PRIMING Study Protocol

Study Title:	**PRIMING: P**emb**R**ol**I**zu**M**ab and stereotactic body radiotherapy **I**n metastatic **N**on-small-cell lun**G** cancer patients
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LIST OF ABBREVIATIONS

#	Fractions
AE	Adverse events
ALK	Anaplastic lymphoma kinase gene
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APC	Antigen presenting cell
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATP	Adenosine triphosphate
C	Cycle
CD	Cluster differentiation
CI	Chief Investigator
CNS	Central nervous system
CR	Complete response
CRFs	Case Report Forms
CT	Computerised tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumour deoxyribonucleic acid
CTLA-4	Cytotoxic T-lymphocyte antigen-4
D	Day
DCR	Disease control rate
DLT	Dose limiting toxicity
DSUR	Development Safety Update Report
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor gene
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
Gy	Gray
HIV	Human immunodeficiency virus
HMGB1	High-mobility group protein B1
HR	Hazard ratio
i.v.	Intravenous
ID	Identification
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational Medicinal Product
IR	Ionising radiation
irAE	Immune-related adverse events
IRD	Institutional Review Board
irECI	Immune-related events of clinical interest
irRC	Immune-related response criteria
ITIM	Immunoreceptor tyrosine-based inhibition motif

ITSM	Immunoreceptor tyrosine-based switch motif
Kg	Kilogram
L	Litre
MAD	Maximum administered dose
mg	Milligram
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare Products Regulations
mmol	Millimoles
MRC	Medical Research Council
MSD	Merck Sharp & Dohme
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NCRI CTRad	National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group
NK	Natural killer cells
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand-1
PD-L2	Programmed death ligand-2
PFS	Progression free survival
PI	Principal Investigator
PR	Partial response
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
RDSU	Research & Development Statistical Unit
REC	Research Ethics Committee
RECIST	Response evaluation criteria in solid tumours
RM-CTU	Royal Marsden Clinical Trials Unit
RP2D	Recommended phase 2 dose
SAE	Serious adverse events
SBRT	Stereotactic body radiotherapy
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SRS	Stereotactic radiosurgery
STAT-3	Signal transducer and activator of transcription 3
SUSAR	Suspected unexpected serious adverse event
TIL	Tumour infiltrating lymphocytes
TLCO	Carbon monoxide transfer factor
TPS	Tumour proportionate score
UK	United Kingdom
ULN	Upper limit of normal
USM	Urgent safety measures

Protocol Signatures

Chief / Principal Investigator Signature:

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations, the guidelines of Good Clinical Practice (GCP) the Declaration of Helsinki, the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control that will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Name: Dr Fiona McDonald

Signature:

Date:

Sponsor Signature:

On behalf of sponsor:

Name: Ms Julie Curtis

Signature:

Date:

Statistician Signature:

The signatures below constitute approval of this protocol by the signatory.

Name: Ms Ranga Gunapala

Signature:

Date:

1 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab and stereotactic radiotherapy
Trial Phase	Phase I
Clinical Indication	Advanced non-small cell lung cancer (NSCLC)
Trial Type	Interventional
Type of control	Single arm study: No treatment control
Route of administration	Intravenous Pembrolizumab and External Beam Stereotactic Body Radiotherapy (SBRT)
Trial Blinding	Unblinded, open label, dose escalation phase I study, with a subsequent cohort expansion phase.
Treatment Groups	**Part A – Dose escalation cohort.** • **DOSE LEVEL 1:** Patients will receive an initial dose of pembrolizumab in week 1 dosed at 200 mg. They will then receive lung SBRT dosed at 30 Gy in 3 fractions (#) (Monday, Wednesday & Friday) in week 3. Treatment with pembrolizumab will be continued dosed at 200 mg given every 3 weeks. • **DOSE LEVEL 2:** Patients will receive an initial dose of pembrolizumab at week 1 dosed at 200 mg. They will then also receive lung SBRT dosed at 54 Gy in 3# (Monday, Wednesday & Friday) in week 3. Treatment with pembrolizumab will be continued dosed at 200 mg given every 3 weeks. If dose limiting toxicities are seen at dose level 1 the study will be terminated. **Part B – Expansion cohort.** An additional 12 patients will be recruited for this cohort. Patients will receive an initial dose of pembrolizumab at 200 mg in week 1. This will be followed in by lung SBRT in week 3, dosed at the maximum tolerated dose determined in Part A (3# – Monday, Wednesday & Friday). Treatment with pembrolizumab will be continued dosed at 200 mg given every 3 weeks.
Number of trial patients	Up to 24 patients may be recruited to the study depending on the dose levels tolerated – up to 12 patients will be recruited to the dose escalation phase in a 3+3 design, and the dose expansion phase will recruit a further 12 patients.
Duration of trial	24 months
Participation	Until progression, intolerance or withdrawal from the trial.
Study Objectives	*Primary* 1. To assess the safety and tolerability of lung SBRT in combination with pembrolizumab. 2. To determine the recommended dose of lung SBRT to be used in combination with pembrolizumab in a phase 2 trial. *Secondary* 1. To describe the safety profile of lung SBRT in combination with pembrolizumab. 2. To assess clinical benefit by calculating the overall responses rates (ORR) and disease control rate (DCR). 3. To assess responses rates in squamous versus non-squamous histological subtypes of NSCLC. 4. To assess response rates in relation to tumour PD-1/PD-L1 expression. 5. To assess progression free survival (PFS) and overall survival (OS). *Exploratory*

	1. To identify biomarkers that correlate with immunological response to therapy. 2. To analyse peripheral blood samples for ctDNA.
Study Endpoints	*Primary* 1. To establish the maximum tolerated dose (MTD) and recommended dose for phase 2 trials (RP2D) of lung SBRT that can be safely combined with pembrolizumab. *Secondary* 1. To assess the rates of acute toxicity (defined as up to 12 weeks after the last fraction of lung SBRT) using CTC AE v4.0. 2. To assess the rates of late toxicity (defined as from 12 weeks after last fraction of lung SBRT until 28 days after the last dose of pembrolizumab) using CTC AE v4.0. 3. To calculate the ORR and DCR using RECIST v1.1 & irRC. 4. To calculate the ORR and DCR in a squamous versus non-squamous histological subtype using RECIST v1.1 & irRC. 5. To assess the frequency of PD-1/PD-L1 expression distribution in responders and non-responders. 6. To measure the PFS and OS at 6 and 12 months. *Exploratory* 1. To characterize tumour infiltrating lymphocytes and tumour antigens in the tumour biopsies. These immunohistochemistry analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2. 2. To assess for levels of ctDNA before and after lung SBRT
Summary of Main Inclusion Criteria	1. Patients should be ≥18 years old on the day of signing the informed consent. 2. Patients must have a histological or cytological diagnosis of NSCLC. 3. Patients should have non-radically treatable stage IIIB or IV disease. If they are known to have a driver mutation for which there is a small molecule targeted therapy, they must have had disease progression or be intolerant of this. 4. Patients must have measurable disease as assessed by RECIST v1.1. 5. Patient should have an ECOG performance status 0-1. 6. Patients should be able to tolerate a course of stereotactic radiotherapy as assessed by the investigator. 7. Patients should have disease within the lung, away from critical structures, suitable for treatment to part of lesion with lung SBRT. 8. Patients must have adequate organ function including MRC dyspnoea score <3 and adequate baseline lung function tests, with an FEV_1 >0.8L or >30% of predicted and a TLCO >30%
Summary of Main Exclusion Criteria	1. Patients who have taken any investigational medicinal product or have used an investigational device within 4 weeks of the first dose of pembrolizumab. Patients may participate in additional observational studies. 2. Patients who have received prior chemotherapy, targeted small molecule therapy or radiotherapy within 4 weeks prior to the first dose of pembrolizumab. 3. Patients with a diagnosis of immunodeficiency or be receiving systemic steroid therapy (>7.5 mg of prednisone / >1 mg of dexamethasone or their

	equivalent dose) or any other form of immunosuppressive therapy within 7 days prior to the first dose. 4. Patients with evidence of active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. 5. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). 6. Patients with evidence of active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided the brain metastases are stable and there is no evidence of new or enlarging brain metastases. 7. Patients who have had previous radiotherapy to the lung or other neighbouring region that would preclude the safe administration of lung SBRT. 8. Patients with evidence of interstitial lung disease, or history of pneumonitis (including non-infectious pneumonitis) that required steroids, or current pneumonitis (including non-infectious pneumonitis).
Treatment / Main Study Procedures	During the dose escalation phase, patients will receive an initial dose of pembrolizumab during week 1 dosed at 200 mg, followed by lung SBRT at one of two dosing levels in week 3 (30 Gy in 3# or 54 Gy in 3#). Treatment with pembrolizumab will be continued dosed at 200 mg every 3 weeks. Additionally, there will be an expansion cohort phase where patients will receive an initial dose of pembrolizumab dosed at 200 mg in week 1, followed by lung SBRT which will be given at the MTD in week 3, as determined during the dose escalation phase. Treatment with pembrolizumab will be continued dosed at 200 mg given every 3 weeks. Patients will undergo clinical assessment on the day of each administration of pembrolizumab and during the week of lung SBRT. Patients will continue on pembrolizumab until disease progression, unacceptable adverse events, discontinuation of study medication for any other reason or withdrawal from the trial. All clinical assessments should be completed and reviewed before the administration of the next dose. After the end of treatment each patient will be required to attend a safety follow up visit at 30 days or before the initiation of a new cancer treatment, whichever comes first. Patients who discontinue for reasons other than disease progression will be followed-up every 9 weeks for disease status until progression, initiating a new anti-cancer treatment, withdrawing consent, or becoming lost to follow-up. Once a patient has suffered disease progression or initiated a new cancer treatment they will be followed up every 12 weeks to determine their survival status. This will be done by reviewing their medical notes and/or contacting the patient or GP directly. Patients will remain on this follow-up until death, withdrawal of consent or the end of the study.

1 BACKGROUND & RATIONALE

1.1 Background

Lung cancer is the leading cause of cancer mortality with ~35,000 deaths annually in the United Kingdom (UK) in 2012; equivalent to 97 deaths a day. Of over 43,000 cases of lung cancer diagnosed each year in the UK, 87% (~37,700) of patients present with non-small cell lung cancer (NSCLC) and 36% (~13,500) of NSCLC patients will present with advanced metastatic disease (1). The 5 year survival from lung cancer has changed little (from 3% to 8%) over the last 60 years, with progress continuing to lag significantly behind other common cancers.

There is currently no curative therapy for metastatic NSCLC. For patients with good performance status, palliative systemic treatment is the standard of care and is offered to patients with the aim of improving symptoms, optimising quality of life and prolonging survival. Combinations of platinum agents with gemcitabine, vinorelbine, paclitaxel, docetaxel or pemetrexed achieve response rates of 20-30% and a median survival of 10-12 months (2, 3). The choice of chemotherapeutic agents is determined in part by the histological subtype of NSCLC. Over the last 10 years a greater understanding of the molecular basis of NSCLC; particularly adenocarcinoma, has led to the identification of specific mutations which are present in approximately 5-10% patients. For these patients, targeted treatments against the epidermal growth factor receptor (*EGFR*) (4-6) or anaplastic lymphoma kinase (*ALK*) gene rearrangements (7) are also available. These agents have the advantage of a lower toxicity profile, and have been shown to improve progression free survival (PFS) and overall survival (OS) when compared to standard chemotherapy agents in the first and second line settings respectively (7, 8).

Second-line treatment options are limited and response rates are low. NSCLC patients have been highlighted as having an unmet need for further research with the aim of improving the poor outcomes in this common disease. Although traditionally thought to be poorly immunogenic, NSCLC is now one of the most active areas of investigation for immunotherapy. It is speculated that the high mutational burden induced by the carcinogens in smoke may result in numerous neo-antigens that the immune system can respond to once the tumour mediated immunosuppression is blocked.

1.1.1 Immune Evasion in Cancer

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (9). Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favourable prognosis in various malignancies (10-14). In particular the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumours.

In order to effectively evade the immune system, tumours can employ a variety of mechanisms. An initial immunogenic response to tumour cells can occur through the innate immune system for example through

natural killer (NK) cell mediated lysis. NSCLC can evade such an attack through down regulation of NK ligands such as NKG2D or avoid Fas-induced apoptosis (15, 16). The immune system may then develop an adaptive immune response requiring competent cytotoxic T-cells. This is mediated through the MHC system. Antigen presenting cells (APC) capture tumour antigens priming them to T-cells in regional lymph nodes. NSCLC display reduced major histocompatibility complex (MHC) class 1 expression therefore evading the adaptive immune response. After priming, T-cells are released into the circulation and migrate to tumour tissue where they find tumour specific antigens and differentiate into effector T-cells. This process relies on signals from the T-cell receptor and several co-stimulatory and co-inhibitory molecules. However many tumours are able to induce T-cell anergy. This has been effectively demonstrated in NSCLC which induce aberrant expansion of CD4+ FoxP3+ regulatory T-cells, thus inhibiting cytotoxic T-cell and NK cell activity (17).

The immune checkpoint pathway in T-cell responses and under normal conditions through complex processes regulates effector T-cell response. Among the components of this pathway are cytotoxic T-lymphocyte antigen-4 (CTLA4) which is expressed on the cell surface of a cytotoxic T-cell once it becomes active allowing binding with B7-1 and B7-2 on the APC keeping cytotoxic activity in check.

Another key component of this pathway is the PD-1/PD-L1 immune checkpoint pathway. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions.

1.1.2 Targeting the PD-1/PD-L1 axis

PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 and has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD-L2) (15, 16). The structure of murine PD-1 has been resolved (18). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signalling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signalling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 ζ , PKCθ and ZAP70 which are involved in the CD3 T-cell signalling cascade (15, 19-21). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signalling proteins (22, 23). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and NK cells (24, 25). Expression has also been shown during thymic

development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (25).

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumours (22, 26-28). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signalling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (22).

Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. Abnormal expression PD-L1 is identified in 19% to 100% of NSCLC tumours, depending in part on the antibody, histology, and technique reported (29-32) although the figure is more likely to around the 50% mark (30, 33). Some groups have noted that PD-L1 expression seems to be more commonly observed in sarcomatoid and adenocarcinoma subtypes of lung cancer, and it has been associated with poor prognosis (29, 30). TILs seem to be absent in PD-L1+ regions of tumours (30). High PD-L1 positive frequencies have also been seen in head and neck, cervical (29%), glioblastoma multiforme (25%), bladder (21%) and oesophageal cancer (20%). Within oesophageal cancer, PD-L1 expression is higher in the squamous population compared to other histologies (34). PD-L1 expression may be directly regulated by signal transducer and activator of transcription 3 (STAT-3) and appears to be further stimulated by immunosuppressive cytokines, such as IL-27. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumour immune evasion and should be considered as an attractive target for therapeutic intervention.

1.1.3 Rationale for combining anti-PD-1 effects with radiation

It is now well recognised that the host's immune system senses the effects of ionising radiation (IR) in irradiated tissues. Evidence that the integrity of the immune system determines the dose required to control experimental tumours is more than 30 years old when reduced therapeutic efficacy was noted in mice that lacked an adequate T-cell response (35).

