed below:

- Fatigue
- Dermatitis Radiation
- Oesophagitis
- Radiotherapy induced rib fracture
- Chest wall pain
- Cough
- Dyspnoea
- Late radiation fibrosis
- Forced expiratory volume decreased
- Carbon monoxide diffusing capacity decreased

7.2. *Investigational Product*

7.2.1. Nivolumab

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody, that binds to the PD-1 receptor and blocks interaction with its ligands PD-L1 and PD-L2. Interaction between PD-1 and its ligands is a negative regulator of T cell activity and has been shown to alter T cell mediated immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells (APC) and may be expressed by tumour or other cells in the tumour microenvironment, results in inhibition of T cell proliferation and cytokine secretion. Nivolumab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[17]

7.2.2. Product information

Product Description: (Other names = MDX-1106, ONO-4538, anti-PD-1)

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01)* Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	100 mg/Vial (10 mg/mL).	Carton of 5 vials	10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.	Clear to opalescent, colorless to pale yellow liquid. May contain particles	**BMS-936558-01 Injection** must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

*Nivolumab may be labeled as BMS-936558-01 Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab Investigator Summary of Product Characteristics (SmPC).

7.2.3. Storage and Handling

The Investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light) as per the SmPC. Temperature monitoring will be as per local practice. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by

authorized personnel according to local regulations. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact Sponsor immediately.

7.2.4. Disposal

Sponsor/Investigator drug destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and must be followed. The procedures must be filed with the sponsor SOPs and a copy provided to BMS upon request
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed and identification of the person disposing the containers. The method of disposal, i.e. incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for sponsor to review throughout the clinical trial period as per the study agreement.

7.2.5. Dose Calculation and Administration

Nivolumab will be given every 14 days at a flat dose of 240 mg intravenously over 30 minutes for 13 cycles. This will be followed by 480mg intravenously every 28 days for 7 cycles (20 cycles in total). There are no premedications recommended for nivolumab on the first cycle.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to section 8.21.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how the subject tolerates the treatment. A delay of up to 3 days for administrative reasons will not be considered a treatment delay.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection is to be infused, diluted to a volume of 100 ml 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Care must be taken to

assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

8. PHARMACOVIGILENCE

8.1. *Adverse Event Definition*

An adverse event (AE) is defined as any untoward undesired or unplanned occurrence (including deterioration of a pre-existing medical condition) in a patient administered a pharmaceutical product or undertaking a protocol-specified procedure. An AE can therefore be any unfavourable and unintended sign symptom, or disease and/or laboratory or physiological observation associated with the use of a medicinal product or protocol-specified procedure but does not necessarily have to have a causal relationship to this treatment or procedure. Any worsening (i.e. any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of nivolumab, is also an AE. Please note, only clinically significant abnormal laboratory values will be recorded as adverse events. Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, onset of menses or menopause occurring at a physiologically appropriate time. AEs may also occur in screened patients during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

8.2. *Adverse Reaction Definition*

An AE assessed by the Principal Investigator or delegated co-investigator as reasonably likely to be related to the administration of a medicinal product or protocol-specified procedure.

8.3. *Evaluating Adverse Events*

AEs will be evaluated by an investigator who is a qualified medical physician.

8.4. *Determining Adverse Event Severity and Grade*

AE severity and grade will be evaluated according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any AE which changes CTCAE grade over the course of a given episode should be closed at the date the severity changed and a new AE recorded on the AE case report forms from that date at the new severity.