However it is only recently that the radiation oncology community has started to exploit the clinical potential of the immunogenic effect of IR (36). IR induced cell death can generate tumour cell antigens for dendritic cell presentation. IR can generate immunogenic cell death perhaps more effectively than chemotherapy. The 3 steps required in this process include: cell surface translocation of calreticulin, the

extracellular release of high-mobility group protein B1 (HMGB1) a non-histone nuclear protein, and release of adenosine triphosphate (ATP). Tumour cells that receive radiation undergo phenotypic changes that enhance their susceptibility to immune effectors (37-39). Enhanced expression of death receptors (40, 41), MHC class 1 molecules (37, 42, 43), co-stimulatory molecules (44), adhesion molecules (45-47), and stress-induced ligands (48-50) on tumour cells exposed to radiation increased their recognition and killing by T-cells in vitro and/or in vivo in several cancer models.

Theoretically if combined with the ideal immunotherapeutic agent, radiotherapy can engage both the innate and adaptive arms of the immune system, with the potential to convert the irradiated lesion into an in situ vaccine that elicits tumour-specific T-cells. Preclinical studies have demonstrated this in several tumour types with a variety of immunotherapeutic agents including Flt3 ligand, CpG, antiCTLA4, antiCD137 with anti-PD-1 and viral therapies. The majority of studies demonstrate release of tumour antigen leading to the induction of anti-tumour T-cell effect, while other studies demonstrate up regulation of MHC class I on tumour cells. One study examined mice bearing established orthotopic AT-3 mammary tumours and strikingly all mice treated with anti–CD137 and anti-PD-1 combined with single- or low-dose fractionated radiotherapy were cured. $CD8^+$ T-cells were essential for curative responses to this combinatorial regime. CD137 expression on tumour-associated $CD8^+$ T-cells was largely restricted to a subset that highly expressed PD-1. PD-1 signalling within the AT-3 tumours was a critical limiting factor to the therapeutic efficacy of anti-CD137 therapy, alone and in combination with radiotherapy (51).

Stereotactic Body Radiotherapy (SBRT) has rapidly evolved over the past 5-10 years due to advances in radiation technology and is a focused radiation therapy that precisely and accurately delivers high biological doses of radiation to tumour lesions while sparing the nearby normal organs. The use of SBRT results in high rates of local tumour destruction with minimal side effects. In the UK, SBRT is actively being developed with support from the National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group (NCRI CTRad) quality assurance group to ensure a high-quality SBRT National framework with unified protocols for clinical trials. It is therefore timely to appropriately evaluate the safety of this new technology in novel drug radiation combinations. Retrospective and prospective cohort studies reporting outcomes for SBRT for the treatment of oligo-metastatic disease sites have been succinctly reviewed (52). In general these studies demonstrate high rates of local disease control with acceptable rates of toxicity, using a risk adapted approach to dose and fractionation based on the surrounding normal tissue structures. There is a wealth of data supporting the safety of a dose of 54 Gy in 3# over a week for peripheral lung lesions not in contact with the chest wall (53, 54).

The concept of combining SBRT with immune checkpoint inhibitors has been explored with pre-clinical work from some groups suggesting that combined modality treatment with SBRT may be more efficacious than low dose radiotherapy. In a mouse orthotropic cell line glioma model, stereotactic radiosurgery (SRS)

with 10 Gy was tested in combination with anti-PD-1 antibodies. Anti-PD-1 antibodies led to long term cures in a subset of mice, which was not seen with either treatment modality alone (55). Post treatment analysis of brain tissue showed increased cytotoxic T-cells in the combined modality arm and decreased regulatory T-cells. However the interaction between dose and immune effect is far more complex. Verbrugge *et al* demonstrated this complex interaction by irradiating B16-OVA murine with melanoma with up to 15 Gy, given in various fraction sizes. For single fractions, tumour control and number of tumour-specific T-cells were radiation dose dependent. However, at the highest dose, there was also an increase in regulatory T-cells, which tend to down regulate the immune response. Fractionated irradiation at 7.5 Gy/# seemed to produce the best tumour control and tumour specific T-cell response while still maintaining low regulatory T-cell numbers (51). A further study supports fractionating radiation treatment in conjunction with immunotherapy, by testing anti-CTLA-4 antibodies with radiation in a mouse breast cancer model. Mice were treated with 20 Gy × 1#, 8 Gy × 3#, or 6 Gy × 5# in combination with monoclonal antibody against CTLA-4. Authors found that fractionated but not single-dose radiotherapy induces an abscopal effect when used with anti-CTLA-4 antibody (56). However, another preclinical study comparing ablative radiation doses against fractionated radiation noted that ablative radiation, such as a single dose of 20–25 Gy, dramatically increased T-cell activity and tumour control. When 5 Gy × 4# given over 2 weeks were compared against a single 20 Gy dose, radiation-initiated immune responses and tumour reduction appeared to be abrogated by the fractionated radiation [48]. As is evident the relationship between radiotherapy dose, fraction size and immune interplay is a complex one and clinical studies are urgently needed to assess how to optimally harness the effect on radiation on the immune system.

1.1.4 Pembrolizumab Clinical Trial Data

1.1.4.1 Pembrolizumab

Pembrolizumab (Keytruda®; previously known as SCH 900475/MK3475) is a potent and highly selective humanized monoclonal antibody of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

1.1.4.2 Clinical Trial Data

Pembrolizumab has also showed excellent activity in the second-line setting for advanced NSCLC and was granted accelerated drug approval with the Food and Drug Administration (FDA) following the results from the expanded phase 1 study, KEYNOTE-001 (57), and the most recent data from KEYNOTE-010 (58). KEYNOTE-001 included 495 patients with advanced NSCLC, with both squamous and non-squamous histology. Of the patients treated, 81% had received at least one-line of prior treatment. The dose expansion assessed multiple doses. After a median follow-up of 10.9 months, the median OS was 12.0 months for all patients, and 10.4 months in previously treated patients. The median PFS was 3.7 months for all patients,

and 3.0 months in previously treated patients. ORR was 19.4% in all patients, and 18.0% in previously treated patients. The median duration of response was again more impressive than the PFS at 12.5 months (range: 1.0–23.3 months). When stratified for PD-L1 expression (Table 1), they showed that tumour proportionate score (TPS) of ≥50% was predictive of better response, PFS and OS. Interestingly, the response rates in smokers were twice as high when compared with non-smokers and there was little difference between squamous and non-squamous histological subtypes (57).

KEYNOTE-010 was a head-to-head assessment of pembrolizumab (2 mg/kg and 10 mg/kg) with docetaxel in the second-line setting. The median OS was again in favour of pembrolizumab (2 mg/kg: 10.4 months, HR=0.71, *P-value*=0.0008; and 10 mg/kg: 12.7 months, HR=0.61, *P-value*<0.0001) over docetaxel (8.5 months). The median PFS was 3.9-4.0 months, with no difference across the arms. When stratified for PD-L1 expression, PD-L1 positive patients (TPS ≥50%), the median OS was again in favour of pembrolizumab (2 mg/kg: 14.9 months, HR=0.54, *P-value*=0.0002; and 10 mg/kg: 17.3 months, HR=0.50, *P-value*<0.0001) over docetaxel (8.2 months). Likewise, for this patient population, the median PFS was again in favour of pembrolizumab (2 mg/kg: 5.0 months, HR=0.59, *P-value*=0.0001; and 10 mg/kg: 5.2 months, HR=0.59, *P-value*<0.0001) over docetaxel (4.1 months). The response rate was ~30% in PD-L1 positive patients receiving pembrolizumab versus 8% receiving docetaxel, and in all patients, this was 18% versus 9%, respectively (58).

Recent data supports the use of PD-1 inhibition in treatment-naïve advanced NSCLC patients. KEYNOTE-024 compared pembrolizumab against investigators choice of platinum-based doublet chemotherapy, enriched for PD-L1 positive patients (TPS ≥50%). This shown a significant difference in median PFS favouring pembrolizumab (10.3 versus 6.0 months), and a significant difference in OS, again in favour of pembrolizumab (1-year OS of 80.2% versus 72.4%). The response rate was significantly higher in the pembrolizumab arm compared chemotherapy (44.8% versus 27.8%). The toxicity data did not reveal any new adverse events that were not already known about pembrolizumab, and again it was in support of pembrolizumab over platinum-based doublet chemotherapy (59). KEYNOTE-042 is of a similar design in an Asian population, but stratified patients into two PD-L1 positive groups: low expression (1-49%) and high expression (≥50%; NCT02220894), the results of which are still awaited.

Adverse events of grade 3-5 occurred in 13-16% of the patients receiving pembrolizumab, and 35% of the patients receiving docetaxel. Treatment discontinuation due to treatment-related adverse events was seen in 4-5% of patients receiving pembrolizumab compared with 10% receiving docetaxel. Treatment-related deaths occurred in three patients in the 2 mg/kg arm (2 with pneumonitis, and 1 with pneumonia), 3 patients in the 10 mg/kg arm (1 each with myocardial infarction, pneumonia, pneumonitis), and 5 patients on docetaxel (1 each with acute cardiac failure, dehydration, febrile neutropenia, interstitial lung disease, and respiratory tract infection). Immune-related adverse events occurred in ~20% of patients receiving pembrolizumab, with the most common being hyperthyroidism (4-6%), hypothyroidism (8%), and

pneumonitis (4-5%). The immune-related adverse events of grade 3-5 severity occurring in ≥1% of patients were pneumonitis (2%) and severe skin reactions (1-2%) (58).

These data have resulted in pembrolizumab being granted breakthrough therapy designation with the FDA for patients with NSCLC whose cancers have progressed on or after platinum-containing chemotherapy, as well as targeted agents in those with *EGFR* mutations and *ALK* gene rearrangements (60).

KEYNOTE-001 also validated the PD-1 biomarker using the anti-PD-1 antibody clone 22C3 (Merck) and immunohistochemistry. Tumour slides were stained and scored for neoplastic membranous staining (i.e. the TPS) as <1%, 1-49%, or >50%. Using receiver operatory characteristic curve analysis they found that a PD-L1 score of >50% (strong) was the best predictor of efficacy of pembrolizumab, with a response rate of 45.2% (95%CI: 33.5 – 57.3) and a median PFS of 6.3 months. The media OS has not yet been reached. The response rates in patients who scored PD-L1 1-49% was 16.5% (95%CI: 9.9 – 25.1) and in those who scored PD-L1 <1% was 10.7% (95%CI: 2.3 – 28.2). As responses were seen across all PD-L1 scores, this clinical trial will explore the combination of pembrolizumab and lung SBRT unenriched for PD-L1 strong (57).

1.2 Rationale for the Trial

The abscopal effect refers to a rare phenomenon of tumour regression at a site distant from the primary site of radiotherapy (61). Radiotherapy has been shown to induce abscopal effects in several types of cancer, including melanoma, lymphoma, renal-cell carcinoma and NSCLC (62-65). The effect is attributed to activation of the systemic immune response. Radiation-induced inflammation is known to increase antigen presentation, subsequent tumour recognition, and can ultimately, enhance the tumour-directed immune response (66). This effect may be more pronounced in response to ablative rather than conventional dosage or fractionation schedules (67). More recently, the abscopal effect has been described in the context of patients receiving immunotherapy concurrently with radiotherapy. Formenti *et al* described a case of abscopal response in a patient with advanced NSCLC who received palliative hepatic radiotherapy while on ipilimumab. The response was seen 2.5 months following radiotherapy (68). Experimental data from multiple cancer models have provided sufficient evidence to propose a paradigm shift, whereby some of the effects of radiation are recognised as contributing to systemic antitumor immunity. Therefore, the traditional palliative role of radiotherapy in metastatic disease is evolving into that of a powerful adjuvant for immunotherapy. This combination strategy adds to the current anticancer arsenal and offers opportunities to harness the immune system to extend survival, even among metastatic and heavily pretreated cancer patients (36). Combination trials of immunotherapy and SBRT are required to explore the potential for radiation enhancing the effects of immunotherapy with the aim of improving outcomes for patients with NSCLC (36). The initial step is to assess the tolerability and safety of immunotherapy with SBRT. This clinical trial protocol will look at the safety and tolerability of pembrolizumab, an anti-PD-1 monoclonal antibody, given in combination with lung SBRT in patients with advanced NSCLC.

2 STUDY OBJECTIVES & ENDPOINTS

2.1 Study Objectives & Hypothesis

2.1.1 Primary Objective & Hypothesis

- Objective: To assess the safety and tolerability of lung SBRT with pembrolizumab and to determine the RP2D of lung SBRT to be used in combination with pembrolizumab.
- Hypothesis: Lung SBRT can be safely administered in combination with pembrolizumab without significant DLTs.

2.1.2 Secondary Objectives

- To describe the safety profile of lung SBRT in combination with pembrolizumab.
- To assess clinical benefit with overall responses rate (ORR) and disease control rate (DCR).
- To assess responses rates in squamous versus non-squamous histological subtypes of NSCLC.
- To assess response rates in relation to tumour PD-1/PD-L1 expression.
- To assess progression free survival (PFS) and overall survival (OS).

2.1.3 Exploratory Objectives

- To identify biomarkers that correlate with immunological response to therapy.
- To analyse peripheral blood samples for ctDNA.

2.2 Study Endpoints

2.2.1 Primary Endpoint

- To establish the MTD and RP2D of lung SBRT that can be safely combined with pembrolizumab.

2.2.2 Secondary Endpoints

- To assess the rates of acute toxicity (defined as up to 12 weeks after the last fraction of stereotactic radiotherapy) using CTC AE v4.0.
- To assess the rates of late toxicity (defined as from 12 weeks after last fraction of lung SBRT until 28 days after the last dose of pembrolizumab) using CTCAE version 4.0.
- To calculate the ORR and DCR using RECIST v1.1 & irRC.
- To calculate the ORR and DCR in squamous versus non-squamous histological subtype using RECIST v1.1 & irRC.
- To assess the frequency of PD-1/PD-L1 expression distribution in responders and non-responders.
- To measure the PFS and OS at 6 and 12 months.

2.2.3 Exploratory Endpoints

- To characterise TILs and tumour antigens in the tumour biopsies. These immunohistochemistry analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2.
- To assess for levels of ctDNA pre- and post- SBRT.

3 STUDY DESIGN

3.1 Summary of Study Design

This is a single centre non-randomised open label phase 1 trial of lung SBRT to part of a lung lesion in patients with advanced NSCLC in combination with pembrolizumab. This study will recruit up to 24 patients whose lung cancer has progressed beyond one line of palliative chemotherapy, and an EGFR or ALK inhibitor if an *EGFR* driver mutation or *ALK* gene rearrangement is present, respectively, and now requires further palliative systemic treatment.

3.2 Treatment Regimen

The study will be conducted in two parts; an initial lung SBRT dose escalation phase (Part A), followed by a lung SBRT dose expansion cohort (Part B). The dose escalation phase is based on a 3+3 design such that patients will be treated in cohorts of 3-6 patients. A maximum of 12 patients will be allocated to one of two doses of lung SBRT in combination with pembrolizumab to determine the MTD, DLTs and RP2D. If there is more than one DLT in cohort 1, this treatment combination will be deemed as being unacceptable, and it would lead to termination of the study. Note, there is no de-escalation in cohort 1. During the dose expansion cohort, 12 patients will have lung SBRT dosed at the RP2D determined during the dose escalation phase in combination with pembrolizumab to obtain additional safety and response data. Maintenance pembrolizumab will continue until disease progression, unacceptable toxicities, the patient withdraws consent to the trial, or the patient has completed 24 months of treatment. A maximum of 24 patients will be treated in the study.

All patients will receive pembrolizumab on cycle (C) 1 day (D) 1, in Part A and B of the study. All patients will receive lung SBRT on C1D15, C1D17, and C1D19 as per lung SBRT protocol (See Appendix 3). Although C1D1 can occur +/- 3 days, C1D15, C1D17, and C1D19, must be scheduled for a Monday, Wednesday and Friday, respectively. Patients in part A will receive lung SBRT dosed at 30 Gy in 3# in cohort 1, or 54 Gy in 3# in cohort 2. Patients in Part B will receive the RP2D of lung SBRT, determined in Part A. All patients in Part A and Part B will receive pembrolizumab dosed at 200 mg every 3 weeks, until disease progression, unacceptable toxicities, the patient withdraws consent from the trial, or the patient has completed 24 months of treatment.