8.5. *Determining AE Causality*

The Investigator must endeavour to obtain sufficient information to assess the causality of the AE and must provide his/her opinion whether the event has any relationship to the administered study treatment / procedure. This may require instituting supplementary investigations of significant AEs based on their clinical judgment of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

Causality is the relationship of an AE to the IMP and will be determined as follows:

Definite:	• There is clear evidence to suggest a causal relationship.
	• Starts within a time related to the IMP administration and
	• No obvious alternative medical explanation.
Probable:	• There is evidence to suggest a causal relationship
	• Starts within a time related to the IMP administration and
	• Cannot be reasonably explained by known characteristics of the patient's clinical state.
Possible:	• A causal relationship between the IMP and the AE is at least a reasonable possibility.
	• Starts within a time related to the IMP administration
	• However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Unlikely:	• There is little evidence to suggest there is a causal relationship.
	• There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
	• The time association is such that the trial drug is not likely to have had an association with the observed effect.
Not related:	• The AE is definitely not associated with the IMP administered.

8.6. *Non serious Adverse Event Collection and Reporting*

The collection of nonserious AE information should begin at the subject's written consent to participate in the study. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and up to 100 days following the last dose of study treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as serious adverse events (SAEs) if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

8.7. *Laboratory Test Abnormalities*

All laboratory test results captured as part of the study are to be reviewed by the Investigator or qualified designee.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE (see 8.9)
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy
- any laboratory abnormality that the investigator considers to be related to the IMP

8.8. *Management of Immune-Mediated Adverse Events*

In some cases, the natural history of AEs associated with immunotherapy can differ from and be more severe than AEs caused by agents belonging to other therapeutic classes. Early recognition and management may mitigate severe toxicity. Local guidelines should be followed for the management of immune-mediated toxicities.

8.9. *Serious Adverse Events*

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death

- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g. medical, surgical) to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Development of new cancer (secondary malignancy) and potential drug induced liver injury (DILI) are also considered important medical events. (See section 8.20 for the definition of potential DILI)
- Suspected transmission of an infectious agent (e.g. pathogenic or non-pathogenic) via the study drug is an SAE
- Although pregnancy and overdose are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 8.17 for reporting pregnancies and 8.14 for overdose)
- Any component of a study endpoint that is considered related to study therapy (e.g. death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see next section for reporting details).

NOTE:

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure

- routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anticancer therapy in the absence of any other SAEs

8.10. *Reporting of SAEs*

All SAEs regardless of causality and any pregnancy or overdose that occur from the time of signed consent until 100 days from the final dose of nivolumab must be reported to the RM-CTU on the SAE report form within 24 hours of the investigator / designee becoming aware of the event. All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g. a follow-up skin biopsy). The Investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

The SAE form should be sent by Fax or Email to the RM-CTU, who in turn will inform BMS within 24 hours at worldwide.safety@bms.com

The SAE Report form should be sent to **SAE Email Address:** Stile.study@rmh.nhs.uk **SAE Facsimile Number:** 0208 915 6762

The SAE form must be completed, assessed for causality and expectedness against the current version of the SmPC, then signed and dated by the Chief Investigator or an appropriately qualified designated individual identified on the delegation log. The report will then be reviewed by the Chief Investigator (or a nominated representative) to confirm relatedness and expectedness. The NCI-CTCAE version 4.0 must be used to grade each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the Sponsor (via RM-CTU) on a new SAE report form. The Sponsor (via RM-CTU) will in turn submit the updated report to BMS. Please refer to the SAE completion guidelines for further information.

8.11. *Determining SAE Causality and Expectedness*

Assessment of causality and expectedness for all SAEs will be made by the Chief Investigator or designee against the Reference Safety Information (RSI). The RSI for assessing the expectedness of adverse events is contained in section 4.8 of the Summary of Product Characteristics (SmPC) and for SBRT in Section 7.1.5 of this protocol. If updated versions of the SmPC are released during the course of the trial then assessment of expectedness will be made against the current regulatory approved version.

8.12. *Serious Adverse Reaction (SAR):*

An adverse event that is both serious and in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments based on the information provided.

8.13. *Suspected Unexpected Serious Adverse Reaction (SUSAR):*

A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information for that product. In this study the reference safety information is contained within section 4.8 of the Nivolumab SmPC.

8.14. *Reporting of SUSARs*

All SUSARs must be reported using the SAE report form within 24 hours of the Chief Investigator/designee becoming aware of the event to the Sponsor (via RM-CTU) as follows:

The SAE Report form should be sent to

SAE Email Address: Stile.study@rmh.nhs.uk

SAE Facsimile Number: 0208 915 6762

Who will in turn notify BMS, Independent Ethics Committee (IEC)/Institutional review, appropriate regulatory authorities and the participating Chief Investigators

The Sponsor (via RM-CTU) will in turn notify BMS, relevant Independent Ethics Committee (IEC) / Institutional review, appropriate regulatory authorities and the participating Chief Investigators in accordance with regulatory requirements and within the timelines as defined below:

- For fatal and life-threatening SUSARs the Sponsor (via RM-CTU) should report at least the minimum information as soon as possible and in any case no later than **7 days** after being made aware of the case.

- SUSARs which are not fatal and not life-threatening are to be reported within **15 days**

Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised. Follow-up information for SUSARs that result in death or are life-threatening must be sent to the Independent Ethics Committee (IEC) / Institutional review, appropriate regulatory authorities and the participating Chief Investigators within an **additional 8 days after being first reported.**

8.15. *Annual Reporting of Serious Adverse Events*

The Development Safety Update Report (DSUR) will be submitted annually on the anniversary of regulatory approval for the trial. This report will be submitted to regulatory authorities and Independent Ethics Committees (IEC) in accordance with all applicable global laws and regulations. Copies will be forwarded to BMS and Investigators.

8.16. *Urgent Safety Measures*

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior notification from the competent authority. However the Chief investigator/delegate must notify the Medicines and Healthcare Products Regulations (MHRA) the Research Ethics Committee (REC) and the Sponsor (via RM-CTU who will in turn inform BMS) of the new events and the measures taken and the plan for further action within 3 days of the measure being implemented. Should the site initiate a USM, the Investigator must inform the Sponsor (via RM-CTU) immediately either by:

- The date of the USM;
- Who took the decision; and
- Why action was taken.

The Sponsor (via RM-CTU) will notify the MHRA and the Main REC within three days of USM initiation. RM-CTU will distribute the response and any subsequent amendments to the trial site.

Chief Investigator Contact Details

Name: Dr Merina Ahmed

Address: The Royal Marsden NHS Foundation Trust
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Sutton SM2 5PT

Email: merina.ahmed@rmh.nhs.uk

8.17. *Pregnancy*

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure (including within 23 weeks of last IMP), the investigational product will be permanently discontinued in an appropriate manner.

The Investigator must immediately notify the sponsor and Bristol-Myers Squibb of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS].

Any pregnancy that occurs in a female partner of a male study participant should be reported to sponsor and Bristol-Myers Squibb (including within 31 weeks of last IMP). Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Note that the investigator must obtain consent from the patient for provision of any information regarding the pregnancy and its outcome.

8.18. *Overdose*

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE. In this study, any administered dose greater than 20% of the correct prescribed dose as per Section 4.2.2 will be deemed an overdose regardless of sequelae.

8.19. *Other Safety Considerations*

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

8.20. *Drug Induced Liver Injury (DILI)*

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.21. *Management of Nivolumab Related Infusion Reactions*

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to

occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v.4.0 guidelines.

For treatment recommendations, please refer to local treatment standards and guidelines as appropriate.

8.22 *Management of Immunotherapy related colitis*

Patients with symptoms of grade 3 colitis must have a confirmed histological inflammation via flexible sigmoidoscopy or colonoscopy. These patients should be managed according to local guidelines. Patients should be managed locally by appropriately trained specialists. Patients whose symptoms are refractory to infliximab should be considered for Vedoluzimab dosing (appendix 8). This is a non-funded drug and individual cases must be referred to Bristol-Meyer Squibb for consideration of funding.

9. STATISTICAL CONSIDERATIONS

9.1. *Sample Size Justification*

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 (See Section 4.7.4)

Table 3: 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%.