In the dose escalation phase, a minimum of 3 patients will be required per dose level being assessed. A minimum gap of 1 week will be left between the treatment of the first and the second, and between the second and the third patients with the combination of pembrolizumab and lung SBRT to mitigate against multiple patients suffering from acute toxicity. The DLT period for this study is 12 weeks from the last dose of lung SBRT (i.e. at C6D1). The dose escalation will be considered by the Safety Review Committee (SRC) once the 3rd or 6th patient in the cohort has completed the DLT period. If no DLT is observed at a dose level,

then lung SBRT will be dose escalated to the next dosing level (see Table 1). If 1 out of 3 patients experience a DLT, then the cohort will be expanded to 6 patients. If 1 in 6 patients experience a DLT, then the dose will be escalated to the next dosing level. However, if ≥ 2 in 6 patients experience a DLT then the maximum administered dose (MAD) will have been reached, and the RP2D will be the previous dosing level that will be used for the dose expansion cohorts. If the MAD is seen at dose level 1 then the study will be terminated. While waiting for 3 or 6 patients to complete the DLT period, no additional patients will be recruited. Further patients can only be recruited after the SRC has reviewed the toxicity data for the cohort and taken a decision to dose escalate to the next cohort or expand the current cohort to 6 patients.

Once the MTD has been determined the trial enters the dose expansion phase (unless the MTD is dose level 1). Here, 12 patients will be treated with the RP2D of SBRT combined with pembrolizumab.

If there is ongoing clinical benefit at 24 months, the CI/PI will need to discuss with the sponsor and MSD, on a case by case basis for the continuation of pembrolizumab.

Table 1: Lung SBRT dose levels and pembrolizumab dosing during the dose escalation and dose expansion phase.

Dose Level	Pembrolizumab Dose	Lung SBRT to part of a lung lesion
1	200 mg i.v. over 30 minutes, every 3 weeks	30 Gy in 3# (Monday, Wednesday, Friday)
2	200 mg i.v. over 30 minutes, every 3 weeks	54 Gy in 3# (Monday, Wednesday, Friday)
Dose expansion	200 mg i.v. over 30 minutes, every 3 weeks	RP2D

SBRT: Stereotactic Ablative Body Radiotherapy; Gy: Gray; i.v.: intravenous; mg: milligrams;
RP2D: Recommended Phase 2 Dose; #: fraction.

3.2.1 Dose Limiting Toxicities

The rate of entry and escalation to the next dose level will depend upon assessment of the toxicity profile of patients entered at the previous level. Acute toxicity will be assessed up to and including 3 months following the final fraction of radiotherapy (i.e. at C6D1). The MRC dyspnoea score (Appendix 2) will be used to assess dyspnoea at baseline/on treatment and the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0 will be used to grade all drug and lung SBRT observed toxicities (Appendix 4). The SRC will consider dose escalation once the 3rd or 6th patient in the cohort has completed the DLT period and review the toxicities before recruitment to the next dose level can begin or the cohort is expanded to 6 patients.

Any DLT must be a toxicity that is considered probably, possibly or definitely related to the combination of pembrolizumab and lung SBRT. DLT is defined as follows:

Haematologic:

- Neutropenia with fever grade ≥ 3
- Thrombocytopaenia with bleeding grade ≥ 3

Non-Haematologic:

Any NCI CTCAE ≥ 3 grade non-haematological toxicity that is definitely, probably or possibly related to the combination of pembrolizumab and lung SBRT including the following:

- Increased MRC dyspnoea score > 2 grades from baseline and/or acute dyspnoea grade ≥ 4 (or CTCAE dyspnoea grade ≥ 3) persisting for > 7 days (including weekend).
- Pneumonitis/pulmonary infiltrates grade ≥ 3 persisting for > 7 days (including weekend).
- Oesophagitis grade ≥3 persisting for > 7 days (including weekend).
- Toxicity leading to interruption of radiotherapy for >7 days (including weekend).

Escalation to the next dose level will not proceed until the following criteria are satisfied by the SRC:

- If 0 out of 3 patients experience a DLT, escalation to the next dose level can proceed.
- If 1 out 3 patients experiences a DLT, a further 3 patients will be recruited at that dose level.
    - If 1 out 6 patients experiences a DLT, then escalation to the next dose level can proceed.
    - If ≥ 2 out of 6 patients experience a DLT, the MAD will have been reached. The RP2D will be the dose level prior to when the DLTs were observed or dose level 2 if no DLTs were observed. All patients in the expansion cohort will have lung SBRT dosed at the RP2D (see Figure 1).
- If 2/3 patients experience a DLT then the MAD will have been reached and the expansion cohort phase will begin at the previous dose level unless this occurs at dose level 1.
- If dose level 1 is not tolerated due to DLTs, the expansion cohort will not go ahead and the trial will be terminated.

3.3 Study Schema

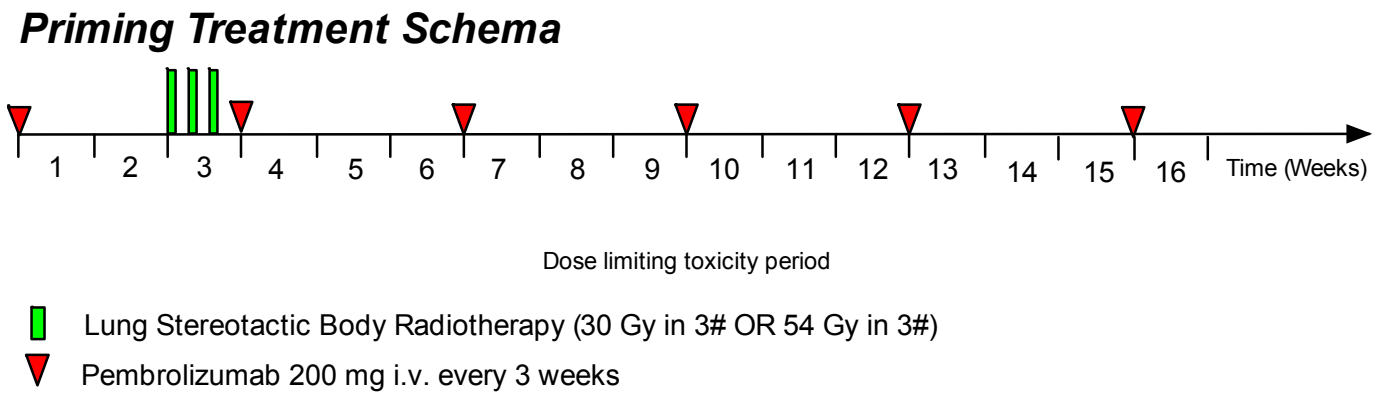

Figure 1: Schematic diagram of study events. All patients will receive a fixed dose of pembrolizumab at 200 mg i.v. every three weeks. The lung SBRT will be administered at week 3 on Monday, Wednesday and Friday. The first cohort will be dosed at 30 Gy in 3# and the second cohort will be dosed at 54 Gy in 3#.

3.4 Follow-Up after stopping Pembrolizumab

3.4.1 30 Day Safety Follow-Up Visit

All patients will be required to attend a safety follow-up visit 30 days after the last dose of pembrolizumab or before the initiation of a new anti-cancer treatment, whichever comes first. All adverse events (AEs) and serious adverse events (SAEs) that occur prior to the safety follow-up visit should be reported as described in section 7. After the safety follow-up any unresolved AEs at the patient's last visit should be followed up for as long as medically indicated, but without further recording in the CRF.

3.4.2 Follow-Up for Discontinued Pembrolizumab without Disease Progression

Patients who discontinue pembrolizumab for any reason other than disease progression will move into the follow-up phase and should be assessed every 9 weeks (63 ± 7 days) and by radiologic imaging as per standard of care to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, withdrawal or end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

3.4.3 Survival Status Follow-Up Phase

Once a patient experiences confirmed disease progression or starts a new anti-cancer therapy, the patient moves into the survival follow-up phase and will be followed up every 12 weeks to determine their disease status. This will be done by reviewing their medical notes and / or contacting the patient or GP directly. Patients will remain on this follow-up until death, withdrawal of consent, or the end of the study, whichever occurs first.

3.5 Study Termination

The 'end-of-trial' is defined as the date when the last patient has completed the 'off-study' visit or the final follow-up visit, whichever is happens last.

3.5.1 Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to patients
4. Plans to modify or discontinue the development of the study drug
5. If DLT is seen at dose level 1 in 2 out of 3 or 2 out of 6 patients

In accordance with the conditions of supply agreement with MSD, ample notification will be provided to the sponsor (via RM-CTU) and sites should alterations to the drug supply change. This is to allow time for appropriate adjustments to be made in regards to the patient's treatment.

3.6 Treatment after End of Study

Following participation in the study patient care will be decided by the local doctor according to standard practice.

4 SELECTION OF PATIENTS

4.1 Screening and Enrolment

The Investigator at site will keep a record of all patients screened for entry into this study. Copies of the screening logs will be filed in the Site File. For each patient, the primary reason for exclusion will be recorded. Diagnostic data obtained as part of the patient's standard care will be used to determine eligibility provided they fall within the protocol defined timelines. Written informed consent must be obtained prior to the patient undergoing any study specific procedures.

4.2 Registration

When the patient signs the consent form they will be allocated a trial ID that will be used to identify the patient for all future assessments.

Patients can be registered and allocated a trial ID number by contacting the RM-CTU on:

Telephone: 020 89156667

Fax: 020 8915 6762

Email: Priming.Trial@rmh.nhs.uk

Between Monday to Friday, 9 am to 4 pm.

Once all the screening assessments have been completed and the data entered on the CRFs the patient will be assessed for eligibility. If eligible the patient will begin on the trial. If the patient is not eligible then the local investigator will make alternative arrangements for the treatment of the patient. The trial ID will be a unique number that once assigned will become the permanent study identifier for that patient. In the event a patient is registered onto the study but does not begin treatment, then that patient's trial ID will not be reassigned. Treatment will begin within 7 days from the date eligibility has been confirmed. To ensure patient confidentiality patients will only be identified on CRFs, other trial specific forms and all communication to RM-CTU using their assigned trial ID. It is the CI's responsibility to maintain a confidential record of the identity i.e. full name, date of birth and hospital number for the patients enrolled in this study and their assigned trial ID. At the end of the study this record should be archived along with the Site File.

4.3 Patient Replacement Strategy

Additional patients may be enrolled in a given cohort to ensure that the required number of evaluable patients in each cohort is achieved. A patient that discontinues the trial for progressive disease within 3 months of the last dose of radiotherapy will not be evaluable for DLTs and therefore will need to be replaced. A patient that discontinues the trial for a drug-related AE will not be replaced and will be counted in the evaluable population of patients for the respective cohort. However, patients found to have active

pneumonitis on C1D1 of pembrolizumab or day 1 of radiotherapy will be removed from the trial and can be replaced. Also patients who do not reach follow-up 3 months post completion of lung SBRT for reasons other than progression or toxicity can be replaced by new patients in that cohort to ensure there is a minimum or 3 (or 6 if required) patients in each cohort.

4.4 Entry Criteria

The following eligibility criteria were designed to select patients for whom the protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. Eligibility criteria may not be waived by the investigator.

4.4.1 Inclusion criteria

In order to be eligible for participation in this trial, the patient must:

1. Patients should be ≥18 years old on the day of signing the informed consent.
2. Patients must have a histological or cytological diagnosis of NSCLC.
3. Patients should have non-radically treatable stage IIIB or IV disease.
4. Patients must have measurable disease as assessed by RECIST v1.1.
5. Patients must have had disease progression or be intolerant of standard first line palliative chemotherapy for non-small cell lung cancer. If they are known to have a driver mutation for which there is a small molecule targeted therapy, they must have had disease progression or be intolerant of this.
6. Patient should have an ECOG performance status 0-1.
7. Patients should be able to tolerate a course of stereotactic radiotherapy as assessed by the investigator.
8. Patients should have disease within the lung, away from critical structures, suitable for treatment to part of a lesion with lung SBRT.
9. Patients must have adequate organ function including MRC dyspnoea score <3 and adequate baseline lung function tests, with an FEV_1 > 0.8L or >30% of predicted and a TLCO > 30%
10. Demonstrate adequate organ function as detailed in Table 2 (based on bloods within 10 days of C1D1).
11. Have provided tissue from an archival tissue sample or newly obtained tissue sample.
12. Female patient of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication (C1D1). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
13. Female patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days

after the last dose of study medication. Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

14. Male patients should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
15. Be willing to provide informed consent for the trial.

Table 2: Adequate Organ Function Laboratory Values. These should be within 10 days of C1D1.

System	Laboratory Value
Haematological	
• Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
• Platelets	100 x 10^9/L
• Haemoglobin	≥90 g/L or ≥5.6 mmol/L
Renal	
• Serum creatinine **OR** • Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for patient with creatinine levels > 1.5 X institutional ULN
[a]Creatinine clearance should be calculated per institutional standard.	
Hepatic	
• Serum total bilirubin **OR** • Direct bilirubin	≤ 1.5 X ULN **OR** ≤ ULN for patients with total bilirubin levels > 1.5 ULN
• AST (SGOT) and ALT (SGPT)	≤ 3.0 X ULN **OR** ≤ 5.0 X ULN for patients with liver metastases
Coagulation	
Prothrombin Time (PT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

4.4.2 Exclusion Criteria

The following patients must be excluded from participating in the trial:

1. Patients who have taken any investigational medicinal product or have used an investigational device within 4 weeks of the first dose of pembrolizumab. Patients may participate in additional observational studies.
2. Patients who have received prior chemotherapy, targeted small molecule therapy or radiotherapy within 4 weeks prior to the first dose of pembrolizumab.
3. Patients with a diagnosis of immunodeficiency or be receiving systemic steroid therapy (>7.5 mg of prednisone / >1 mg of dexamethasone or their equivalent dose) or any other form of immunosuppressive therapy within 7 days prior to the first dose.
4. Patients with evidence of active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.
5. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

6. Patients with evidence of active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided the brain metastases are stable and there is no evidence of new or enlarging brain metastases.
7. Patients who have had previous radiotherapy to the lung or other neighbouring region that would preclude the safe administration of lung SBRT.
8. Patients with evidence of interstitial lung disease, or history of pneumonitis (including non-infectious pneumonitis) that required steroids, or current pneumonitis (including non-infectious pneumonitis).
9. Patients with evidence of additional malignancy that is progressing or requires active treatment.
10. Patients with a history or current evidence of any condition, therapy, or laboratory abnormality that might confound trial results, interfere with the patient's participation or is not in the best interest of the patient.
11. Patients with psychiatric or substance abuse disorders that would interfere with patient's participation.
12. Patients who are pregnant / breastfeeding or expecting to conceive within the duration of the trial, starting with the screening visit through 120 days after the last dose.
13. Patients with a history of HIV, HIV 1/2 antibodies, Hepatitis B or Hepatitis C.
14. Patients who have received a live vaccine within 30 days prior to the first dose of trial treatment.
15. Patients with known hypersensitivity to the active substance pembrolizumab or to any of the excipients listed in the SmPC.