9.2. *Endpoint Definitions*

9.2.1. Primary Endpoint

- Rate of grade ≥ 3 pneumonitis with adjuvant nivolumab after stereotactic body radiotherapy (SBRT) within 6 months of the final fraction of radiotherapy. A rate that exceeds 20% will be deemed unacceptable and will lead to a rejection of the null hypothesis

The rate of grade ≥ 3 pneumonitis events observed within the 6 month period from the final fraction of radiotherapy will be calculated along with a one-sided 95% CI using the exact method. For the purposes of this study 6 months is defined as 26 weeks.

9.2.2. Secondary Endpoints

- Frequency of treatment related of all grades and grade ≥3 as per CTCAE v. 4.0

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 and the proportion of grades 1-4 and separately grades 3-4 will be reported. Toxicity 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 stereotactic body radiotherapy (SBRT)

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 again along 95% exact CIs. The median number of doses received will be presented along with its interquartile range (IQR).

- 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. All rates of relapse will be calculated along with their 95% exact CIs using Kaplan-Meier methods.

- OS rate 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 (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow-up. OS rates will be estimated using the Kaplan-Meier method. The OS rate at 6, 12 and 24 months will be reported along with 95% CIs.

- 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 will be censored at last follow up date. DFS rates will be estimated using the Kaplan-Meier method and the DFS rate at 6, 12 and 24 months will be presented along with 95% CIs.

*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.

- Estimation of the health related quality of life (HRQoL) score at each time point of analysis

All questionnaires (see Appendix 10) 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.

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. We do not anticipate that the new treatment schedule of this amendment will alter the toxicity profile of nivolumab or the survival rates, however, a further sensitivity analyses may take place to exclude any patients that have received the q2W treatment schedule throughout the treatment period. This analysis will be applied only to endpoints assessed beyond 6 months (after C13 of treatment).

9.2.3. Exploratory Endpoints

These analyses are purely exploratory and a separate SAP will be drafted before their analysis.

- Assessment of rates of toxicity within percentage of predicted FEV1 bands

  Grade 3/4 toxicity rates of specific interest (e.g. pneumonitis) will be tabulated against FEV1 bands.

  FEV1 bands will be as per the GOLD criteria (see Appendix 2):

  - ≥80%
  - ≥50 - <80%
  - ≥30 - <50%
  - <30%

- Assessment of rates of toxicity within percentage of predicted DLCO bands

  Grade 3/4 toxicity rates of specific interest (e.g. pneumonitis) will be tabulated against DLCO bands.

  DLCO will be divided into four groups as per percentage of predicted as follows:

  - ≥80%
  - ≥60 - <80%
  - ≥40 - <60%
  - <40%

- DFS and OS rates in PD-L1 expressers (≥1%) and non-expressers (<1%) (BMS assay)

  DFS and OS rates at 6, 12 and 24 months will be described according to PD-L1 expression.

- PD-L1 Status will be stratified according to expression as follows:

PD-L1 Expression	Category
< 1%	Non-Expresser
≥ 1%	Expresser
≥ 50%	High Expresser

- DFS and survival rates in squamous and non-squamous subgroups

  DFS and OS rates at 6, 12 and 24 months will be described according to squamous and non-squamous subgroups

  - Analysis of research bloods for ctDNA

9.3. *Interim Analysis*

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).

9.4. *Timing of Analysis*

The primary endpoint will be analysed once all patients have reached the primary time-point i.e. 6 months from the final fraction of radiotherapy. A subsequent analysis will address the secondary endpoints once the data are mature enough i.e. follow up data of 24 months (and beyond up to 5 years if available).

10. REGULATORY & ETHICS COMMITTEE APPROVAL

10.1. *Good Clinical Practice*

This study will be conducted in accordance with the conditions and principles of Good Clinical Practice (GCP), as defined by the Medicines for Human Use (Clinical Trials) Regulations (2004), as amended and in accordance with the ethical principles set out in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol, the subject informed consent documents and any substantial amendments will receive approval/favourable opinion from REC prior to implementation. The protocol, relevant associated documents and substantial amendments to these documents will also be approved by the competent authority (MHRA) before

being implemented. The only exception to this is an Urgent Safety Measure (USM), which may be implemented immediately if required to protect participants from immediate hazards to their health and safety. The MHRA and REC will be notified immediately and in any event within 3 days if such a measure is taken.

All potential serious breaches of GCP within this study must be reported to the Sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g. loss of medical licensure, debarment).

10.2. *Research Ethics Committee*

Before study initiation, the Investigator must have written and dated approval/favourable opinion from the REC for the protocol, consent form, subject recruitment materials (e.g. advertisements) and any other written information to be provided to subjects. The Investigator or Sponsor should also provide the REC with a copy of the SmPC or product labelling information to be provided to subjects and any updates.

The Investigator or Sponsor will provide the REC with relevant reports, updates and other information (e.g. expedited safety reports, amendments, and administrative letters) according to regulatory requirements and sponsor / RM-CTU SOPs.

10.3. *Informed Consent*

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (As per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

` 3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4) Obtain the REC's written approval/favourable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information

5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject

6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The Investigator, or a person designated by the Investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements.

The consent form must also include a statement that the sponsor and regulatory authorities have direct access to subject records. BMS may need to review certain patient records with regard AE/SAE reporting

and investigating. Any data shared outside of the investigator site will be identifiable only by trial number.

Subjects unable to give their written consent (e.g. stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in or to be withdrawn from, the clinical study at any time must be respected.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

11. DATA HANDLING AND STUDY MANAGEMENT

In accordance with the principles of GCP, the Investigator will maintain complete, accurate, legible and easily retrievable data. Such data shall also be secured in order to prevent loss of data.

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigator's Study Files and CRFs. The Investigator will ensure the Study Files are maintained with the CRFs and protocol/amendments, REC and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae and authorization forms, all correspondence and other appropriate documents.

Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays,

subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

11.1. *Data collection tools and source document identification*

Data will be collected and maintained in accordance with GCP. CRFs for the recording and collecting of data will be developed along the lines of other trials run at RMH. All forms will be anonymised with a reference number and completed by the site staff in a legible manner using permanent ink. Corrections to data on CRFs will only be made by crossing out the incorrect data with a single line and writing the correct data next to the deleted data. The incorrect data must never be obliterated using correction fluid or similar preparations. Each correction will be initialed and dated by the person making the correction. The Investigator will sign and date all CRFs to indicate that, to his/her knowledge, the data contained in the CRF are complete and accurate. A MACRO (v4.0) database will be used to store the data related to the study. Personnel who have access to the database are legally bound by the confidentiality agreement in their contract of employment. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

Data management will be carried out by RM-CTU using an electronic database and in accordance with the data management plan agreed by the RM-CTU. Data entry will be carried out by appropriately trained personnel at participating centres. Queries will be raised centrally by the trial manager / trial monitor and sent to the participating centre for resolution.

11.2. *Archiving*

The Chief Investigator is responsible for the secure archiving of essential documents, CRFs and the trial database as per the sponsor's policy. All essential/source documents will be archived for a minimum of five years after conclusion of the study in accordance with local procedures (gSOP-17). The Principal Investigator at each site is responsible for archiving all source documents, CRFs and the investigator site file for a minimum of 5 years following the end of the trial. Destruction of essential documents will require authorization from the sponsor.

11.3. *Delegation of responsibilities*

This trial is sponsored by the Royal Marsden NHS Foundation Trust. This trial will be conducted in accordance with the professional regulatory standards required for non-commercial research in the NHS under the research governance framework for health and social care and good clinical practice. The following responsibilities have been delegated to:

11.3.1. Royal Marsden Clinical Trial Unit (RM-CTU)

RM-CTU has overall responsibility for facilitating and coordinating the conduct of the trial and is also responsible for collating data obtained, and undertaking and reporting all analyses. The responsibilities of RM-CTU for the day-to-day management of the trial will include the following.