5 STUDY PLAN AND PROCEDURES

5.1 Study Schedule

From study entry, patients will be assessed every 21 days, prior to the administration of each dose of pembrolizumab. During the week of lung SBRT patients will have an additional clinical review. Patients will continue to be assessed and stay on Pembrolizumab until they have disease progression, suffer unacceptable toxicities, withdraw the study ends or have completed 24 months of pembrolizumab. Treatment beyond progression or beyond 24 months needs to be discussed with the study sponsor and MSD. Patients will be required to attend a safety visit 30 days after their last dose of Pembrolizumab.

If the patient has not progressed at the last dose of pembrolizumab they will be reviewed every 9 weeks until the start of new anti-cancer therapy, disease progression, death, withdrawal or end of the study. Patients that have progressed or begin a new anti-cancer treatment will enter into the survival follow up phase and an update will be sought every 12 weeks to assess for disease status until death, withdrawal of consent, or the end of the study, whichever occurs first. Survival follow up can be done over the phone.

The schedule of assessments to be performed at each visit is summarised in Table 3. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator. Furthermore, additional evaluations/testing may be clinically indicated for reasons related to patient safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis B, Hepatitis C, etc.) and will be performed in accordance with local regulations.

Table 3: Study Schedule of Assessments

Trial Phase:	**Screening period**	**Dose escalation phase**					**Maintenance phase** DLT period (Pembrolizumab 200 mg q3wkly)			**Maintenance phase** Beyond DLT period (Pembrolizumab 200 mg q3wkly)				**End of Treatment** *(If applicable)*	**Post-Treatment**		
			Radiotherapy phase (30 Gy in 3# OR 54 Gy in 3#)												**Safety Follow-up (SFU)**	**Follow Up Visits**	**Survival Follow Up**
Treatment Cycle/Title:		C1, D1	C1, D15	C1, D17	C1, D19	C2, D1	C3, D1	C4, D1	C5, D1	C6, D1	C7, D1	C8, D1	C9, D1	*Discontinuation of Pembrolizumab*	*30 days after last dose*	*Every 9 weeks from SFU*	*Every 12 weeks from SFU*
Scheduling (Day):	*-28 to -1*					*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±3*	*±7*	*±7*	*±7*	*±7*
Informed Consent	X																
Inclusion/Exclusion	X																
Clinical history	X																
Full Physical Exam	X	X												X	X		
Directed Phys. Exam			X	X	X	X	X	X	X	X	X	X	X				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MRC dyspnea score	X		X	X	X	X	X	X	X					X			
Medications	X	X	X	X	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		
Vital Signs & Weight	X	X	X			X	X	X	X	X	X	X	X	X	X		
Height	X																
Haem & Biochem	X[6]	X[7]				X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X	X		
FT3, FT4 and TSH	X[6]	X					X		X		X		X	X	X		
PT and aPTT	X[6]																
Pregnancy Test	X[7]																
Urinalysis	X[6]																
Pembrolizumab		X				X	X	X	X	X	X	X	X				
Radiotherapy			X[5]	X[5]	X[5]												
Pulmonary function[3]	X												X				
Imaging	CT[1] & CXR[2]				CXR	CXR	CXR	CT	CXR		CT			CT		CT	
PD-L1 assessment[4]	X																
Research Blood		X				X			X					X			
Survival Status																	X

1. Imaging with a CT scan should occur during the screening period as a baseline and then every 9 weeks (3 cycles) for the first 6 months, then every 12 weeks after 6 months (regardless of treatment delays). Imaging with CT scanning can occur 7 days before the visit to ensure that the results are available at the visit.
2. Chest x-ray will be performed during the dose limiting toxicity period in order to monitor for pneumonitis.
3. Full pulmonary function tests should be performed every 6 months from radiotherapy.
4. Dose escalation and expansion cohort will not be enriched for PD-L1 strong patients. PD-L1 testing will be batched and performed once all patients are on study.
5. Lung SBRT will be administered at dose level being tested on C1D15, C1D17 and C1D19 during the dose escalation phase, and at the RP2D for C1D15, C1D17 and C1D19 during the dose expansion phase.
6. Screening laboratory investigations will be valid for 10 days from C1D1.
7. Safety laboratory investigations will be valid for 3 days from D1 visit.

5.2 Administrative Procedures/Assessments

5.2.1 Informed Consent

It is the responsibility of the Investigator / designee to give each patient, prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. Sufficient time should be allowed for the patient to decide on trial entry. Patients must be informed about their right to withdraw from the trial at any time. Written patient information must be given to each patient before enrolment. The written patient information is an approved patient information sheet (PIS) according to national guidelines.

The Investigator must obtain documented written informed consent from each potential patient prior to participating in a clinical trial. Consent must be documented by the patient's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterwards, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent. Only the Chief Investigator (CI), Co-Investigators and those Sub-Investigator(s) delegated responsibility by the CI, having signed the delegation of responsibilities log, are permitted to gain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol.

A copy of the signed and dated consent form should be given to the patient before participation in the trial. The original consent form should be stored in the site file with a copy also being placed in the patient's medical notes. Results from tests conducted as part of patients' standard care may be used as part of screening to determine eligibility as long as the tests were conducted within the acceptable time window.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the REC approval/favourable opinion in advance of use. The patient should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the patient's dated signature. The informed consent will adhere to REC requirements, applicable laws and regulations.

5.2.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee to ensure that the patient qualifies for the trial.

5.2.3 Demographic Data, Medical History and Treatment History

Demographic data collected will include date of birth and race/ethnicity. A medical history will be obtained by the Investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history. In addition to the medical history the Investigator or qualified designee will obtain details the patient's current disease status and treatment history including prior and current details regarding disease status, in addition to all prior cancer treatments including systemic treatments, radiation and surgeries.

5.2.4 Subsequent Anti-Cancer Therapy Status

Patients that discontinue from pembrolizumab for any other reason than disease progression will have a follow-up visit every 9 weeks in which the Investigator should review all new anti-cancer therapy initiated after the last dose of pembrolizumab. If a patient initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the patient will move into survival follow-up.

5.2.5 Survival Status

The Investigator or qualified designee will assess the patient for survival status. The assessment will include the patient status and if applicable details of patient death or detail if patient has been lost to follow-up.

5.2.6 Prior and Concomitant Medications Review

5.2.6.1 Prior Medications

The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the patient within 28 days before starting the trial. Treatment for the disease for which the patient has enrolled in this study will be recorded separately and not listed as a prior medication.

5.2.6.2 Concomitant Medications

In addition the investigator or qualified designee will record all medication, if any, taken by the patient during the trial. All medications related to reportable SAEs and events of clinical interest (ECIs) should be recorded as defined in Section 7.

5.3 Clinical Procedures/Assessments

5.3.1 PD-L1 Assessment

To participate in the trial patients need available tissue of a tumour lesion not previously irradiated (tumours progressing in a prior site of radiation are allowed) for PD-L1 characterisation. This specimen will be evaluated at a central laboratory for expression status of PD-L1 using PD-L1 IHC 22C3 pharmDx (Dako) assay. If no tissue is available then following informed consent they should undergo a biopsy of a tumour lesion for biomarker analysis. NOTE: Patients participating in this trial will be unselected for their PD-L1 status.

5.3.2 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each patient for potential new or worsening AEs as specified in the schedule of study assessments (Table 3) and more frequently if clinically indicated. AEs will be graded and recorded from confirmation of entry into the trial until the patients 30 day safety follow up visit according to NCI CTCAE v4.0 (see Appendix 4). Toxicities will be characterised in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown aetiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) or a potentially an immune-related adverse event (irAE). See Appendix 5 and the separate ECI guidance document regarding the identification, evaluation and management of AEs of a potential immunological aetiology. Please refer to section 7 for detailed information regarding the assessment and recording of AEs.

5.3.3 MRC dyspnoea Score

The investigator or qualified designee will assess the patient's dyspnoea using the MRC Dyspnoea Score (Appendix 2) at screening period and the time points defined in the study schedule of assessments (Table 3).

5.3.4 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam at screening period and the time points defined in the study schedule of assessments (Table 3). Clinically significant abnormal findings should be recorded as AEs during the trial.

5.3.5 Directed Physical Exam

For cycles that do not require a full physical exam as described in the schedule of assessments (Table 3), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

5.3.6 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the schedule of study assessments (Table 3). Vital signs should include temperature, pulse, respiratory rate, oxygen saturation, weight and blood pressure. Height will be measured at screening only.

5.3.7 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the study schedule of assessments (Table 3).

5.3.8 Pulmonary Function Tests

Full lung function tests assessments will be performed at screening, prior to the dosing of pembrolizumab (+/- 5 days) and during the maintenance phase of the of the DLT period as specified in the study schedule of assessments (Table 3).

5.3.9 Pregnancy Tests

Female patients of childbearing potential should have a negative urine or serum pregnancy during screening and within 72 hours prior to receiving the first dose of study medication as specified in the study schedule of assessments (Table 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5.3.10 Haematology, Biochemistry and Urinalysis (including, β-hCG, PT, aPTT, fT3, fT4 and TSH)

All Laboratory tests will be performed at screening and then certain assessments at every visit as defined in the schedule of study assessments (Table 3). Sample will be analysed by the local study site laboratory using standard methods for routine tests. Laboratory tests for screening can be performed within 10 days prior to the first dose of treatment. After this all pre-dose laboratory procedures should be conducted no more than 72 hours prior to dosing. Results must be reviewed by the investigator / designee and found to be acceptable prior to each dose of trial treatment. The variables detailed in Table 4 will be measured.

Table 4: Required Laboratory Assessments

Haematology	Chemistry	Urinalysis	Other
Haematocrit	Albumin	Blood	PT
Haemoglobin	Alkaline phosphatase	Glucose	aPTT
Platelet count	Alanine aminotransferase (ALT)	Protein	Free triiodothyronine (fT3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free thyroxine (fT4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If results are abnormal)*	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Uric Acid	Urine pregnancy test †	
Absolute Lymphocyte Count	Calcium Corrected		
	Chloride		
	Glucose		
	Phosphate		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		
	Creatinine Clearance		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

5.3.11 Tumour Imaging and Assessment of Disease

5.3.11.1 Baseline tumour imaging

Imaging should be undertaken to confirm that the patient has disease in the thorax, where lung SBRT is considered appropriate and the lesion is measurable using RECIST v1.1. The scan will also be assessed for an extra-thoracic disease.

5.3.11.2 Timing of Disease Assessment

Tumour imaging may be performed by CT. The initial tumour imaging will be performed no more than 28 days prior to confirmation of eligibility. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within the correct time window.

On-study imaging will be performed at screening every 3 cycles (every 9 weeks) for the first 6 months (± 7 days) then every 12 weeks after 6 months (± 7 days), and should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. Tumour imaging and assessment per local standard of care should be performed for patient management and may include additional imaging (e.g. bone scan). Imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

5.3.11.3 Confirmation of Disease Response

Per RECIST v1.1 & irRC (Appendix 6 & 7), response should be confirmed by a repeat radiographic assessment no less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated.

Immunotherapeutic agents may produce anti-tumour effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumour burden or even the appearance of new lesions. Therefore standard RECIST v1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

Therefore, RECIST v1.1 will be used with the following adaptations:

- If radiologic imaging shows initial progressive disease (PD), tumour assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression.
    - Patients may continue treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:
        - Absence of signs and symptoms indicating disease progression
        - No decline in ECOG performance status
        - Absence of rapid progression of disease
        - Absence of progressive tumour at critical anatomical sites requiring urgent alternative medical intervention. When feasible, patients should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumour flare in the first few months after the start of immunotherapy, but with subsequent disease response. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

- If repeat imaging shows a reduction in the tumour burden compared to the initial scan demonstrating PD, treatment may be continued /resumed.
- If repeat imaging confirms progressive disease, patients will be discontinued from study therapy.
    - NOTE: If a patient with confirmed radiographic progression (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumour dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor.
      Clinically stable patients should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD) to continue study treatment.

In determining whether or not the tumour burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

5.3.11.4 Confirmation of Disease Progression

Disease progression should be confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable patients. Patients who have unconfirmed disease progression may continue on treatment until progression is confirmed.
Clinically stable is defined by one or more of the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumour at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

5.3.12 Tumour Tissue Collection and Correlative Studies Blood Sampling

5.3.12.1 Archival Tumour tissue samples

For patients where a screening biopsy is not feasible, archival tumour material must be provided. If archived biopsy (block or slides) are sent it must contain tumour tissue. If no block is available, 10 or more freshly prepared (generated within the last 6 months) unstained 5 micron sections should be provided. Archival tumour blocks will be returned to source at the end of the study or, upon request, earlier if required for the patient's clinical management. Cut sections will be retained by the study team. These are archived samples and as such participating patients will not need to attend extra visits or undergo extra procedures. All collected archival samples will be classed as pre-treatment samples and used as such in the immunological evaluation as described below.

5.3.13 Tumour Biopsies and Research Blood Samples

For patients without archived samples, tumour biopsies will be obtained during the screening period. If the patient consents optional research blood samples will be obtained at C1D1, C2D1, C5D1 and at the end of study visit (Table 3). Tumour and blood samples from this study may undergo proteomic, genomic and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and radiotherapy. Assays may include, but are not limited to:

- **Characterization of TILs and tumour antigens**
  Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin embedded (FFPE) tumour tissue before and after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, the following: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2.
- **ctDNA & CTCs**
  Research blood samples will be analysed for ctDNA and CTCs. Analysis of CTCs will include, but not necessarily limited to the following, the diagnostic performance of PD-L1 testing will be assessed in CTC compared with IHC, correlation with response and disease progression.

5.3.14 Chain of Custody of Biological Samples

In all cases, patients will be consented for the collection and use of their biological samples and a full chain of custody will be maintained for all samples throughout their lifecycle. The Investigator is responsible for maintaining a record of full traceability of biological samples collected from patients while these are in storage at the site, either until shipment or disposal. Anyone with custody of the samples e.g. sub-contracted service provider will have to keep full traceability of samples from receipt to further shipment or disposal (as appropriate). RM-CTU will keep overall oversight of the entire lifecycle through internal procedures and monitoring of study site.

5.4 Total Blood Volume

The total volume of blood that will be drawn from each trial patient for the assessments described in the sections above is shown in Table 5.

Table 5: Volume of blood

	Sample volume (ml)	No. of samples	Total volume (ml)
Routine Haematology	6[1]	11	66
Routine Chemistry	8[1]	11	88
		Routine Total:	154
Research Blood Samples OPTIONAL	Up to 60	4	240
		Study Total:	394

[1] *Blood volumes may vary according to local practice*

6 TREATMENTS

6.1 Lung SBRT

6.1.1 Planning and Delivery

Radiotherapy planning and delivery should be carried out in accordance with the current RTT QA guidelines for stereotactic radiotherapy trials available on request from RM-CTU and included as Appendix 3 within the protocol. As only part of a lung lesion may be treated the target coverage planning goals will be for the defined target volumes.

6.1.2 Toxicity Assessments

Dyspnoea score and toxicity grading with CTCAE v4.0 will be recorded and will include pneumonitis, lung fibrosis, oesophagitis, skin toxicity, myelitis and fatigue. Side-effects that are seen with lung stereotactic radiotherapy include pericarditis, dysphagia, gastrointestinal bleeding, gastrointestinal ulceration, esophagitis, gastritis, nausea, vomiting, cough, pneumonitis, dyspnoea, fatigue, skin erythema, chest wall pain, and rib fracture. All other AEs will be documented in addition.

6.2 Pembrolizumab

6.2.1 Investigational Product

The Investigational Medicinal Product (IMP) for this study is pembrolizumab. A potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab potentiates existing immune responses only in the presence of antigen and does not non-specifically activate T-cells. Pembrolizumab will be manufactured by MSD according to Good Manufacturing Practice and will be provided in the formulation as described in Table 6. Additional information about the investigational product can be found in the Summary of Product Characteristics (SmPC).

Table 6: Product Description

Product Name & Potency	Formulation
Pembrolizumab 100 mg/ 4mL	Solution for Injection

6.2.2 Product Preparation

Please refer to the RM CTU Pharmacy Manual for preparation of the pembrolizumab for infusion.

6.2.3 Storage and Handling

6.2.3.1 Storage

The original solution for infusion should be stored at refrigerated conditions (2 – 8 °C). Vials should be stored in the original box to ensure the drug is protected from light.

Prepared infusion solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, reconstituted vials and/or IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

6.2.3.2 Handling

Infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or 5% Dextrose Injection, USP (5% dextrose) and the final concentration of pembrolizumab in the infusion solutions should be between 1.0 mg/mL and 10.0 mg/mL. Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available. Pembrolizumab should **NOT** be mixed with other diluents unless instructed by the MSD in writing. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.

Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimise agitation of the reconstituted drug product between the pharmacy and the clinic.

PLEASE DO NOT:

- **Use if discoloration is observed.**
- **Shake or freeze the vial(s).**
- **Administer the product as an (intravenous (iv) push or bolus).**
- **Combine, dilute or administer it as an infusion with other medicinal products**.
- **Co-administer other drugs through the same infusion line.**

Further details on the preparation of the drug product can be found in the RM CTU pharmacy manual. At each site the Principle Investigator/designee e.g pharmacist at each participating site is responsible for ensuring that all trial Medication must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an

authorized person at the trial site. Trial medication may not be used for any purpose other than that stated in the protocol.

6.2.4 Packaging and Labelling Information

Pembrolizumab will be supplied by MSD as solution for injection. Pembrolizumab will be packaged, labelled and delivered to the participating sites free of charge by MSD. The IMP will be supplied specifically for the trial and should not be used for any other purpose than that stated in this protocol. The drug will be labelled in accordance to Good Manufacturing Practice Annex 13.

6.2.5 Returns and Reconciliation

The Principle Investigator/designees is responsible for keeping accurate accountability accurate records for pembrolizumab including the amount dispensed to and returned for each patient and the amount remaining on site at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used trial medication will be destroyed at the site per institutional policy. It is the Principle Investigator's/designees responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.2.6 Doses and Treatment Regimens

All patients will receive pembrolizumab administered as per standard procedures following manufacturer's instructions. Trial treatment should begin on the day of confirmation of eligibility or as close as possible to the date on which treatment is allocated/assigned.

Table 7: Pembrolizumab and lung SBRT schedules

Dose level	Lung SBRT Dose	Drug	Dose Frequency	Route of Administration	Dose
1	30 Gy in 3#	Pembrolizumab	3 weekly	IV infusion	200 mg
2	54 Gy in 3#	Pembrolizumab	3 weekly	IV infusion	200 mg
Expansion cohort	RP2D	Pembrolizumab	3 weekly	IV infusion	200 mg

6.2.7 Timing of Dose Administration

During the induction and maintenance phase, the pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the schedule of study assessments (Table 3). The pembrolizumab administration may be administered up to 3 days before or after the scheduled Day 1 during the induction and maintenance phase due to administrative reasons. During the

induction and maintenance phase of the trial, the pembrolizumab will be administered on a 3 weekly cycle (Table 3).

Maintenance pembrolizumab will continue until disease progression, withdrawal of consent, or unacceptable toxicity. Patients obtaining complete response or having completed 24 months of pembrolizumab have the option of discontinuing treatment, with a view to restarting treatment on disease progression. Retreatment should be discussed with the Chief Investigator. Study related assessment and procedures should be as for the beyond DLT Pembrolizumab Maintenance phase (see Table 3). Patients do not need to re-sign the consent form for restarting treatment, provided their consent is on the most up-to-date version of the Patient Information Sheet Consent Form.

All trial treatments will be administered on an outpatient basis. Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals or infusion length may be increased due to toxicity as described in Section 6.2.3). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The RM CTU Pharmacy Manual contains specific instructions for pembrolizumab, reconstitution, preparation of the infusion fluid, and administration. In addition, infusion length may be increased due to toxicity as described in Section 7 and Table 9.

The RM CTU pharmacy manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion, and administration.

6.2.8 Blinding/Masking

This is an open-label trial; therefore, the Sponsor, Investigator and patient will know the treatment administered.

6.2.9 Drug Dose Selection/Modification

6.2.9.1 Dose Selection

Pembrolizumab is being given using standard 200 mg flat dosing every three weeks. The Pembrolizumab dosing interval may be increased due to toxicity as described in Section 3.1.1. Details on the preparation and administration of pembrolizumab are provided in the RM CTU Pharmacy Manual. These guidelines contain specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid and administration.

6.2.9.2 Dose Modification

Pembrolizumab will be withheld for drug-related Grade 4 haematological toxicities, and non-haematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 8 below.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With Investigator and Sponsor agreement, patients with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of AEs, see Section 7 and Table 8. Patients who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab should be discontinued from trial treatment.

Events of Clinical interest (ECI) can be potential irAEs and dose modifications for these toxicities should they occur can be found in Appendix 5 and as per the MSD guidance document for pembrolizumab ECI version 3.0.

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 be placed back on study therapy 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.

Table 8: Dose modification guidelines for drug-related adverse events.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhoea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1. If recurrent Grade pneumonitis occurs pembrolizumab should be permanently discontinued.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

6.3 Concomitant medications

Concomitant medications will be recorded at screening and at every visit during the treatment phase of the study in the case report form (CRF) in the concomitant therapy section.

6.3.1 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the ongoing trial. If there is a clinical indication for one of these or other prohibited medications or vaccinations then the patient may be discontinued from trial therapy. The Investigator should discuss any questions regarding this with the chief investigator (or delegate).

The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the Chief Investigator, and the patient.

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intra-nasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic aetiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Chief Investigator or delegate.
- Radiation therapy not specified in this protocol
    - Note: Subsequent radiotherapy whilst on maintenance treatment to the thorax will not be permitted. Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the chief investigator, as long as it does not involve re-irradiation to any part of the lung.

Patients who in the assessment by the investigator, require the use of any of the aforementioned for their clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary. The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.3.2 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescriptions, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment or initiation of other anti-cancer therapies should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should only be recorded for SAEs and overdose and liver toxicity ECIs as defined in Section 7.

6.4 Rescue Medications & Supportive Care

6.4.1 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

6.4.1.1 Diarrhoea

Patients should be carefully monitored for signs and symptoms of:

- Enterocolitis (diarrhoea, abdominal pain, blood or mucus in stool, with or without fever)
- Bowel perforation (peritoneal signs and ileus).

In symptomatic patients, infectious aetiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

- In patients with severe enterocolitis (Grade 3):
    - Pembrolizumab will be ***permanently discontinued*** and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
- In patients with moderate enterocolitis (Grade 2):
    - Pembrolizumab should be ***withheld*** and anti-diarrhoeal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). If symptoms are not improving within 48 hours of starting steroids for grade 3 enterocolitis, consider infliximab . When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1

month. Guidelines for continuing treatment with pembrolizumab can be found in Appendix 5.

All patients who experience diarrhoea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via i.v. infusion.

6.4.1.2 Nausea/vomiting

Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

6.4.1.3 Infection

Patients with a documented infectious complication should receive oral or i.v. antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

6.4.1.4 Immune-related adverse events

Please see Section 7.5 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic aetiology.

6.4.1.5 Management of Infusion Reactions

Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnoea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritus/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumour pain (onset or exacerbation of tumour pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. Table 9 below shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab.

6.5 Supportive Care Guidelines for Immune-related Adverse Events (irAE) and Immune-related Events of Clinical Interest (irECI)

Immune-related Adverse Events (irAEs) may be defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies

that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. If an irAE is suspected, efforts should be made to rule out cancer, infectious, metabolic, toxin or other etiologic causes prior to labelling an AE as an irAE. Patients who develop a Grade 2 or higher irAE should be discussed immediately with the Chief Investigator or delegate.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 10.

Table 9: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Paracetamol Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be pre-medicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be pre-medicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Paracetamol 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 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 ventilator support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Paracetamol Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) at http://ctep.cancer.gov		

Table 10: General Approach to Handling irAEs

irAE	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold pembrolizumab. For recurrent grade 2 pneumonitis, pembrolizumab should be discontinued permanently.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. Based on limited data from clinical studies in subjects whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.
Grade 3 and Grade 4	Withhold pembrolizumab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. Based on limited data from clinical studies in subjects whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.
Please Note: If an irAE does not resolve or improve to ≤ Grade 1 within 12 weeks after last administration of pembrolizumab, study therapy discontinuation should be considered after discussion with a Merck Clinical Director via the RM-CTU trial manager.		

Details for managing specific irAEs are summarised below:

Immune-mediated pneumonitis

Monitor subjects for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold pembrolizumab for moderate (Grade 2) pneumonitis, and permanently discontinue pembrolizumab for recurrent moderate (Grade 2), severe (Grade 3) or life-threatening (Grade 4) pneumonitis.

Immune-mediated colitis

Monitor subjects for signs and symptoms of colitis and exclude other causes of colitis. Administer corticosteroids for Grade 2 (if persists for >3 days) or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold pembrolizumab for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue pembrolizumab for life-threatening (Grade 4) colitis.

Immune-mediated hepatitis

Monitor subjects for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and exclude other causes of hepatitis,.

Administer corticosteroids (initial dose of 0.5 – 1.0 mg/kg/day for grade 2 events, and 1 – 2 mg/kg/day for grade 3 or greater events, of prednisone or equivalent, followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab.

Immune-mediated nephritis

Monitor patients for changes in renal function and exclude other causes of nephritis. Administer corticosteroids for grade 2 or greater events (initial dose of 1 – 2 mg/kg/day prednisone or equivalent, followed by a taper), withhold pembrolizumab for moderate (Grade 2), and permanently discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) nephrits.

Immune-mediated endocrinopathies

Monitor subjects for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and exclude other causes of hypophysitis. Administer corticosteroids to treat secondary adrenal insufficiency and other hormone replacement as clinically indicated, withhold pembrolizumab for moderate (Grade 2), withhold or discontinue pembrolizumab for severe (Grade 3) or for life-threatening (Grade 4) hypophysitis.

Monitor subjects for hyperglycemia or other signs and symptoms of type 1 diabetes. Exclude other causes of diabetes. Administer insulin for type 1 diabetes, and withhold pembrolizumab in cases of severe hyperglycemia until metabolic control is achieved.

Thyroid disorders have been reported in subjects receiving pembrolizumab and can occur at any time during treatment; therefore, monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hyperthyroidism may be managed symptomatically. Withhold pembrolizumab for severe (Grade 3) hyperthyroidism, and permanently discontinue pembrolizumab for life-threatening (Grade 4) hyperthyroidism. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. For subjects with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of pembrolizumab may be considered.

Other immune-related AEs

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% (unless otherwise indicated) of subjects treated with pembrolizumab: uveitis, myositis, Guillain-Barré syndrome, pancreatitis and severe skin reactions (1.1%).

In addition a set of irAEs have also been classified as immune-related events of clinical interest (irECI) a full list of these can been found in events of clinical interest guidance and Appendix 5. Patients with symptomatic irECIs should immediately stop receiving pembrolizumab and be evaluated to rule out non treatment related causes of the event. Overdose and liver toxicity irECIs irrespective of relationship to the study drug should be reported within 24 hours of the investigator being aware to the Sponsor (via RM-CTU) who will in turn notify MSD. If the irECI is determined to be associated please refer to ECI guidance document and Appendix 5 for the recommendations on the management of these irECIs. If the event is not considered to be associated with the study drug the physician should exercise individual clinical judgment on the event management based on the patient. Any additional questions of the collection or information on management of irECIs should be directed to the Sponsor (via RM-CTU).

6.6 Supportive Care Guidelines for Pneumonitis

Patients with symptomatic pneumonitis should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the patient is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 11.

Table 11: Recommended Approach to Handling Pneumonitis

Study drug associated pneumonitis	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold pembrolizumab, may return to treatment if improves to Grade 1 or resolves within 12 weeks Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.	Consider pulmonary consultation with bronchoscopy and biopsy/BAL. Conduct an in person evaluation approximately twice per week Consider frequent Chest X-ray as part of monitoring Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Consider antibiotics
Grade 3 and Grade 4	Discontinue pembrolizumab	**Hospitalise patient** Bronchoscopy with biopsy and/or BAL is recommended. Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed add prophylactic antibiotics for opportunistic infections. The use of infliximab may be indicated as appropriate.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis: May increase dosing interval by one week in subsequent cycles
- Second episode of pneumonitis: Permanently discontinue pembrolizumab if upon re-challenge the patient develops pneumonitis ≥ Grade 2

6.7 Diet/Activity/Other Considerations

6.7.1 Diet

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhoea, nausea or vomiting.

6.7.2 Contraception

Pembrolizumab may have adverse effects on a foetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either, two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from screening throughout the study period up to 120 days after the last dose of study therapy. Male patients with partners of child bearing potential will also be required to agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an oestrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). Patients should be informed that taking the study medication may involve unknown risks to the foetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

6.7.3 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will

be reported to the Sponsor and to MSD without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or newborn to the Sponsor (via RM-CTU) without delay and within 24 hours. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the RM-CTU and followed as described above and in Section 7.

6.7.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrolment.

6.7.5 Treatment of Overdose of IMP

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. Please see section 7 for definitions and reporting procedures.

6.8 Permanent Discontinuation of Trial Medication and Withdrawal from the Study

6.8.1 Permanent Discontinuation of Trial Medication

A patient may be permanently discontinued from the trial medication for any of the following reasons:

- The subject withdraws consent.
- Confirmed radiographic disease progression, please see Section 6.3.11.4.

  Note: For unconfirmed radiographic disease progression. A patient may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Administrative reasons
- Completion of 24 months of pembrolizumab

Trial patients will not be enrolled more than once. The primary reason for discontinuation should be recorded on the CRF. Once the trial medication has been discontinued the patient should complete the end of treatment (if applicable) and safety follow-up visit procedures as listed in the schedule of study

assessment (Table 3). After the end of treatment, patients will continue to be assessed for AE and SAE monitoring until completion of the safety follow up visit.

Follow-up actions for patient discontinuing the trial are as follows:

- All patients will be required to:
  - Attend a safety follow-up 30 days after their last dose of pembrolizumab,
- If a patient **progresses or begins a new anti-cancer treatment** they will be required to:
  - Undertake survival status assessments every 12 weeks until death, withdrawal of consent, lost to follow up or the end of the study.
- If a patient discontinues for reasons other than progression during treatment and **does not withdraw their consent to follow up** they will be required to:
  - Attend follow-up assessments every 9 weeks until disease progression, initiation of a new anti-cancer treatment death, end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

6.9 Withdrawal from the Study

Patients have the right to discontinue study treatment any time for any reason, without prejudice to their medical care. Withdrawal from the study refers to discontinuation of both study medication and study assessments; this can occur at any time according to the following reasons:

- Patient decision
- Lost to follow-up
- Death
- PI decision

Patients may withdraw consent at any time for any reason or have trial treatment stopped at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. When a patient discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation, these are listed in the schedule of study assessments (Table 3). Any AEs which are present at that time should be followed in accordance with the safety requirements outlined in Section 7.