- Ensuring an appropriate ethics opinion has been sought, and any amendments have been approved
- Giving notice of amendments to protocol, make representations about amendments to the Main REC and MHRA as applicable
- Notifying sites and Sponsor that the trial has ended
- Raising and resolving queries with local Investigators
- Keeping records of all SAEs, overdose incidents and pregnancies reported by Investigators
- Notifying the Main REC, MHRA and Investigators of related SAEs

11.3.2. Bristol-Myers Squibb

- Provision of IMP
- BMS will notify the Chief Investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e. not previously described in the SmPC). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). BMS will email the Chief Investigators of any SUSAR, including international, as soon as it is released.

11.3.3. Participating sites

- Putting and keeping in place arrangements to adhere to the principles of GCP
- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving of documentation once the trial has ended.

- Taking appropriate urgent safety measures
- Responsibilities are defined in an agreement between an individual participating centre and RM-CTU, which must be signed and in place before recruitment can commence
- Sites wishing to participate in this study will be required to provide evidence that they are equipped to deliver the protocol treatment for the duration of the study

11.3.4. Independent Data Monitoring Committee (IDMC)

Responsibilities of the IDMC are as follows:

- Review relevant safety data and make recommendations regarding escalation to enrolment of patients with ECOG performance status 2
- Review safety data and make recommendations regarding escalation to enrolment of patients with multifocal and central primary NSCLC treated with SBRT and IMP
- Monitor the progress of the trial and ensure emerging safety information is evaluated and protocol and GCP principles are adhered to

The IDMC terms of reference, roles and responsibilities will be defined in a charter. Further internal or external expert opinion may be sought as necessary.

11.3.5. Trial Management Group

In order to oversee the conduct and progress of the trial, a Trial Management Group (TMG) will be convened, and the membership will include the CI, statistician, trial manager and other members of the study team as appropriate. A charter will be created to define the membership, remit, frequency and format of meetings.

11.4. *Insurance*

The usual NHS indemnity processes are in place to cover negligent harm caused through participation in this study. In terms of liability, NHS Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Therefore compensation is available in the event of clinical negligence being proven.

11.5. *Publication Policy*

The results of this study will be disseminated by presentation at academic meetings and publication in peer-reviewed journals. Investigators will be asked to contribute to co-authorship of any publications arising from this study. No publications will be allowed without agreement of the Chief Investigator.

Authorship for the main reports from the study will consist of the Chief Investigator, co-Investigators, and other members including the study statistician and key research nurses. Authorship credit will be given according to the criteria defined by the ICMJE (http://icmje.org) which is based on 1. Substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data, 2. Drafting the article or revising it critically for important intellectual content and 3. Final approval of the version to be published. Authors should meet conditions 1, 2 and 3. Other Investigators who have contributed to the study will be acknowledged in the study report. The Investigators will make every attempt to report on the results of the study regardless of outcome.

11.6. *Funding*

This trial is funded by a grant from BMS, who are also supplying the IMP free of charge for use in this trial.

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Appendix 1 – Women of Child Bearing Potential (WOCBP)

Women of childbearing potential (WOCBP)

"Women of childbearing potential" is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level greater than 40 mIU/mL.

Women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. At a minimum, subjects must agree to the use of 2 methods of contraception, with 1 method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION
For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:
_ combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1:
o oral
o intravaginal
o transdermal
_ progestogen-only hormonal contraception associated with inhibition of ovulation 1:
o oral
o injectable
o implantable 2
_ intrauterine device (IUD) 2
_ intrauterine hormone-releasing system (IUS) 2
_bilateral tubal occlusion 2

_ vasectomised partner [2,3]
_ sexual abstinence [4]

1 Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method).
2 Contraception methods that in the context of this guidance are considered to have low user dependency.
3 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.

The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

LESS EFFECTIVE METHODS OF CONTRACEPTION
Acceptable birth control methods that result in a failure rate of more than 1% per year include:
_ progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
_ male or female condom with or without spermicide [5]
_ cap, diaphragm or sponge with spermicide [5]

5 A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

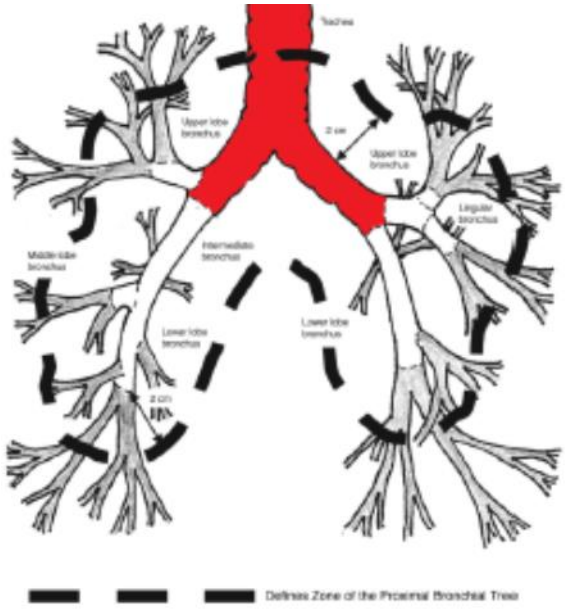
Appendix 2 – GOLD Classification

COPD Stage	Severity	Postbronchdilator FEV1/FVC	FEV1 % pred
0	At risk [#]	> 0.7	≥ 80%
I	Mild COPD	≤ 0.7	≥ 80%
II	Moderate COPD	≤ 0.7	50% - 80%
III	Severe COPD	≤ 0.7	30% - 50%
IV	Very severe COPD	≤ 0.7	< 30%

Appendix 3 - MRC Dyspnoea Scale

MRC DYSPNOEA SCALE	
Grade	**Degree of breathlessness related to activities**
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100m or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

Appendix 4 – Definition of a Central Lesion



"Ultracentral" lung cancer is defined as centrally located NSCLC with a planning target volume (PTV) overlapping the trachea or main bronchi. (red shaded area on diagram)
Tekatli 2016 [16]

Appendix 5 - Tumour Sample PD-L1 Assessment

Pre-treatment tumor tissue specimens in the form of a paraffin embedded block or a minimum of 10 unstained slides, with a single section on positively charged slides will be submitted for local PD-L1 immunohistochemistry (IHC) assessment using the Dako PD-L1 IHC 28-8 pharmaDx assay. These biopsy

samples should be excisional, incisional, punch or core needle. Fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 positive if membrane staining is observed. PD-L1 expression will be reported as the percentage of tumour cells that express PD-L1.

Appendix 6 – Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AR reporting.

(http://ctep.cancer.gov/reporting/ctc.html)

Appendix 7 - ECOG Performance Status

0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
As published: Oken et al Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655. [49]	

Appendix 8 – Management of Specific AE Algorithms

- A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory aetiologies should be considered and appropriately treated.
- Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.
- Management of toxicities should follow local guidelines.

Appendix 9 – Health Related Quality Of Life Assessments

A) EORTC QLQ-C30 (Version 3)

http://www.eortc.be/qol/files/C30/QLQ-C30%20English.pdf

B) EORTC QLQ- LC13

http://www.eortc.be/qol/files/LC13/LC13%20English.pdf

C) Patient Generated Subjective Global assessment – Box 4

Box 4. Activities and Function: Over the past month I would generally rate my activity as:

0- Normal with no limitations

1- Not my normal self, but able to be up and about with fairly normal activities

2- Not feeling up to most things, but in bed or chair less than half the day

3- Able to do little activity and spend most of the day in bed or chair

4- Pretty much bedridden, rarely out of bed

As published in:
Ottery FD (2000): Patient-Generated Subjective Global Assessment. In: The Clinical Guide to Oncology Nutrition, ed. PD McCallum & CG Polisena, pp 11–23. Chicago: The American Dietetic Association