Patients who a) attain a complete response or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment on disease progression. Retreatment should be discussed with the Chief Investigator. Study related assessment and procedures should be as for the beyond Pembrolizumab Maintenance phase (see Table 3). Patients do not need to re-sign the consent form for restarting treatment, provided their consent is on the most up-to-date version of the Patient Information Sheet Consent Form. After discontinuing treatment following assessment of complete response, these

patients should return to the site for a 30 days safety follow-up visit and then proceed to the follow-up period of the study.

7 PHARMACOVIGILANCE

7.1 Adverse events

7.1.1 Adverse Event Definition

An 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 pembrolizumab, is also an AE. 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.

7.1.2 Adverse Reaction Definition

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

7.1.3 Disease Progression

Disease progression of the cancer under study is not considered an AE unless it results in hospitalisation.

7.1.4 New Cancers

The development of a new cancer should be regarded as an SAE and reported accordingly.

7.1.5 Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the study will be recorded as AEs. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator, or until a diagnosis that explains them is made.

7.1.6 Pregnancy and Lactation

Pregnancy and lactation are not considered AEs, however these events should be reported to the RM-CTU following guidance in section 7.7

7.2 Assessing and Recording Adverse Events

All AEs will be recorded from the time of the first dose until the safety follow-up in the CRF. They will be followed up according to local practice until the event has stabilised or resolved, or the follow-up visit has taken place, whichever is the sooner. SAEs will also be recorded throughout the study. The reporting timeframe for AEs meeting any serious criteria is described in section 7.4.1.

Follow-up of AEs with a causality of possible, probable or highly probable will continue until the events resolve, stabilise or the patient completes the trial. Any unresolved AEs at the patient's last visit should be followed up for as long as medically indicated, but without further recording in the CRF.

If an Investigator learns of any AE that he/she consider serious, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to pembrolizumab, the Investigator should notify the RM-CTU. Late toxicities will be recorded and reported as with other AEs.

The following details will be collected in the CRF for each AE:

- AE description / diagnosis
- Date of onset and date of resolution
- NCI-CTCAE grade maximum intensity
- Seriousness
- Investigator causality rating against the study medication (yes or no)
- Expectedness
- Action taken with regard to study medication
- Outcome

For the pre-registration period AEs will not be collected in patients that have not undergone any protocol-specified procedure or intervention. If the patient requires a blood draw, fresh tumour biopsy etc. for the study then the patient will be required to consent to the main study and AEs will be captured as described above.

7.3 Evaluating Adverse Events

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

7.3.1 Determining AE 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.

7.3.2 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 judgement 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.

7.4 Serious adverse events (SAEs)

An SAE is defined as any untoward medical occurrence or effect that at any dose that:

- Results in death;
- Is life-threatening or places the patient, in the view of the investigator, at immediate risk of death from the event as it occurred[1];
- Requires in-patient hospitalisation or prolongs existing in-patient hospitalisation[2]
- Results in persistent or significant incapacity or disability;
- Is a new cancer
- Is a congenital anomaly or birth defect;
- Is associated with an overdose (whether accidental or intentional). Any AE associated with an overdose is considered a SAE.
- Is any other medically important event.[3]

[1] This does not include an AE which hypothetically might have caused death if had it occurred in a more severe form.
[2] Hospitalisation is defined as an unexpected inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).
[3] A medically important event may not result in death, not be life threatening, or not require hospitalisation but may be considered a SAE when, based upon appropriate medical judgment, the event that may jeopardise the patient and require medical or surgical intervention to prevent one of the outcomes listed above.

7.4.1 Reporting SAEs

All SAEs regardless of causality, pregnancy or overdose that occur from the first dose until the 30 day safety follow-up or the initiation of a new anticancer therapy, whichever is earlier, must be reported on the SAE report form within 24 hours of the investigator / designee becoming aware of the event.

The SAE/ECI report form should be sent to
Email : Priming.Trial@rmh.nhs.uk
Fax: 020 8915 6762
who will in turn notify MSD of the event.

The SAE form must be completed, assessed for causality and expectedness against the current version of the Investigator Brochure, then signed and dated by the Principal 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 MSD. Please refer to the SAE completion guidelines for further information.

Additionally, any SAE considered by an investigator who is a qualified physician to be related to the IMP or protocol-specified procedure that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor (via RM-CTU) who will inform MSD.

7.4.2 Events exempt from being reported as SAEs

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the CRF.

1. Elective admissions to hospital for procedures which were planned and documented in the medical records at the time of consent are not SAEs, and do not require SAE reporting.

2. Hospitalisation for administration of the IMP, or to facilitate study procedures such as pharmacokinetic sampling according to the trial protocol, is also exempt from being reported as an SAE.

3. Progressive disease and death due to disease are not considered SAEs, unless they fulfil the seriousness criteria, as listed in Section 7.5. All cases of progressive disease and death should be reported in the CRFs

7.4.3 Determining SAE Causality and Expectedness

Assessment of causality and expectedness for all SAEs will be made by the PI/designee and Chief Investigator or delegate against the SmPC (Reference Safety Information Appendices). 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. The Reference Safety Information (RSI) for assessing the expectedness of adverse events is contained in section 4.8 of the Summary of Product Characteristics (SmPC).

7.5 Events of Clinical Interest

7.5.1 Definitions of Evidence of Clinical Interest (ECI)

Selected non-serious and SAEs can also be classified as Events of Clinical Interest (ECI) and must be reported as described in section 7.5.2.

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab, as defined in Section 7.6 that is not associated with clinical symptoms or abnormal laboratory results.
2. A Drug induced liver injury (DILI) defined as elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal

   AND / OR

   An elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal

   AND / OR

   An alkaline phosphatase lab value that is greater or equal to 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
3. Any AEs identified in the below Table 12 can be classified as immune-related events of clinical interest. A detailed narrative of overdose and liver toxicity ECIs should be reported as described in section 7.5.2

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Patients should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an immune-related event. Patients who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.5.2 Reporting of ECIs

Overdose and liver toxicity ECIs whether or not related to the pembrolizumab, occurring from the first dose until 30 days following the last treatment dose, or the initiation of a new anticancer therapy, whichever is earlier, must be recorded on the AE e-case report forms and reported using the SAE/ECI report form within 24 hours of the PI/designee becoming aware of the event to the Sponsor (via RM-CTU) as follows:

The SAE / ECI report form should be sent to Email: Priming.Trial@rmh.nhs.uk Fax: 020 8915 6762 who will in turn notify MSD of the event.

Table 12: Immune related Aes considered ECIs

Pneumonitis - ***(classified as ECI if ≥ Grade 2)***		
Acute interstitial Pneumonitis	Interstitial Lung Disease	Pneumonitis
Colitis - ***(classified as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitishemorrhagic	Gastrointestinal perforation
Necrotising colitis	Diarrhoea	
Endocrine – ***(classified as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)***		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Type 1 diabetes mellitus (if new onset)		
Hematologic – ***(classified as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***		
Autoimmune haemolytic anaemia	Aplastic anaemia	Thrombotic thrombocytopenic purpura
Idiopathic thrombocytopenia purpura	Disseminated intravascular coagulation	Haemolytic uraemic syndrome
Any grade 4 anaemia regardless of underlying mechanism		
Hepatic - ***(classified as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion reactions - ***(classified as ECI for any grade)***		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic - ***(classified as ECI for any grade)***		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular - ***(classified as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***		
Uveitis	Iritis	
Renal - ***(classified as ECI for ≥ Grade 2)***		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations - (report as ECI if ≥ ***Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***	
Skin - ***(classified as ECI for any grade)***		
Dermatitis exfoliate	Erythema multiforme	Stevens-Johnson Syndrome
Toxic epidermal necrolysis		
Skin - ***(classified as ECI for ≥ Grade 3)***		
Pruritus	Rash	Rash generalised
Rash maculo-papular	Any rash clinical significant in the physicians judgement.	
Other - ***(classified as ECI for any grade)***		
Myocarditis	Pancreatitis	Percarditis
Any other grade 3 event which is considered immune-related by the physician.		

7.6 Definition of an Overdose for this Protocol and Reporting of Overdose

At present no specific information is available on the treatment of overdose of pembrolizumab. For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20%. In the event of overdose the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE(s) is associated with ("results from") the overdose of pembrolizumab, the AE(s) should be recorded on the AE CRF and reported as a SAE, even if no other seriousness criteria are met.

If an overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is again recorded as an AE on the CRF and reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose either SAE or ECI must be reported within 24 hours of the PI or designee becoming aware of the event to the Sponsor (via RM-CTU) as follows:

The SAE / ECI report form should be sent to Email: Priming.Trial@rmh.nhs.uk Fax: 020 8915 6762 who will in turn notify MSD of the event.

7.7 Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them), that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. All patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, foetal death, intrauterine death, miscarriage and still birth must be reported as SAE (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported with the parents' consent. Such events must be reported within 24 hours to the Sponsor (via RM-CTU) as follows:

The SAE / ECI report form should be sent to Email: Priming.Trial@rmh.nhs.uk Fax: 020 8915 6762 who will in turn notify MSD of the event.

7.8 Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as an SAE that is judged to be related to any dose of study drug administered to the patient.

7.9 Definition of Suspected, Unexpected, Serious, Adverse Reactions (SUSARs)

A SUSAR is a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. reference safety information appendices of investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product). For lung stereotactic radiotherapy, the anticipated side-effects are listed in Section 6.1.2. Hospitalisations due to these adverse events, where causality is ascribed to lung stereotactic radiotherapy, will be reported as an SAE, but not escalated to a SUSAR.

7.10 Reporting of SUSARs

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

The SAE / ECI report form should be sent to
Email: Priming.Trial@rmh.nhs.uk
Fax: 020 8915 6762
who will in turn notify MSD, relevant Independent Ethics Committee (IEC) / Institutional review, appropriate regulatory authorities and the participating Principal Investigators of the event.

The Sponsor (via RM-CTU) will in turn notify the MSD, relevant Independent Ethics Committee (IEC) / Institutional review, appropriate regulatory authorities and the participating Principal 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 seven 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.

7.11 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 MSD and Investigators.

7.12 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 CI/delegate must notify the Medicines and Healthcare Products Regulations (MHRA) the Research Ethics Committee (REC) and the Sponsor (via RM-CTU) 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:

Email: Priming.Trial@rmh.nhs.uk
Telephone: 020 8642 6503
Fax: 020 8915 6762

The notification must include:

- 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.

CI Contact Details

Name:	Dr Fiona McDonald
Address:	The Royal Marsden NHS Foundation Trust
	Downs Rd
	Sutton SM2 5PT
Email:	fiona.mcdonald@rmh.nhs.uk

8 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1 Statistical Analyses

The final analysis will be conducted after one of the following conditions is met.

- The trial is terminated early (for example, due to toxicity).
- All patients have had the opportunity for treatment and have completed their 'off-study' visit.

Once one of the conditions is met, a data cut-off date will be established. All patient visits occurring on or before this date will be analysed and summarised in the final clinical study report. Any data collected after this date will be summarised in a supplemental report.

All data will be analysed using the statistical software STATA version 13. Quantitative data will be presented as number of observations, means, standard deviations, minimum and maximum values. Categorical data will be presented as frequencies and proportions. When appropriate, data will be presented either with 95% confidence intervals or exact binomial confidence intervals. Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or did not complete the required safety observations will be described and evaluated separately. Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

8.1.1 Primary Endpoint

For the primary endpoint of establishing the MTD and RP2D of lung SBRT that can be safely combined with pembrolizumab, the toxicity rate will be stated as the proportion of patients who have had a DLT calculated along with an exact binomial 95% confidence interval. All toxicities will be tabulated by type, grade and dose level.

8.1.2 Secondary Endpoints

Acute and late toxicity data will be tabulated by type, grade and dose level with the number, proportions and frequencies of grades 1-4 and grade 3-4 grades reported. The duration of clinical benefit assessed by overall response rate (ORR) defined as complete response (CR) or partial response (PR) and disease control rate (DCR) defined as CR, PR or stable disease (SD) using RECIST v1.1 & irRC (Appendix 6 & 7) will be calculated as a proportion of total treated with a 95% confidence interval. Differential response rates, defined as mixed responses , where some sites of disease shows a response to treatment, while other sites of disease show disease progression, will be measured as (yes/no). This will be calculated as proportions in the squamous cell and non-squamous cell histological sub-type giving associated 95% confidence intervals. Any differences will be assessed using a Chi squared test for proportions on differential response rates between histological subtypes. PD-L1 staining is referred to as tumour proportionate score, reported as a percentage

from 0–100%. It is classed as weakly positive (1 – 49%); strongly positive if >50%; and negative if <1%. The effect of PD-L1 expression on response rates will be measured using the proportion of patients recorded to be weakly positive, strongly positive or negative and tested using a Chi Squared test for proportions on expression level between responders and non-responders. PFS will be measured from the start of radiotherapy until radiological or clinical evidence of progression or death and will be censored at date of last follow-up for surviving patients. OS will be measured from the start of radiotherapy until death and will be censored at date of last follow-up for surviving patients. Median PFS and OS will be calculated using Kaplan-Meier methods giving associated 95% confidence intervals, respectively. All patients from Part A and Part B will be used to analyse secondary endpoints.

8.1.3 Exploratory Endpoints

Exploratory endpoints will be presented in a descriptive fashion. We will:

- Describe the patterns of TILs and tumour antigens in archival tumour biopsies. These immunohistochemistry analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2.
- Blood will be analysed for ctDNA pre- and post- SBRT.

8.1.4 Timing of analyses

Toxicity data will be reviewed by the Safety Review Committee prior to any decision regarding dose escalation or opening of new dose cohorts.

Part A can be analysed once the last patient in cohort 2 has completed the DLT period which is 12 weeks from the last dose of lung SBRT (i.e. at C6D1). For parts A and B, end of treatment is until disease progression, or unacceptable toxicities, or the patient withdraws consent to the trial or when patient has completed 24 months of treatment. End of study is when the last patient has completed the off-study or the final follow-up visit, whichever happens last.

8.2 Sample Size

During the dose escalation phase a standard 3+3 design will be used to recruit patients into two lung SBRT dose cohorts, firstly dose level 1 and then dose level 2, and both given the same pembrolizumab fixed dose level. Each cohort will require a minimum of 3 and a maximum of 6 patients. This means that there will be a minimum of 6 and maximum of 12 patients required for dose escalation. There will then be an additional 12 patients in the expansion phase. This number has been arbitrarily chosen to get a better appreciation for the toxicity profile of the dose/treatment that maybe taken forward in a phase II study.

9 REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Good Clinical Practice

The study will be conducted in accordance with the conditions and principles of GCP as defined in the clinical trials regulations.

9.2 Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

Before starting the trial, the protocol, patient information sheet, consent form, any other written information that will be provided to the patients and any advertisements that will be used and details of any patient compensation must be approved by the Royal Marsden Committee for Clinical Research. Once approved, the study will then be submitted to the relevant Ethics Committee for their review and approval. Prior to the shipment of IMP and the enrolling any patients the Investigator at each site is responsible for any site specific assessments and obtaining local Research &Development approval for the study. All participating sites will be required to sign an agreement with RM-CTU which includes requirement to sign and adhere to the trial protocol.

Any protocol amendment should be agreed with the SRC and be approved by the Sponsor prior to submission and review by the REC. Once favourable opinion from IEC has been obtained the amendment can be implemented. It is the responsibility of the PI to submit amendment to the R&D department for R&D approval Amendments requiring IEC approval may be implemented only after a copy of the IEC/IRB's approval letter has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or IEC/IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

9.3 Annual Safety Reports and End of Trial Notification

It is the responsibility of the Sponsor to submit the DSUR annually to the MHRA/REC on the anniversary of the studies MHRA/REC approval. This will facilitate the authorities continuing review of the study. These authorities will also be informed of the end of the study by the Sponsor (via RM-CTU) within 90 days of the trial completion. Copies of these reports will also be held within the Site File.

9.4 Regulatory Authority Approval

The study will be performed in compliance with UK regulatory requirements. Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Authority (MHRA) will be obtained prior to the start of the study. In addition, the MHRA must approve amendments (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

9.5 Notifications of Serious Breaches to GCP and/or the Protocol

The Sponsor (via RM-CTU) will notify the MHRA and REC in writing of any serious breaches of:

a. The condition and principles of GCP in connection with the trial.
b. The protocol.

This will be done within 7 days if becoming aware of that breach, in accordance with the applicable UK regulations as amended from time to time.

For the Purpose of the regulations a "serious breach" is one which is likely to effect to a significant degree:

a. The safety or physical integrity of the subjects of the trial; or
b. The scientific integrity of the trial.

Systematic or persistent non-compliance by the site with GCP and/or the study protocol, including failure to report SAEs occurring on trial within the specified timeframes, may be deemed a serious breach.

9.6 Insurance and Liability

The Sponsor has secured indemnity from the manufacturer of pembrolizumab for patients in relation to adverse side effects for medicine-induced injury. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements for clinical negligence. A copy of the relevant insurance policy/indemnity scheme or summary shall be provided on request.

9.7 Contact with General Practitioner (GP)

It is the Investigator's responsibility to inform the patient's GP by letter that the patient is taking part in the study provided the patient agrees to this, and information to this effect is included in the PIS and ICF. A copy of the letter should be filed in the Site File. A template letter approved by the IEC/IRB will be provided by the Sponsor (via RM-CTU) to all participating sites.

9.8 Confidentiality

The Chief investigator must ensure that the patient's confidentiality is maintained in compliance with the UK Data Protection Act of 1998. On the CRFs or other documents submitted to the RM-CTU, patients should be identified by their initials and a patient study number only.

In compliance with GCP guidelines, it is required that the investigator and institution permit authorised representatives of the Sponsor and of the regulatory agency(s) direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

All pharmacogenetic samples and the information associated with the samples will be coded and stored appropriately to ensure confidentiality of the patient's information and to enable destruction of the samples if requested. Since the evaluations are not expected to benefit the patient directly or to alter the treatment course, the results will not be placed in the patient's medical record and will not be made available to members of the family, the personal physician, or other third parties, except as specified in the informed consent.

9.9 Data Collection and Documentation

It is the Investigator's responsibility to ensure that all relevant data is clearly recorded in the medical records. The Investigator must allow the RM-CTU direct access to relevant source documentation for verification of data entered into the CRF, taking into account data protection regulations. The clinical data should be recorded in the CRF and the following must be verifiable by the source data: patient consent, medical history, patients eligibility for participation in the trial, study treatment administration (pembrolizumab and radiotherapy), routine haematology and biochemistry and response to treatment.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the Sponsor appointed to audit the trial, or by REC. Details will remain confidential and patients' names will not be recorded outside the hospital.

The Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure:

- Sufficient data is recorded for patients to enable accurate linkage between hospital records and CRFs
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits
- Original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent
- All essential documents must be retained after the trial ends to comply with current legislation

No study document will be destroyed without prior written agreement between the Sponsor (via RM-CTU) and the PI. Should the PI wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

9.10 End of Trial

The 'end-of-trial' is defined as the date when the last patient has completed the 'off-study' visit or the final follow-up visit, whichever happens last.

10 DATA AND STUDY MANAGEMENT

10.1 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial are classified as source data. Source data are contained in source documents; these are defined as original documents, data, and records e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' 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, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

10.2 Language

All CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by patients must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

10.3 Data Collection

The medical records/medical notes should be clearly marked and allows easy identification of a patient's participation in the clinical trial. The Investigator (or delegated member of the site study team) must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy data into the CRF.

10.4 Recording of Data

Patients' data will be documented on a trial specific CRF designed by RM-CTU. Upon signing the informed consent form, the patient is assigned a trial identification number.

The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the CRFs. Only the Investigator, and those personnel who have completed the Study Team Responsibilities Signature Log/Delegation Log as authorised by the PI, should enter or change data in the CRFs. All protocol required investigations must be reported in the CRF. The Investigators must retain all original reports, traces and images from these investigations for future reference. The data will be entered in a clinical trials database (Macro V4) with password-protected access. If a patient withdraws from the study, the reason must be noted on the CRF.

The CRF will be signed by the Investigator or by an authorised staff member. Study specific information will be entered into a CRF visit by visit. Data that are derived should be consistent with the source documents or the discrepancies should be explained. All CRF data should be anonymous, *i.e.* identified by study patient

number, initials and date of birth. Once the patient is 'off study' and the CRF has been fully completed, the Investigator must provide a signature to authorise the complete patient data.

10.5 Data Management

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 and Research & Developmental Statistical Unit (RDSU). 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.

10.6 Study Management Structure

10.6.1 Delegations 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:

10.6.1.1 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 that the trial has ended
- Raising and resolving queries with local investigators
- Keeping records of all SAEs, overdose incidents, pregnancies and ECI's reported by investigators
- Notifying the Main REC, MHRA and Investigators of related SAEs

10.6.1.2 MSD

- Provision of pembrolizumab and study support costs

10.6.1.3 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
- Centres wishing to recruit to this study will be asked to provide evidence that they can deliver protocol treatment.

- 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.

10.7 Protocol Compliance and Amendments

All participating sites will be required to sign an agreement with RM-CTU which includes requirement to sign and adhere to the trial protocol.

Any protocol amendment should be agreed with the SRC and be approved by the Sponsor prior to submission and review by the relevant Ethics Committee and MHRA where required. Once favourable opinion from REC and if applicable the MHRA has been obtained the amendment can be distributed to sites implemented. It is the responsibility of the Principal Investigator to submit amendment to their R&D department for R&D approval.

10.8 Trial Management

The RM-CTU will be responsible for the day-to-day coordination and management of the trial. This includes all duties relating to safety reporting. If applicable a trial agreement will be signed between the site and RM-CTU. Once all relevant trial approvals are in place an initiation (visit or teleconference) will be conducted. In addition, training and ongoing advice will be provided by trial training workshop(s), site initiation and ongoing site support to each participating site by Trial Management Group (TMG).

10.9 Safety Review Committee (SRC)

A SRC will be set up and membership will include Chief Investigator, Co-Investigators, Trial Statistician, Trial Manager and will be chaired by a member intellectually and financially independent of trial investigators. Investigators and other key study personnel will be invited to join the SRC as appropriate. The SRC has operational responsibility for the conduct of the trial. The SRC is responsible for monitoring recruitment, safety and governance of the trial as well as collaborating with subsequent translational sub-studies. The SRC will also review any safety concerns and can convene a meeting of the SRC if significant concerns exist.

The role of the SRC is to:

- Review relevant safety data and make dose escalation decisions for all studies
- Reviews all SAEs and emerging safety data both from RM Sponsored studies and external SUSARS received from MSD
- Monitor progress of the trials and ensure emerging safety information is evaluated and protocol and GCP principles are adhered to.

10.10 Monitoring

During the trial RM-CTU is responsible for monitoring data quality in accordance with relevant standard operating procedures. Incoming data will be monitored for protocol compliance and if any inconsistent or missing data is identified queries will be sent to the site for resolution. Any systematic inconsistencies may trigger an onsite monitoring visit. The trial statistician will periodically examine the data for anomalies and outliers, such as too few or too many events. Queries will be raised by the trial coordinators in such situations and communication with the clinical teams will take place. In addition statistical monitoring of unusual dates and inconsistent data will take place. Again these will raise queries via the trial coordinators. If an on-site monitoring visit is required, RM-CTU will contact the site to agree convenient date. The site must ensure that relevant site file and patient notes are available for review. RM-CTU staff conducting onsite monitoring will review the investigator site file and carry out source data verification to confirm compliance with the protocol, trial agreement.

10.11 Quality Control and Quality Assurance

Quality Control (QC) will be performed according to RM-CTU internal procedures. The study may be audited by a Quality Assurance (QA) representative of the Sponsor. All necessary data and documents will be made available for inspection.

10.12 Clinical Study Report

Clinical data will be presented at the end of the trial based on final data listings. The CI together with the trial statistician will prepare a brief clinical study report / publication based on the final data listings. A summary of the report must be provided to the Research Ethics Committee and the MHRA within 1 year from the submission of the end of trial notification.

10.13 Record Retention

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified in accordance with current legislation.

RM-CTU will maintain essential documents to facilitate the management of the trial, audit and inspection in accordance with Royal Marsden General Standard Operating Procedures and in compliance with the clinical trial regulatory requirements.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. All medical records and TMF documentation will be retained for a minimum of 5 years after the study has concluded.

10.14 Reporting and Publication

The trial results will be submitted for publication in a relevant medical journal with authorship according to the criteria defined by the ICMJE (http://www.icmje.org). These state that authorship credit should be based 1) substantial contributions 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.

Draft publications (manuscripts, abstracts, slides and posters) should be circulated to the relevant parties to allow sufficient time for review prior to submission. There will be a fifteen (15) day period to review abstracts or posters and a thirty (30) day period to review slides and manuscripts and respond to the author with any revisions.

11 APPENDICES

11.1 Appendix 1 – 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. (69)	

11.2 Appendix 2 – MRC Dyspnoea scale

Grade	
0	Climbs hills or stairs without dyspnoea
1	Walks any distance on flat without dyspnoea
2	Walks over 100 yards without dyspnoea
3	Dyspnoea on walking 100 yards or less
4	Dyspnoea on mild exertion, e.g. undressing
5	Dyspnoea at rest

As published: *Bleehen et al. A randomised trial of three or six courses of etoposide cyclophosphamide methotrexate and vincristine or six courses of etoposide and ifosfamide in SCLC: Survival and prognostic factors. Medical Research Council Lung Cancer Working Party Br J Cancer 1993; 68(6): 11506. (70)*

11.3 Appendix 3 - Radiotherapy Planning and Delivery Guidelines

1. **Positioning and Immobilisation**

- Patients will be supine and positioned to aid comfort, stability and setup reproducibility. Knee and / or ankle supports will be used.
- For the majority of patients, the arms will be positioned above the head using a chest board and consideration will be given to using a vacuum bag to aid comfort and stability, particularly for treatment of vertebral lesions.
- For patients with apical lung lesions, the arms may be positioned by their sides and the patient immobilised in a 5-point shell.

2. **Localisation Imaging**

- Respiratory correlated 4DCT
- Maximum slice thickness will be 3 mm.
- The extent of the scan is from above the cricoid to below the liver.
- IV contrast will be considered, unless medically contraindicated, where it will aid target delineation e.g. contouring of brachial plexus avoidance structure using vessels as a surrogate.

3. **Target Delineation**

- GTV = Radiologically visible lesion or part of a lesion up to 3 cm in diameter, not in a 'central' location (See Figure A below), contoured on lung windows. Additional diagnostic imaging can be used to aid target delineation.
- CTV = GTV. No additional margin is added for microscopic disease.
- ITV = Encompasses either the CTV at maximum inhale and maximum exhale generated by fusing the individual GTV from 4DCT dataset as well as any additional tumour seen on cine loop.
- PTV = ITV + 5 mm.

4. **Organ at Risk Delineation**

- See Table A below.
- Additional guidance can be found in the online Radiation Therapy Oncology Group (RTOG) normal tissue atlases, available at: https://www.rtog.org/CoreLab/ContouringAtlases.aspx

5. **Dose Fractionation Schedules**

- Dose level 1: 30 Gy in 3 fractions over 5 days.
- Dose level 2: 54 Gy in 3 fractions over 5 days.

6. **Physics Planning**

- Type B or Monte Carlo algorithm is mandatory.
- Dose grid resolution on the final dose calculation must be ≤2 mm.

Table A: Contouring of normal tissue structures.

Spinal Canal PRV	The spinal canal will be contoured at least 10 cm above and below the extent of the PTV and taken to represent the cord. A centre dependent margin should be added to the canal to create the spinal canal PRV dependent on immobilization technique (e.g. 3 – 5 mm) on which the dose constraints should be assessed. This structure is used to assess both spinal cord and cauda equina dose constraints.
Brachial Plexus	Contouring, on head and neck windowing, will start at the neural foramina at the C4-C5 level and move caudally; the region from the lateral aspect of the spinal canal laterally to the small space between the anterior and middle scalene muscles will be contoured. At the levels at which no neural foramina are present, the space or soft tissue between the anterior and middle scalene muscles will be contoured. Contouring will continue in the space between the anterior and middle scalene muscles; Inferiorly the major trunks of the ipsilateral brachial plexus will be contoured by using the subclavian and axillary vessels as a surrogate. They will be contoured from the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries), following along and ending after the neurovascular structures cross the 2nd rib.
Lungs	Normal lung will consist of both lungs as one structure (including all inflated and collapsed regions of lung and excluding the proximal airways), contoured on lung windows, considered together as one organ (minus the GTV when treating lung lesions).
Trachea	Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.
Bronchial Tree	The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides. The following airways will be included according to standard anatomical relationships: the distal 2 cm of trachea, the carina, the right and left main stem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the 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.
Great Vessels	The great vessels (aorta and vena cava) will be contoured using mediastinal window to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured at least 10 cm above and below the extent of the PTV. For right sided lesions, the vena cava will be contoured, and for left sided lesions, the aorta will be contoured.
Oesophagus	The oesophagus should be contoured as a solid structure from the upper sphincter (cricoid level) down to the gastro-oesophageal junction using mediastinal windowing. The delineation limit is the outer wall of the oesophagus.
Heart and Pericardium	The heart will be contoured along with the pericardial sac using mediastinal windowing. The superior aspect is defined as the superior aspect of the pulmonary artery (as seen on coronal reconstruction of the CT) and the caudal border should be defined by the lowest part of the left ventricle's inferior wall that is distinguishable from the liver.
Chest Wall	The chest wall will be defined as the 2 cm rind of the ipsilateral hemi-thorax outside the thoracic cavity and contoured at least 5 cm above and below the PTV.

7. **Target Coverage, Maximum Dose, Conformity Parameters and OAR Dose Constraints**

- Target Coverage: Aim for the dose received by 95% and 99% of the PTV to be greater than 100% and 90% respectively (D95≥100% and D99>90%).
- Maximum Dose: This should ideally be within 110-140% (of the prescribed dose, 105-145% mandatory) and be located within the GTV. This is equivalent to prescribing to approximately the 70-95% isodose (relative to the maximum).
- Target Dose Conformity: Where possible the conformity constraints should be met (see Table B below).
- OAR dose constraints will be achieved for all patients (see Table C below).
- If the dose constraint for an OAR is not reached, the dose in the PTV will be reduced in order to meet the OAR constraint. Two approaches are possible:
- Reduced prescription dose: The prescribed dose can be reduced but to no less than 90% of the BED.
- Inhomogeneous PTV dose: In case of overlap of the PTV with OAR, the dose to the CTV (or ITV if applicable) can 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. The dose in 95% of the PTV should still at least be 80%.

8. **Image Guidance for Treatment Verification and Delivery**

- CBCT (or 4D CBCT imaging where appropriate and available) and on-line correction prior to each fraction will be performed with manual adjustment under direct visualization of the tumour if required.
- The position of critical OAR will be checked, especially the spinal cord and any changes in anatomy.
- Repeat CBCT scans will be considered after correction prior to treatment delivery and again after treatment delivery if clinically indicated for additional verification.

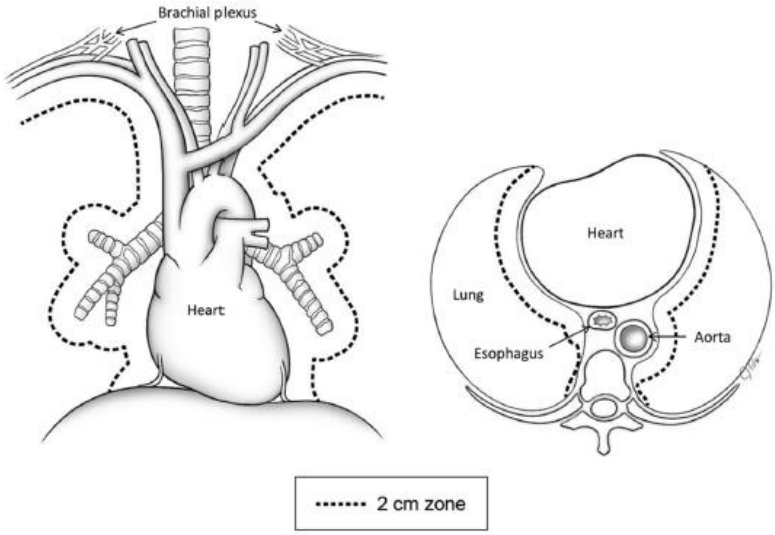

Figure A: Recommended definition of a **central thoracic lung lesion**: a lesion within 2 cm in all directions of any mediastinal critical structure, including the bronchial tree, oesophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve.

Table B: Dose Conformity Requirements

PTV (cc)	R100		R50		D_{max} (>2 cm from PTV) SBRT in 3 #	
	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory
<20	<1.25	1.25-1.40	<12	12-14	<35.1Gy	35.1-40.5Gy
20.1-40	<1.15	1.15-1.25	<9	9-11	<37.8Gy	37.8-43.2Gy
>40.1-60	<1.10	1.10-1.20	<6	6-8	<37.8Gy	37.8-43.2Gy
60.1-90	<1.10	1.10-1.20	<5	5-7	<37.8Gy	37.8-43.2Gy
>90.1	<1.10	1.10-1.20	<4.5	4.5-6.5	<37.8Gy	37.8-43.2Gy

R100 = Vol(100%)/Vol(PTV) = Ratio of prescription isodose volume to the PTV
R50 = Vol(50%)/Vol(PTV) = Ratio of 50% prescription isodose volume to the PTV
Dmax (>2 cm from PTV) = Maximum point dose at least 2 cm from the PTV in any direction

Table C: OAR Dose Constraints

OAR	Constraint	SBRT in 3 #	
		Optimal	Mandatory
Brachial Plexus	DMax (0.5 cc)	< 24 Gy	< 26 Gy
Normal Lungs (Lungs – GTV)	$V_{20\ Gy}$	-	< 10%
	$V_{12.5\ Gy}$	-	< 15%
Trachea and Proximal Bronchial Tree	DMax (0.5 cc)	< 30 Gy	< 32 Gy
Great Vessels	DMax (0.5 cc)	-	< 45 Gy
Heart	DMax (0.5 cc)	< 24 Gy	< 26 Gy
Oesophagus	DMax (0.5 cc)	-	< 25.2 Gy
Spinal Cord (Spinal Canal PRV)	DMax (0.1 cc)	< 18 Gy	< 21.9 Gy
	D1.2 cc	< 12.3 Gy	-
Chest Wall	DMax (0.5 cc)	< 37 Gy	-
	D30 cc	< 30 Gy	-
Skin	DMax (0.5 cc)	< 33 Gy	-
	D10 cc	< 30 Gy	-

11.4 Appendix 4 - 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)

1. Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

2. Components and Organization SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

3. CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

4. Definitions

A brief definition is provided to clarify the meaning of each AE term.

5. Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

6. Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.5 Appendix 5 - Identification, Evaluation and Management of immune related events of clinical interest (irECIs)

ECI	Grade	Action to be taken	Supportive Care
Pneumonitis –	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Consider bronchoscopy and biopsy/BAL, ID Consult and frequent chest x-ray for monitoring. • Conduct in person evaluation twice a week	• 1-2mg/kg/day prednisone or equivalent. • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to 10mg prednisone or less or equivalent per day within 12 weeks.
	Grade 3 and 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue pembrolizumab • Hospitalise patient • Bronchoscopy with biopsy and/or BAL is recommended.	• methylprednisolone 125mg IV. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks ○ Prednisone 1 to 2 mg/kg/day or dexamethasone 4mg every 4 hours • If IV steroids do not reduce initial symptoms within 48-72 hours treat with additional anti-inflammatory measures. At symptom relief discontinue anti-inflammatory and start steroid taper over 45-60 days. If symptoms worsen during this period refer to Section 6 and 7.
• 1st episode - May increase dosing interval by one week in subsequent cycles • 2nd episode of - Pneumonitis, permanently discontinue pembrolizumab if upon re-challenge patient develops Pneumonitis ≥ Grade 2			
Colitis –	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2 (For grade 2 diarrhoea that persists > 3 days)	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Symptomatic treatment ○ Consider GI consult & endoscopy to rule out colitis	• Prednisone 1-2mg/kg/day or equivalent • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to 10mg or less of prednisone or equivalent per days within 12 weeks. • If symptoms worsen or persist >1 week treat as grade 3.

	Grade 3	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold pembrolizumab • Rule out bowel perforation • Recommend gastroenterologist consult &biopsy with endoscopy	• methylprednisolone 125mg IV followed by prednisone 1 to 2 mg/kg/day or dexamethasone 4mg every 4 hours. • Symptoms grade 1 or less initiate steroid taper for no less that 4 weeks. • Taper 6-8 weeks in patients with diffuse or severe ulceration and/or bleeding • If IV steroids do not reduce initial symptoms within 48-72 hours treat with additional anti-inflammatory measures. At symptom relief discontinue anti-inflammatory and initiate steroid taper over 45-60 days. If symptoms worsen during this period refer to Section 6 and 7.
	Grade 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue pembrolizumab	• Manage as per grade 3
Endocrine – Hypo and hyperthyroidism	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2 Hyperthyroidism and Grade 2- 4 Hypothyroidism	• **Report overdose and liver toxicity ECIs** - see Section 6 and 7. • Monitor thyroid function until returned to baseline. • Consider consultation with endocrinologist. • Pembrolizumab can continue while on this treatment.	• Thyroid hormone and/or steroid replacement therapy. • Hyper – non-selective beta blockers for initial therapy • Hypo – thyroid hormone replacement therapy as per standard of care.
	Grade 3 Hyperthyroidism	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Rule out infection and sepsis.	• IV methylprednisone 1-2mg/kg followed by prednisone 1-2mg/kg per day. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. Replacement of appropriate hormones may be required. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4 Hyperthyroidism	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue pembrolizumab	• Manage as per grade 3
Endocrine – Hypophysitis or other symptomatic endocrinopathy	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2 – 4	• **Report overdose and liver toxicity ECIs** - see Section 6 and 7. • Withhold pembrolizumab	• Prednisone 40mg p.o. or equivalent per day. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. Replacement of appropriate hormones may be required.

		• Rule out infection and sepsis. • Monitor thyroid function until returned to baseline. • Consider pituitary gland imaging • Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. • Consider endocrinologist consult.	• Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
Type 1 Diabetes Mellitus and ≥ grade 3 hyperglycaemia	Type 1 Diabetes Mellitus and ≥ grade 3 hyperglycaemia	• **Report overdose and liver toxicity ECIs** if appropriate see Section 6 and 7 • Hold pembrolizumab if new onset of diabetes or grade 3-4 hyperglycaemia with evidence of beta cell failure. • Consultation with endocrinologist • Consider islet cell antibodies and antibodies to GAD, IA-2 ZnT8 and insulin.	• Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4hyperglycaemia associated with metabolic acidosis or ketonuria. • Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.
Haematologic	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Consider Haematology consultation	• Prednisone 1-2mg/kg daily • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 3	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold pembrolizumab, may restart if Grade 1 or resolved within 12 weeks • Recommend Haematology consultation	• IV methlyprednisone 125mg or Prednisone 1-2mg/kg p.o. (or equivalent) as appropriate. • Permanently discontinue pembrolizumab is if corticosteroid dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.

	Grade 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue pembrolizumab • Recommend Haematology consultation	• IV methlyprednisone 125mg or Prednisone 1-2mg/kg p.o. (or equivalent) as appropriate.
Hepatic – Drug induced Liver Injury (DILI). *Please refer to Section 6 and 7 for definitions of (DILI)*	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold Pembrolizumab if AST or ALT >3.0 to 5.0 X ULN and/or total bilirubin is >1.5to 3.0 X ULN • Monitoring Liver function until values return to baseline	• 0.5-1mg/kg/day methlyprednisone 125mg or oral equivalent. • LFT grade 1 or less initiate steroid taper for no less than 4 weeks. Consider prophylactic antibiotics and resume pembrolizumab. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks. • Permanently discontinue pembrolizumab for patients with liver mets who begin treatment with grade 2 elevation of AST or ALT and AST or ALT increase ≥50% relative to baseline and lasts ≥ 1 week.
	Grade 3	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue pembrolizumab if AST or ALT > 5.0 X ULN and/or total bilirubin is >3.0 X ULN • Consider consultation and biopsy to establish aetiology	• High dose IV glucocorticosteroids for 24-48hours. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks ○ prednisone 1 to 2 mg/kg/day or dexamethasone 4mg every 4 hours. • If serum transaminase levels do not decrease or symptoms worsen please refer to Section 6 and 7. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue pembrolizumab	• Manage as per grade 3
Neurologic	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• **Report overdose and liver toxicity ECIs** within 24 hours • Consider withholding pembrolizumab • Consider Neurology consult and biopsy for diagnosis.	• Consider 1-2mg/kg daily of prednisone as appropriate • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 3 and 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue pembrolizumab • Obtain Neurology consultation	• 1-2mg/kg daily of prednisone or equivalent. • If condition worsens consider IVIG or other immunosuppressive therapies • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks.

		• Consider biopsy for diagnosis.	
Ocular	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• **Report overdose and liver toxicity ECIs** within 24 hours • Evaluation by ophthalmologist recommended	• Topical steroids – 1%prednisolone acetate suspension and iridocyclitics • Permanently discontinue **IF** symptoms persist despite treatment.
	Grade 3	• **Report overdose and liver toxicity ECIs** within 24 hours • Evaluation by ophthalmologist recommended • Withhold pembrolizumab & consider discontinuation.	• 1-2mg/kg of prednisone daily. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Evaluation by ophthalmologist recommended • Permanently discontinue pembrolizumab	Manage as per grade 3
Renal	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold Pembrolizumab	• 1-2mg/kg of prednisone daily. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 3 and 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue Pembrolizumab • Renal consultation and biopsy as appropriate	• 1-2mg/kg of prednisone daily. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks.
Skin – Rash and pruritus	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• Symptomatic treatment	• Topical glucocorticosteroids or urea-containing cream in combination with oral anti-pruritics • Treatment with oral steroids at PIs discretion
	Grade 3	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold Pembrolizumab • Consider dermatology consult & biopsy for diagnosis.	• 1mg/kg/day prednisone or equivalent or dexamethasone 4mg 4xdaily • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• **Report overdose and liver toxicity ECIs** within 24	• Initiate steroids starting with 1-2mg/kg prednisone or equivalent..

		hours • Discontinue pembrolizumab • Dermatology consultation • Consider biopsy for diagnosis & clinical photographs	• Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks.
Skin – Dermatitis exfoliative, erythemamulitforme, Stevens Johnson syndrome[§], toxic epidermal necrolysis[§]. § If it is suspected that the patient has SJS or TEN, pembrolizumab should be withheld. The patient should be referred to a dermatologist for management. If SJS and TEN is confirmed, then pembrolizumab should be permanently discontinued."	Grade 1 (Asymptomatic)	• No action	• Intervention not indicated
	Grade 2	• **Report overdose and liver toxicity ECIs** within 24 hours • Symptomatic treatment	• Topical glucocorticosteroids or urea-containing cream in combination with oral anti-pruritics. Treatment with oral steroids at PIs discretion
	Grade 3	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold Pembrolizumab • Consider dermatology consultation and biopsy for diagnosis.	• 1mg/kg/day prednisone or equivalent or dexamethasone 4mg 4xday. • Symptoms grade 1 or less initiate steroid taper for no less than 4 weeks. • Permanently discontinue pembrolizumab is if dose cannot be reduced to prednisone 10mg or less or equivalent per day within 12 weeks.
	Grade 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue pembrolizumab • Dermatology consultation • Consider biopsy for diagnosis & clinical photographs	• Initiate steroids starting with 1-2mg/kg prednisone or equivalent.. • Symptoms grade 1 or less, initiate steroid taper for no less than 4 weeks.
Other: • **Myocarditis[¶]** • **Pericarditis** • **Pancreatitis** • **Any additional Grade 3 or higher event which the physician considers to be immune related** ¶ "Ensure that other causes of myocarditis are adequately evaluated to exclude other aetiologies	Grade 2 or Grade 1 that do not improve with symptomatic treatment.	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold Pembrolizumab • Consider biopsy for confirmation of diagnosis.	• Systemic corticosteroids may be indicated. • If so: • Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, Pembrolizumab treatment may be restarted and the dose modified as specified in the protocol
	Grade 3	• **Report overdose and liver toxicity ECIs** within 24 hours • Withhold Pembrolizumab	• Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

	Grade 4	• **Report overdose and liver toxicity ECIs** within 24 hours • Discontinue pembrolizumab	• Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.

11.6 Appendix 6 - Response Evaluation Criteria in Solid Tumours (RECIST) 1.1

Criteria for Evaluating Response in Solid Tumours

RECIST version 1.1* will be used in this study for assessment of tumour response.

* As published: Eisenhauer et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228. (71)

The following paragraphs are a quick reference and the complete criteria are included in the published RECIST document also available at http://www.eortc.be/RECIST.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumour measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters

will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans). Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to

prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy: Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumour types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to

differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.* Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.* Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

11.7 Appendix 7 - Response Evaluation by Immune Related Response Criteria (irRC)

As published: Wolchok JD et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune related response criteria. Clin Cancer Res 2009;15(23):7412. (72)

Definition of Tumor Response Using irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

Definition of Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all index lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR): Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all index and all new measurable lesions (ie., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by ≥25% when compared to SPD at nadir.
- irStable Disease (irSD): Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- irProgressive Disease (irPD): At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all index lesions and any new lesions) when compared to SPD at nadir.

Definition of Non-Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all non-index lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR) or irStable Disease (irSD): non-index lesion(s) are not considered in the definition of PR, these terms do not apply.
- irProgressive Disease (irPD): Increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- Immune-Related Complete Response (irCR): Complete disappearance of all tumor lesions (index and nonindex together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- Immune-Related Partial Response (irPR): The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
- Immune-Related Stable Disease (irSD): irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- Immune-Related Progressive Disease (irPD): It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
  -At least 25% increase in the sum of the products of all index lesions over baseline SPD calculated for the index lesions.
  -At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

Index Lesion Definition	**Non-Index Lesion Definition**	**New Measurable Lesions**	**New Unmeasurable Lesions**	**Percent change in tumor burden (inc measurable new lesions)**	**Overall irRC Response**
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≥ -50%	irPR
				<-50% to <+25%	irSD
				>+25%	irPD
Stable Disease	Any	Any	Any	<-50% to <+25%	irSD
				>+25%	irPD
Progressive Disease	Any	Any	Any	≥+25%	irPD

Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered. irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

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